WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 7, 377-398. Review Article ISSN 2277– 7105

CHEMICAL CONSTITUENTS AND PHARMACOLOGICAL ACTION OF *ANNONA MURICATTA* – A REVIEW

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Article Received on
12 March 2023,

Revised on 02 April 2023,
Accepted on 23 April 2023

DOI: 10.20959/wjpr20237-27987

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ABSTRACT

A tropical plant species called *Annona muricata L*. is well-known for its edible fruit, which has little known medical benefits but more of toxicological consequences. With the aim of igniting additional research on extracts and fruit pulp used for human consumption, this review concentrates on the phytochemical's concentrations, bioactivity, biological activities, and toxicological aspects of extracts and isolated compounds, as well as the medicinal uses of *A. muricata*. *A. muricata* has been used traditionally in tropical areas to cure a variety of diseases, including cancer, hypertension, inflammation, diabetes, pain, internal and external parasites, respiratory and skin conditions, and internal and external parasites. Alkaloids, phenols, and acetogenins are the most significant of the more than 200 chemical compounds that have been found and isolated from this plant. To support the medicinal potential of this herb, clinical research is also required.

KEYWORDS: *ANNONA MURICATTA LINN*, phytochemical constituents, alkaloids, pharmacology, anticancer activity.

1.0 INTRODUCTION

The compounds that serve as a framework for maintaining health may be found in abundance in herbal plants. The treasure of the classical medical approach can be referred to as plant-derived herbal ingredients since they have a long history of therapeutic usage, higher patient tolerance, and patient acceptability. For the treatment of some diseases, medicinal plants have been employed since the dawn of recorded history. India was most likely the first nation to keep track of helpful medications historically. Gold, lead, mercury, and silver are just a few

of the metals that are said to provide medical benefits, according to the Charaka Samhita, which was written by Acharya Charaka, a famous Ayurvedic scholar of 1500 BC. Metals including copper, gold, iron, lead, mercury, silver, and zinc are used in the Ayurvedic medical system. The holy Vedas, which date from between 3500 and 800 B.C., have numerous allusions to the usage of medicinal plants. For instance, "Virikshayurveda" is one of the earliest books in traditional herbal medicine and was composed before the start of the Christian period, making it one of the most antiquated. Additionally, the "Rig Veda," one of the oldest works of literature, which is thought to have been written around the year 2000 B.C., described the use of cinnamon (Cinnamomum verum), ginger (Zingiber officinale), and sandalwood (Santalum album) not only in religious ceremonies but also in preparations for medical purposes. The earliest known written record of the use of medicinal herbs for medication manufacture was discovered on a Sumerian clay slab from Nagpur that is thought to be about 5000 years old. It had 12 drug production instructions that made reference to more than 250 different plants, some of which contained alkaloids including poppy, henbane, and mandrake. *Rhei rhisoma*, camphor, *Theae folium*, *Podophyllum*, the great yellow gentian, ginseng, jimson weed, cinnamon bark, and ephedra are just a few of the 365 drugs (dried parts of medicinal plants) that are discussed in the Chinese book "Pen T'Sao" on roots and grasses, which was written by Emperor Shen Nung around 2500 BC. There are references to 63 plant species from the Minoan, Mycenaean, Egyptian, and Assyrian cultures in Homer's epics The Iliad and The Odysseys were written around 800 BC. Some of them were given names in honour of mythological figures from these epics; for example, Elecampane (*Inula helenium L.* Asteraceae) was given the name Elena in honour of the goddess who served as the focal point of the Trojan War. The name of the Artemisia genus of plants, which were thought to protect and restore health, was taken from the Greek word artemis, which means "healthy." The sea onion (*Scilla maritima*), mustard, and cabbage were mentioned by Pythagoras, Orpheus, and Herodotus in the year 500 BC. Herodotus also made reference to the castor oil plant. 300 medicinal plants are categorised by physiological action in Hippocrates' writings (459–370 BC): Wormwood and common centaury (*Centaurium umbellatum Gilib*) were used to treat fevers, while garlic was used to treat intestine parasites. Opium, henbane, deadly nightshade, and mandrake were used as narcotics, while fragrant hellebore and haselwort were used as emetic herbs, sea onion, celery, parsley, asparagus, and garlic were used as diuretics, and oak and pomegran. The discovery of America (1492), Vasco De Gama's journeys to India (1498), and Marco Polo's travels (1254–1324) through tropical Asia, China, and Persia all led to the introduction of numerous medicinal plants into

Europe. There were attempts to cultivate domestic therapeutic plants as well as plants imported from the old and new world in the many botanical gardens that sprang up throughout Europe. Several new medicinal plants were added to materia medica with the discovery of America, including tobacco, red pepper, cinnamon, ipecacuanha, cacao, ratanhia, lobelia, jalapa, podophylum, and others. Since the Countess of Chinchon was the first person to utilise it, Cortex Chinae, a quinine-containing extract from Cinchona succirubra Pavon, was brought to European medicine in the 17th century under the term countess' powder. The use of natural products and herbal treatments to treat illnesses dates back thousands of years. The herbal treatments, in contrast to the popular allopathic method, contain tens of thousands of different ingredients that all fight disease at once. In order to improve patient compliance and prevent repetitive administration, phytotherapeutics require a systematic approach to administer the components over time. This can be done by creating brand-new methods for delivering herbal ingredients' medications. The therapeutic value of new drug delivery systems is increased by lowering toxicity, raising bioavailability, and other factors. This reduces the need for repeated administration to overcome non-compliance. Recent times have seen the emergence of the term "nanomedicine," which describes the use of nanotechnology in the treatment, diagnosis, monitoring, and control of biological systems. Lipids, polysaccharides, and synthetic biodegradable polymers have all been used to create the nanocarriers in order to ensure their safety.

As all of the active ingredients work together in synergy to increase the therapeutic value, the efficacy of herbal medicines depends on the overall performance of a variety of active ingredients. Every component that is active has a vital job to play, and they are all interconnected. The majority of medications with a botanical origin, however, have an insoluble nature that causes decreased bioavailability and increased systemic clearance, necessitating repeated administration or higher doses. This renders the substance an unsuitable option for therapeutic usage. In phyto-formulation research, creating nano dosage forms such as liposomes, proliposomes, solid lipid nanoparticles [SLNs], nanoemulsion, polymeric nanoparticles including nanospheres and nanocapsules, enhancing solubility and bioavailability, protecting from toxicities, enhancing pharmacological activity, enhancing stability, enhancing tissue macrophage distribution, sustained delivery, proteolytic delivery, etc. In order to improve activity and address issues with plant-based treatments, nano-sized drug delivery devices for herbal pharmaceuticals may have a future. In order to combat more chronic diseases including asthma, diabetes, cancer, and others, nanocarriers must be

integrated into the regular medical system as a means of drug delivery. Due to its potential for use in medicine, the Annonaceae family species *Muricata* has attracted a lot of attention recently. Several studies have recently focused on the bioactivity and toxicity of this species after numerous studies on the Annonaceae family's therapeutic uses in the past.*A. muricata* is one of these typical fruit trees that has been used for decades due to potential medicinal benefits. The populace is fascinated in this species of the *Annonaceae* family because of the overwhelming evidence proving its pharmacological use.[4-6] The sour and sweet flavour of *annona muricata*'s fruit has earned it the nickname "soursop." Its flavour has earned it the nickname "prickly custard apple." The fruit is referred colloquially as Mullu-sitha-pazham (in Tamilnadu; India). A process called as allelopathy occurs when a plant generates certain biomolecules referred to as secondary metabolites that can harm or profit nearby flora. This plant has an allelopathic impact by preventing the development of nearby plant. The fruit's pulp may be consumed and utilised as a primary component in a variety of dishes and drinks.

1.1. LOCAL NAMES

- Creole (saua sap, kowól);[17]
- Dutch (soursap, sorsaka, zuurzak);[17]
- English (durian blanda, custard apple, soursop);[17]
- Filipino (atti, llabanos, guayabano);[17]
- French (corossol, corosselier, corossolier, corossel, corossol épineux, sappadillo, cachiman épineux, cachimantier);[17]
- German (Sauersack,Stachelannone,stachliger);[17]
- Indonesian (nangka seberng,sirsak);[17]
- Javanese (nangka belanda, sirsak);[17]
- Khmer (tiep banla, tiep barang);[17]
- Lao (Sino-Tibetan) (khièp thét, khan thalot);[17]
- Malay (durina makkah, durian benggala, durian belanda);[17]
- Portuguese (coraçao-derainha, graviola);[17]
- Spanish(coraçao de Rainha, araticu-ponhé, anona espinhosa, catuche, curassol, graviola, guanábana, jaca do pará, pinha azeda, zapote agrio, jaca de pobre);[17]
- Swahili (mstafeli);[17]
- Thai (riannam, thurian-khaek, thurian-thet);[17]
- Tigrigna (anona);[17]

* Vietnamese (mang câù xiêm)[17]

1.3. DISTRIBUTION AND TAXONOMY

Native to the warmest tropical regions of South and North America, *A. muricata* has subsequently spread significantly to other tropical and subtropical regions of the world, including India, Malaysia, and Nigeria.[1] It has recently widely dispersed over the West Indies, from southern Mexico to Peru, and Argentina.[35] In addition, *A. muricata* is widespread throughout tropical and subtropical regions of the world at elevations lower than 1,200 m above sea level, where temperatures range from 25 to 28°C, relative humidity ranges from 60 to 80%, and annual rainfall exceeds 1500 mm.[4&36] It is a tree with a diameter of 15–83 cm, a height of 5-8 metres with a large, glossy, dark-green leaf canopy.[16-18] Young branchlets resemble rusty and shaggy. Heartwood is dark, and sapwood is white. Despite being soft, light, and undurable (specific gravity of 0.4)[17], the wood has been used to make ox yokes.The tree typically produces flowers and fruits throughout the year, but depending on the altitude, there are more distinct seasons[15] The leaves have a silky, lustrous, deep green topmost layer and a pale green bottom half. The leaves might be narrowly obovate, oblong, or elliptic in morphology, with points over both ends. The length and width of the leaves are 1 to 2.5 in (2.5 to 6.25 cm), respectively. Larger solitary yellow blooms on woody stalks can be encountered on the tree (pedicels). Massive, solitary flowers that are yellow or greenish yellow in appearance. The inner three petals are likewise massive, elliptical, and rounded, whereas the outer three are widely ovate with heart-shaped bases. Its fruits are 15-20 cm in diameter, delicious, and heart-shaped. They are also green in colour.[2] The skin is reticulated and bears short spines. Its interior has a cream-colored, granular covering that is readily separated from the multitude of white, fibrous, juicy segments that round the soft, pithy centre.[33] In certain nations, its average weight is 4 kg[15] whereas it weighs around 0.4 and 1.0 kg in Mexico[18] Venezuela[34] but also in Nicaragua[16] The flesh is white and creamy and has a distinctive flavour and scent.[15] When fresh, each fruit can have 55–170 black seeds, which turn light brown when dried.[3] The weight of an *A. muricata* fruit is composed of approximately 67.5% edible pulp, 20% peel, 8.5% seeds, and 4% core. About 68% of the total solids are sugars. The fruit is a poor to fair provider of calcium and phosphorus, but it is a high source of vitamins B (0.07 mg/100g) and C (20mg/100g). The fruit's highly appealing flavour and smell are its most desired qualities.[17] Each tree may produce 12–20, or even 24 fruits. As the tree ages, the yield begins to drop.[36]

1.3. TAXONOMICAL CLASSIFICATION OF *ANNONA MURICATA LINN*

It belongs to the Annonaceae family, which has over 130 genera and 2300 species.[19-20] Cherimoya (*A. cherimola*); paw paw (*Asimina triloba*) and sugar-apple (*A. squamosa*) are also species included in the family. The genus *Annona* comprises over 70 species among which *A. muricata* is the most widely grown[15,19,20] [Table 1]

Table 1: Taxonomical classification of *Annona muricata Linn.*

Kingdom	Plantae
Subkingdom	*Trecheobonta* -vascular plants
Division	*Mangoliophyta*-flowering plants
Super division	*Spermatophyte*-seed bearing plant
Class	*Mangoliopsida*
Subclass	*Mangoliidae*
Order	*Mangoliales*
Family	*Annonaceae*
Genus	*Annona*
Species	*Muricata*

2. WORLDWIDE ETHANOMEDICAL USES OF *ANNONA MURICATA LINN*

In different locations of the world, people use the decoction of fruits, leaves, roots, and bark of the plant for many purposes. *A. muricata* has been utilised in traditional medicine, with stem barks, roots, seeds, and leaves being the most often used ingredients in the production of traditional medicinal concoctions. Similar to other Annona species, the *A. muricata* tree's entire body is used widespread in traditional medicine for the treatment a wide range of human maladies and diseases, including cancer and parasite infections**.**Based on ethnobotanical observations, traditionally fruit juice and leaf or branch infusions have been utilized for curing various deases for example its leaves are traditionally utilized for the treatment of hypertension, asthma, headache, and cough in our local region. it also used as sedative, antispasmodic and as a nervine tonic for heart conditions.[26] Several studies reported that fruits of *A. muricata* are capable of increasing mother's milk. It is also used for treating fever[7], malaria[8-9], liver, heart and kidney affections[10-11], respiratory illness.[12-14] In Benin it is utilized as Insomnia, catarrh, febrifuge.[21] In India it is utilized as suppurative, febrifuge pain and pus from ulcers[7], tonic, spasms, parasites, bechic, insecticidal, astringent and as fish-poison.[11] In colombia it is used as Febrifuge[22], in Madagascar for the treatment of heart palpitation, malaria, liver maladies[23], in Malaysia it is utilized for the treatment of stomach pain, hypertension[24], in Ghana it has been utilized as Anti- malarial agent[25], in Brazil its leaves are used as therapectical agent for snake bite.[27-28] In Indonesia its tree parts

like leaves, root, bark are utilized as insecticidal.[7] The fruit is acknowledged not just as food but also for its juice, which is used as a galactogogue to diagnose liver, heart, and diarrheal infections and diseases.[7] It is utilized against intestinal parasites in South America[7] Malaysian natives treated internal and external parasites with *A. muricata* leaves[7], its oral fruit and juice are consumed as an agent for astringent, dysentery, actagogue, diarrhea[7], in the natives of Brazil[7] used to treat pellagra, the flu, heart parasites, and anxiety. In Haiti[7] it is referred to as "jamaica soursop" and is used to cure a variety of ailments including spasms, anxiety, asthenia, asthma, heart conditions, parasites, diarrhoea, lactagogue, dewormer, dysentery, pain, and diuretic.[7&29] In Colombia, Cuba, Ecuador, panama and Dominican Republic regions it is commonly called as “Cuana´bana”. Cuba natives used this plant for treatment of Catarrh.[12] Ecuador natives used this plants leaves in treatment of Rheumatism.[30] Panama natives used this plants leaves in treatment of dyspepsia, allergy, helminthiasis, diarrhea and also its bark and pulp are used for the stomach ulcer treatment.[31&28] It has been believed to act as an Galactogogue in Dominican Republic and also used in women in labor.[13&28] In South pacific countries its leaves have been utilized for fainting spells, dizziness problems[28] hypertension, diabetes has been treated by Togo natives by utilizing its leaves, they also use it for the curing Malaria.[28&32] In Bolivia, kidney disorders and hypertension are treated traditionally by utilizing this fruit juice.[37] In cameroon its leaves have been medicinally used in Malaria, digestive disorders, typhoid fever, anthelmintic, antimicrobial and anticonvulsant.[9] Its root are traditionally utilized in the treatment of Malaria in the region of Ghana and there it is called as “Apre”.[25] Madagascar and Mauritius natives referred as “Corossol” and in the region of Madagascar its leaves are utilized in the traditional treatment of liver maladies, heart palpitation and malaria[27] and also in the natives of Mauritius these leaves are used in the reduction of hypertension and headache . In the region of Nicaragua, people utilized *Annona muricata* for multiple purpose, especially its leaves are used in the treatment of ringworm, insecticidal, abdominal and back pain, menstrual hemorrhage, abortions, fever, vaginal infection renal and skin disorders, diarrhea.[16&28&10] In New Guinea, Stomach pain has been cured by utilizing the leaves of *Annona muricata.*[11] In Thailand natives used its seed as insecticidal.[11] Ttraditionally hypertension has been handled by Trinidad y Tobago natives by its leaves.[11] Venezuela region native peoples handled liver affectation and stomach pain by its leaves[11] Malaria has been also cured by utilizing its fruit and leaves by the natives of Vietnam South[8] In Caribbea people used this in their traditional medicine for chills, fever, flu, indigestion, nervousness, palpitations, rash, spasms, skin disease, and as a sedative.In Curaçao natives

used this plant for childbirth, gallbladder problems, nervousness, and as a sedative and tranquilizer. Elsewhere it is also used as remedy for pain, ringworm, scurvy, stomach issues, bile insufficiency, cancer, childbirth, diarrhoea, dysentery, fever, heart issues, kidney issues, lactation assistance, lice, liver diseases, malaria, and as a sedative.

3. CHEMICAL COMPOUNDS ISOLATED FROM *ANNONA MURICATTA LINN*

Phytochemicals are constitutive metabolites generated by various plant components through their primary or secondary metabolism. They play crucial roles in the plant's overall development and defence against pests, pathogens, and abiotic stressors as well as in general plant growth.[38] In addition, primary metabolites including proteins, lipids, and carbohydrates are directly related to the development and metabolism of the vegetation. While primary metabolites are not required for life but are engaged in important processes in the plant, such as protection, competition, and species interactions, secondary metabolites are biosynthesized from primary metabolites.[39] Based on their metabolic origins, they may be divided into three main groups[40]

1. Phenolic compounds,
2. Terpenoids, and
3. Nitrogen/sulfur-containing chemicals.

These substances have been researched for use in disorders associated with carcinomatous growths and have shown a variety of anti-cancer capabilities, including anti-proliferation and apoptotic cell death activities. Numerous phytochemical analyses of the *A. muricata* plant's various parts have revealed the presence of a variety of phytoconstituents and metabolites incorporating cyclopeptides, flavonol triglycosides, phenolics, megastigmanes, flavonoids, and essential oils. The fruit of the *A. muricata* tree contains a variety of key minerals, including K, Ca, Na, Cu, Fe, and Mg, which suggests that frequent eating of the fruit can help the body get the nutrients and elements it needs.[41] There have reportedly been 212 bioactive chemicals discovered in *A. muricata*.[42] Acetogenins are the most common substances, followed by alkaloids, phenols, and other substances. The primary plant organs being investigated are leaves and seeds, likely because they have been in use the longest.

3.1. ALKALOIDS

A. muricata contains the alkaloids, reticuline and coreximine, both of which are significant. In that sequence, the alkaloids are more prevalent in the leaves and less so in the roots, stems, and fruits. The three most significant alkaloids are

1. Protoberberine,
2. Apomorphine and
3. Isoquinoline.

3.1.1. Aporphine type of alkaloids

Table 2: Aporphine type of the alkaloid present in various parts of *A.muricata*.

S.No.	Plant part	Alkaloids	Type of the alkaloid	Biological Activity	Ref.
1.	Fruit &Leaf	Annonaine	Aporphine	Antidepressive	[43,44]
2.	Leaf	Annonamine	Aporphine	Cytotoxic	[45]
3.	Fruit &Leaf	Asimilobine	Aporphine	Antidepressive	[43,44]
4.	Stem	Atherospermine	Aporphine	-	[46]
5.	Root	Atherosperminine	Aporphine	-	[46]
6.	leaves	Isoboldine	Aporphine	Antimalarial agent	[47]
7.	Leaves	(S)-Narcorydine	Aporphine	Cytotoxic	[45]
8.	leaves	Liriodenine	Aporphine	-	[47]

3.1.2. Isoquinoline type of the alkaloid

Table 3: Isoquinoline type of the alkaloid present in various parts of *A.muricata*.

S.No.	Plant part	Alkaloids	Type of the alkaloid	Biological Activity	Ref.
1.	Root& Bark	Anomuricine	Isoquinoline	-	[46]
2.	Root& Bark	Anomurine	Isoquinoline	-	[46]
3.	Root& Bark	Coclaurine	Isoquinoline	-	[46]
4.	leaves	(R)-O,Odimethylcoclaurine	Isoquinoline	Cytotoxic	[45]
5.	leaves	(R)-4´O-methylcocaurine	Isoquinoline	Cytotoxic	[45]
6.	leaves	N-methylcoculaurine	Isoquinoline	-	[48]
7.	Leaves	N-methylcoclaurine	Isoquinoline	-	[47]
8.	Leaf	Xylopine	Isoquinoline	-	[49]

3.1.3. Imino sugar type of the alkaloid

Table 3: Imino sugar type of the alkaloids present in various parts of A.muricata are as follows.

S.No.	Plant part	Alkaloids	Type of the Alkaloid	Biological Activity	Ref.
1.	Leaf/stem	Casuarine	Imino sugar	-	[50]
2.	Leaf/stem	DMDP (2,5- Dihydroxymethyl-3,4, dihydroxypyrrolidine)	Imino sugar	-	[50]
3.	Leaf/stem	DNJ (Deoxynojirmycin)	Imino sugar	-	[50]
4.	Leaf/stem	DMJ (Deoxymannojirimycin)	Imino sugar	-	[50]
5.	Leaf/stem	Swainsonine	Imino sugar	Immune Stimulater	[50]

3.2. Acetogenins

The acetogenins are a special group of substances that are thought to be the primary bioactive components of the Annonaceae family. These acetogenins are also known as annonaceous acetogenins. Various plant components, including the leaves, stem, bark, seeds, pulp, and fruit peel, have shown to contain more than 120 acetogenins. The acetogenins' structural characteristics affect *A. muricata's* bioactivity. A significant acetogenin called annonacin is plentiful in fruit and leaves, with lesser levels present in seeds, roots, and peel. According to some research, alkaloids are not as cytotoxic as acetogenins. Due to their distinctive structural makeup and diverse biological functions, AGEs have recently been the subject of several scientific investigations.

Table 4: Acetogenins present in *A.muricata.*

S.No.	Plant part	Acetogenins	Type of the Acetogenins	Biological Activity	Ref.
1.	Seed &root	Cohibin A	Linear, unsaturated, 2OH	-	[51,52]
2.	Seed &root	Cohibin B	Linear, unsaturated, 2OH	-	[51,52]
3.	Seed	Cohibin C	Linear, unsaturated, 2OH	-	[51]
4.	Seed	Cohibin D	Linear, unsaturated, 2OH	-	[51]
5.	Seed	Montecristin	Linear, unsaturated, 2OH	-	[52]
6.	Seed	Bullatalicin	Bis THF nonadjacent, 4OH	Cytotoxic	[52]
7.	Root	Cis-panatellin	Mono THF, 2OH	-	[52]
8.	Root	Cis-reticulatacin-10-one	Mono THF, 2OH 1carbonyl	-	[52]
9.	Root	Cis-uvariamicin I,	Mono THF, 2OH	-	[52]
10.	Root	Cis-uvariamicin IV	Mono THF, 2OH	-	[52]
11.	Root	Cis-solamin	Mono THF, 2OH	-	[52]
12.	root	Cis-panatellin	Mono THF, 2OH	-	[52]
13.	root	Cis-reticulatacin	Mono THF, 2OH	-	[52]
14.	seed	Annoglaxin	Mono THF, 2OH 1carbonyl	-	[53]
15.	seed	Asiminecin	Bis THF adjacent, 3OH	Cytotoxic	[53]
16.	Seed	Cis-squamostatin A	Bis THF nonadjacent, 4OH, 3OH	Cytotoxic	[53]
17.	seed	Cis-squamostatin D	Bis THF nonadjacent, 4OH, 3OH	Cytotoxic	[53]
18.	seed	Desacetyluvaricin	Bis THF adjacent, 2OH	-	[53]
19.	seed	Isodesacetyluvaricin	Bis THF adjacent, 2OH	-	[53]
20.	Leaf	Montanacin	Mono THF, 5OH	Cytotoxic	[54]
21.	Pulp	Xylomatenin	Mono THF, 4OH, unsaturated	-	[54]
22.	Leaf	Asimicinone-9-oxo	Bis THF adjacent, 2OH, 1 carbonyl, keto lactone	Cytotoxic	[54]
23.	Leaf & Pulp	Montanacin D	Mono THF, Mono THP, 2OH, 1 carbonyl	-	[54]
24.	Leaf & Pulp	Montanacin E	Mono THF, Mono THP, 2OH, 1 carbonyl	-	[54]
25.	Seed & Leaf	Gigantecin	Bis THF nonadjacent, 4OH	Cytotoxic, Antitumor	[54]
26.	Leaf&Nectar	Montanacin H	MonoTHF, 4OH, 1 carbonyl	Cytotoxic	[54]

Chemical structures of various types of acetogenins present in *A. muricata*.

1. Chemical structure of linear acetogenins derivatives
2. Chemical structure of epoxy acetogenins
3. Chemical structure of mono THF acetogenins
4. Chemical structure of mono THF, mono THP acetogenins
5. Chemical structure of Bis-THF nonadjacent acetogenins
6. Chemical structure of Bis-THF adjacent acetogenin

3.4. Phenolic compounds

A. muricata is reported to possess approximately to 37 phenolic compounds. Among these, gallic acid and quercetin are the most prominent. It has been observed that the pulp contains flavonoids and lipophilic antioxidant components including tocopherols and tocotrienols. When organic or aqueous extracts have been employed in various investigations, the amount of extractable total phenols is significantly varied. This has to be mentioned because the overwhelming of phenols being readily soluble in water and aqueous infusion is the most typical medical use. The primary phytochemicals thought to be responsible for the antioxidant action are phenolic compounds.

Table 5: Phenolic compounds.present in *A.muricata.*

S.No.	Plant part	phenolic compounds.	Type of the phenolic compound	Biological Activity	Ref
1.	leaves	Emodin	Anthraquinone	-	[55]
2.	Leaves and pulp	Cinnamic acid	Cinnamic acid	-	[55]
3.	Leaves and pulp	Coumarid acid	Flavonoid	-	[55]
4.	Leaves	Daidzein	Flavonoid	-	[55]
5.	Leaves	Glycitein	Flavonoid	-	[55]
6.	Leaves	Gallocatechin	Flavonoid	-	[55]
7.	Leaves	Homoorientin	Flavonoid	Antioxidant	[55]
8.	Leaves	Tangeretin	Flavonoid	-	[55]
9.	Leaves	soferulic acid	Flavonoid	-	[55]
10.	Leaves	Genistein	Flavonoid	-	[55]
11.	Leaves	Chlorogenic acid	Chlorogenic acid	-	[56]
12.	Leaves	Catechin	Flavonoid	Antioxidant	[56]
13.	Leaves	Epicatechin	Flavonoid	Antioxidant	[56]
14.	Leaves	Argentinine	Flavonoid	Antioxidant	[56]
15.	Leaves	Kaempferol	Flavonoid	Antioxidant	[56]
16.	Leaves	Quercetin 3-O neohesperidoside	Flavonoid	Antioxidant	[56]
17.	Leaves	Quercetin –O-rutinoside	Flavonoid	Antioxidant	[56]
18.	Leaves	Quercetin 3-O-a-rhamnosyl	Flavonoid	Antioxidant	[56]
19.	Leaves	Quercetin 3-O-robinoside	Flavonoid	Antioxidant	[56]

20.	Leaves	Quercetin 3-O-glucoside	Flavonoid	Antioxidant	[56]
21.	Pulp	Morin	Flavonoid	Antioxidant	[57]
22.	Pulp	Fisetin	Flavonoid	-	[57]
23.	Pulp	Myricetin	Flavonoid	Antioxidant	[57]

Chemical structures of types of phenols present in *A. muricata*.

A) Chlorogenic acid type.

(B) Flavonoid type.

(C) Hydroquinone type,

(D) Tannin type.

3.5. Other compounds

In the leaves, seeds, and fruit pulp, many investigations have found the presence of other substances such vitamins, carotenoids, amides, and cyclopeptides. N-p-coumaroyl tyramine and cyclopeptides, two amides found in the seeds, have anti-inflammatory and anti-tumor properties. About 37 volatile substances have been isolated in the fruit's pulp, while sesquiterpene derivatives have been discovered in the leaf. Additionally, there are enzymes like pectinase, catalase, and peroxidase in the pulp of the soursop. When fruit is ripening, the enzyme amylase is present, and as the fruit's ethylene level rises, its activity increases by around 18 times.

S.No.	Plant part	Chemical name	Type of the compound	Biological Activity	Ref
1.	Pulp	Carotenes α	Carotenoid	Antioxidant	[57]
2.	Pulp	Carotenes β	Carotenoid	Antioxidant	[57]
3.	Pulp	Lycopene	Carotenoid	Antioxidant	[57]
4.	Pulp	Cryptoxanthin β	Carotenoid	Antioxidant	[57]
5.	Pulp	Tocopherol α	Carotenoid	Antioxidant	[57]
6.	Pulp	Tocotrienol α	Carotenoid	Antioxidant	[57]
7.	Pulp	Tocotrienol γ	Carotenoid	Antioxidant	[57]
8.	Pulp	Lutein	Carotenoid	Antioxidant	[57]

4. PHARMACOLOGICAL ACTIVITIES

Numerous *in vitro*, *in vivo*, and in silico research on *A.muricata* have revealed promise pharmacological action for the benefit of humanity. Antiprotozoal activity, insecticidal activity, and cytotoxic activity are the most common outcomes of *in vitro* research. The remainder complied with antioxidant, antibacterial, antiviral, and other properties. hepato, gastroprotective, antitumorigenic, and hypoglycemic studies are the most often seen in *invivo* research.

4.1. *Annona muricata* for Cancer Diseases

Based on certain *in vitro* studies reports have shown that this plant is poisonous to cancer cell lines without harming normal cells, the *Annona muricata* extracts have displayed a considerable bioactivity.[58] Similar to this, the type of extract used has a significant impact on the outcomes of the other investigation of biological activities. For example, pentanoic and ethanolic solvents were discovered to be the most effective *A. muricata* extracts against cancer cells developing *in vitro w*hereas in A375 cell culture, the activity in both extracts was reported to be 10 and 4.5 times higher, respectively, than the activity in the aqueous extract.[58] By eliciting apoptotic signals in tumour xenograft mice, *A.muricata* leaf/stem extract demonstrated anticancer properties throughout the control of the tumour cell lifecycle.[42] In contrast, hexane extract of leaves were discovered to have the greatest flavonoid concentration and to be the most efficient in inhibiting cell growth when compared to extracts obtained using methanol or chloroform.[59] The suppression of the mitochondrial complex I and the inhibition of ubiquinone-linked NADH oxidase in the plasma membranes of tumorous cells, which results in apoptosis, are the mechanisms by which the muricata extracts exert their cytotoxic effects. Furthermore, it suggests that *muricata* extracts cause apoptosis via (ROS) Reactive Oxygen Species in light of previous discoveries. Results from 2015 showed that *A. muricata* hexane and marketed extracts caused modest cytotoxicity *in vitro* in human pancreatic cancer cells.[59] By minimizing tumour weight and size, exhibiting anti-metastatic properties, and inducing apoptosis in 4T1 cells *in vitro* and *in vivo*, crude extract samples of *A. muricata* leaves had anti-cancerous activities, demonstrating varying degrees of cytotoxicity against human breast cancer cells (MCF-7, MDA-MB-231, and 4 T1).[60] Lung cancer cells exposed to A. *muricata* extract demonstrated apoptotic induction. By causing the G1 cell cycle arrest, *A.muricata* extract also shown anti-colon cancer effects on cell lines.[61] In murine models, an aqueous extract of commercial powder capsules containing the leaf and stem of *A. muricata* also exhibited anti-tumorigenic and antimetastatic effects on pancreatic tumors.[64] In murine models, the ethanolic extract of *A. muricata* leaves shown stronger anti-tumor efficacy than curcumin, a well-known natural chemopreventive. In induced colorectal carcinogenesis, this extract has demonstrated a protective effect on biochemical processes and morphological alterations.[63] Rats with colonic aberrant crypt foci caused by azoxymethane responded favourably to an ethanol extract of *A. muricata* leaves.[62] The extract increases Bax protein, upregulates PCNA and Bcl-2 proteins, and restores the levels of the antioxidant enzymes by acting as acetogenins. Malondialdehyde (MDA), a lipid radical produced by excessive ROS generation, was found to be present in higher

concentrations in patients with colorectal cancer.[62] Treatment with *A.muricata* fruit extract for 5 weeks reduced breast tumour in mice.[65] According to the mechanism of action, several signalling pathways that controlled metabolism, metastasis, the production of necrosis, and cell cycle inhibition were inhibited.[64,65] According to a research, bullatacin was 300 times more effective at reducing a tumour in rats than the pharmaceutical Taxol in levels of 400 mg/kg.[66] At the same time, annonacin decreased tumour growth in mouse models of tumour induction at dosages of 10 mg/kg that were equivalent to those of the prescription medications cisplatin and Adriamycin.[67] Through a mitochondrial-mediated approach, the extract of leaves were capable of triggering apoptosis in colon and lung cancer cells. This antiproliferative impact was linked to G1 phase cell cycle arrest.[68,69] Additionally, the leaf extract dramatically reduced the migration and invasion of colon cancer cells. A TUNEL experiment indicated that the ethanolic extract of the leaves had an apoptosis-inducing impact on myelogenous leukemic K562 cells by activating caspase 3.[70] Current *in vitro* and *in vivo* tests on the *A. muricata* leaf water extract against the benign prostatic hyperplasia (BPH-1) cell line and rat prostates were conducted. After 72 hours, the results indicated that the treatment had a suppressive impact on BPH-1 cells with an IC50 value of 1.36 mg/mL, which was accompanied by an mRNA level upregulation of Bax and a downregulation of Bcl-2. The size of the rats' prostates reduced after two months of treatment with the extract (30 and 300 mg/mL dosages), which was thought to happen through the activation of apoptosis.[71] Even at a modest dose of 30 mg/kg, the leaves prevented mice from developing skin papillomas after they had been given DMBA or croton oil to do so.[63] Methylene blue staining of colorectal samples showed that oral treatment of the extract at two dosages (250 and 500 mg/kg) for 60 days effectively decreased ACF development in rats. According to the immunohistochemical study, this activity was also accompanied by an increase in Bax and a decrease in Bcl-2. The ethanolic extract of the leaves against 1,2-dimethyl hydrazine (DMH)-induced colon cancer likewise showed this notable decrease in ACF development.[72] Additionally, the ethyl acetate extract of *A.muricata* leaves were tested for its ability to inhibit rat colonic aberrant crypt foci (ACF) that were brought on by azoxymethane. An inquiry against HT-29 cells that was directed by an *in vitro* bioassay was conducted after the study, and this resulted in the identification of annomuricin E. In colon cancer cells, this AGE demonstrated mitochondrial-dependent apoptotic activity with an IC50 value of 1.620.24 g/mL after 48 hours.[73] *In vivo* research on 7, 12-dimethylbenzene anthracene (DMBA)-induced cell proliferation in mouse breast tissues likewise revealed this encouraging anticancer impact. Creatine supplementation of *A. muricata* leaves may have preventive

benefits against the onset of breast carcinogenesis, as evidenced by the protective effect against DNA damage brought on by DMBA.[74]

CONCLUSION

The primary species of the *Annonacae* family, *A. muricata*, and its use in traditional medicine practises are covered in detail in this review, along with its botanical characteristics, ethnomedical applications, pharmacology, and phytochemistry. This Annona species is among the many Annonacae members that are widely utilised in traditional remedies all over the world. Phytochemical profiles of their bark, leaves, fruits, and seeds, among other phytochemical constituents, have been recorded.

The primary classes of compounds of Annona species' phytochemistry that have been discovered thus far include acetogenins, alkaloids, phenols, and Carotenoids. Alkaloids are primarily found in the leaves of Annona species, whereas acetogenins are mostly found in the seeds and in lesser amounts in the pulp and leaves. Many studies have been conducted on the chemical profiles of the acetogenins found in various species, as well as on their anticancer activity. It has been found that several cancer cell lines are chemotoxic to acetogenins at low concentrations. These preclinical findings, combined with the published case reports, imply that additional clinical research examining the function of acetogenins in the management of various cancer types are necessary.

Conflicts of Interest

The authors do not have any conflict of interest.

ACKNOWLEDGEMENT

The authors wish to thank DST FIST (DST-FIST-2018(SR/FST/COLLEGE-417/2018) (TPN-2011)) laboratory of the Department for having providing assistance to the ongoing research on the phytochemicals in *A.muricata* which led to the publication of this review on the pharmaceutical aspects of *A.muricata*.

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