

# Review *Annona muricata* (Graviola): Traditional Medicinal Uses and Pharmacological Activities

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**Abstract:** Cancer is the world's second largest cause of death. Currently, most treatments depend on chemotherapy which uses toxic drugs that are also toxic to normal healthy cells. Medicinal plants have gained a global attention due to its therapeutic properties as an alternative medicine maintains health and prevents or treats diseases. *Annona muricata*, also known as Graviola is one of the medicinal plants and has been used traditionally to treat many diseases. Currently *A. muricata* plant particularly the leaves have been used to treat cancer. It is known for its selective cytotoxicity against cancer cells without harming other cells. The objective of this review was to assess the potential effects of *A. muricata* against various diseases specifically cancer. *A. muricata* specially leaves, is found to contain hundreds of bioactive chemical compounds. Acetogenins are the most important phytochemical compound. *A. muricata*, has a wide array of bioactivities against several diseases such as; arthritis, diabetes, parasitic infections, hypertension and cancer. Comprehensive preclinical and clinical studies in vivo and in vitro with significant findings have been included in this review. *A. muricata* has unique defensive mechanism as antiproliferative and anticancer, through depleting cancer cell from ATP and inducing apoptosis. Because of that *A. muricata* is a promising, highly effective and selective medicinal plant and needs to be further investigated in order to determine the magnitude of effects, optimum dosage, long-term safety of use, and possible side effects.

**Keywords:** Traditional medicine; Leaves; Anti-cancer; Apoptosis.

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## I. INTRODUCTION

Medicinal Plant extracts have been used by a large sector of population worldwide for treating various diseases. This has a major impact on the preservation and care of health throughout the world. Currently, the incidence of chronic degenerative diseases is increasing and considered as a serious health concern. A significant public awareness about untreated diseases by modern medicine has caused patients to seek treatment from traditional medicine. Alternative and traditional medicine has been widely used for many generations to treat illnesses before modern medicine. Now it has been used to assist in fighting diseases as an adjuvant therapy and also to prevent side effects of modern medicine [1]. Graviola *Annona muricata* L. is a fruit tree generally used in conventional and alternative medicine. The fruits are commonly used in juices and sweets. Different parts of the plant *A. muricata* can be utilized in a wide range of diseases. Locals of South America and Africa extensively use this plant in their folk medicine. Graviola, *Annona muricata* L. is a promising compound with a wide range of therapeutic properties. Accordingly, it has been extensively studied in the last decades.

## 2. BOTANICAL DESCRIPTION AND DISTRIBUTION

### **Taxonmy**

Graviola (*Annona muricata* L.) has many different names according to the region. It is recognized as Graviola, Soursop, Guan'abana, and other names [2]. The classification of this plant follows Kingdom: Plantae, Division: Angiosperms

(Magnoliophyta), Class: Magnolids, Order: Magnoliales, Family: Annonaceae, Genus: *Annona*, Species: *A. muricata* L. The genus *Annona* contains around 70 species with the most extensively grown *A. muricata* [3].

### Ecology

The *A. muricata* tree measurements are around 5–10 m length and 20–80 cm width with low branches [4, 5]. In general it blooms all the year [3]. It is widespread in the tropical regions of Central and South America, Southeast Asia and most of Africa [3, 6]. The plant is found at heights beneath 1200 m above sea level, with temperatures ranges from 25°C - 28°C, humidity varies between 60% and 80%, and precipitation of 1500 mm. The Graviola is edible, green colored ovoid fruit with prickly skin. The average weigh of the fruit is 4 kg in many regions [3] However, it is much smaller in other regions such as; Mexico, Venezuela, and Nicaragua [4,5,7]. The fruit has white color inside with sweet creamy taste, and contains numerous black seeds [3,8].

### Traditional Medicinal Uses

*Annona muricata* is a medicinal plant with wide range of curative activity. Various parts are used in treating several diseases and ailments, such as the leaves, roots, bark, fruits, and seeds [9]. Leaves and seeds were the major plant studied organs. The plant extract is usually prepared by decoction of the different parts, root, bark, seed or leaf. The leaves were used in the Brazilian Amazon to treat liver. However, the leave extracted oil was used for rheumatism, arthritis, and neuralgia. In Jamaica, Graviola juice was used to treat diarrhea and reduce the intestinal acidity [10]. Currently, *A. muricata* leaves are used for hypertension [11, 12], diabetes [9, 12] and cancer [12-17]. Moreover, different studies suggested that *A. muricata* has been utilized to treat from insects [18], parasites [19], fever [20], sedative [21], respiratory infections [22, 23], malaria [24], gastrointestinal illness [20, 25, 26], liver, heart and kidney problems [9, 27, 28].

### Phytochemistry

The phytochemical inspection of the *A. muricata* extract, usually performed by using aqueous and methanolic extracts has demonstrated the presence of numerous phytochemicals and compounds. The bioactive compounds were found to be over 200 [2]. However, the major phytochemicals are acetogenins (ACGs) after that alkaloids, and phenols. Several minerals such as Ca, K, Na, Cu, Fe and Mg are found in the Graviola, [29]. ACGs and alkaloids are known for their strong therapeutic potentials against neurotoxic activity.

**Acetogenins** (ACGs): annonaceous acetogenins are secondary metabolites with distinctive properties, has been determined as a natural compounds with antitumor activities. Currently, researchers have given particular attention to the ACGs due to the extensive biological activities. At the end of the cytoskeleton ACGs possess fatty acid with a  $\gamma$ -lactone with unbranched C32 or C34 [21]. A large number over 120 of ACGs have been recognized in methanolic, ethanolic extracts of various parts of *A. muricata* such as bark, stem, seeds, leaves, pulp, and fruit peel [30, 31, 2, 7]. ACGs have a wide range of medical properties which can be used against particular targets such as; malaria, parasites and pesticides [32, 33]. However, ACGs have a strong biological activity and a great toxicity against cancer cells with mitochondrial inhibitory effect through blocking ATP production. Thus, ACGs limit the growth of cancer cells. The selective toxicity of ACGs were proved to be against different types of malignant cells without harming the healthy cells [31]. Annonacin, is a toxic compound, was found to be the most abundant ACG and reported in all parts of the *A. muricata*. Annonacin has been reported to promote cytotoxicity and selective cancer cell death [34, 35].

**Alkaloids:** The availability of alkaloids is fundamental to Annonaceae species [1]. Alkaloids occur naturally as secondary compounds containing basic nitrogen atoms. *A. muricata* leaves have the highest concentration of alkaloids [36] which possess several biological activities with great biodiversity. The highest concentration of alkaloids is found in leaves, while seeds or roots have very low concentration. It has been reported that Alkaloids isolated from *Annona* species are capable of dopamine biosynthesis [37]. For this reason, it has been suggested that *Annona* alkaloids could promote antidepressant effects [37], and cytotoxic activity [38]. Another property of the alkaloids in *annona* is the neurotoxic activity through the mechanism of apoptosis [39]. Alkaloids have several pharmacological activities against acetylcholinesterase [40], depression, epilepsy [41], parasites [30], malaria [42], ulcers [43], cytotoxicity [44], larva [45], and anxiety [46].

**Phenolic Compounds:** They are soluble in water thus considered very essential phytochemicals and the most widely therapeutic use is aqueous mixture. It has been found that *A. muricata* contains about thirty-seven phenolic compounds. Quercetin and gallic acid are the most essential phenolic compounds discovered in the leaves of *A. muricata* [47, 48]. However, lipophilic antioxidants such as tocotrienols and tocopherols, as well as flavonoids are found in the pulp [48]. The major phytochemicals compound are phenolics possess a strong antioxidant effect [49]. In addition to all of the above mentioned compounds, *A. muricata* has also vitamins, carotenoids, amides, and essential oil. Carotenoids and vitamins were available identified mainly in fruit pulp, seeds, and leaves [48]. Additionally, 37 volatile compounds were recognized in the *A. muricata* fruit pulp [50], along with 80 essential oils in the leaves with special activities against parasites, diarrhea, rheumatoid, neuralgia [51, 52].

### **Pharmacological Activities**

In vitro studies utilized various parts of *A. muricata* extracted in organic solvents were extensively studied compared to in vivo studies using aqueous preparations [53].

#### **Antioxidant Activity**

A remarkable capacity of antioxidant activity was found in *A. muricata* aqueous and methanolic leaf extracts against H<sub>2</sub>O<sub>2</sub> toxicity. However, in vitro aqueous plant extracts showed greater antioxidant capacity over ethanolic extracts [54, 55]. Enzymatic antioxidants, such as superoxide dismutase, peroxidase, and catalase, besides non-enzymatic antioxidants, including vitamin C and  $\alpha$ -tocopherol were found in both leaves and seeds of the plant. [56].

#### **Antihypertensive Activity (Hypotensive Influence)**

The blood pressure reducing effect of *A. muricata* leaves was evaluated. Rats with normal blood pressure were given aqueous leaf extract. The blood pressure was significantly reduced by the leaf extract in a dose dependent manner without affecting the heart rates. The mechanisms of hypotensive effects were mediated by antagonism of Ca<sup>2+</sup> [57].

#### **Anti-inflammatory Activities (Hepatoprotective Activity)**

The leaves of *A. muricata* have shown hepatoprotective activity preventing accumulation of extracellular matrix (ECM), and liver fibrotic damage induced by dimethylnitrosamine in rats [58]. Another study has determined *A. muricata* leaf extract significantly resist the increase of the biomarkers of liver function, reduced synthetic ability, instability of lysosomal membrane and altered ECM function. The leaf extracts worked as a potent fibro suppressant. *A. muricata* leaves may reverse hepatic fibrosis probably through restoration of liver antioxidant status [58]. Furthermore, aqueous extract of *A. muricata* stem bark has hepatoprotective, anticholestasis and antisinusoidal congestion properties [59], and may treat hepatic jaundice [60].

#### **Anticancer Activity**

Failure of the cell to go through apoptosis is one of the main contributors to carcinogenesis. *A. muricata* anti-cancer activity has been shown on cancer cell lines in vitro, which has been resistant to many drugs. *A. muricata* has a strong ability to selectively inhibit cancer cells growth [61, 62]. Studies have shown that the aqueous extract of commercial powder capsules containing leaf and stem of *A. muricata* have anti-tumor and anti-metastasis activities on pancreatic tumor cell in rats [13]. Studies have shown that *A. muricata* fruit extract has reduced breast tumor in rats in 5 weeks. [62].

Currently, the increasing use of ethnobotanical *A. muricata* extract as an anticancer therapy due to the selective cytotoxic activity of the plant as a growth inhibitor for the tumor cells without affecting the healthy cells [63]. George et al. [63] reported that a hydroalcoholic extract of 1.6 mg/ml and 50 mg/ml concentration of *A. muricata* leaves increased the viability of healthy cells, while 100 mg/ml concentration did not change their viability [47]. This study has reflected the ability of the *A. muricata* to induce healing with minimum effects.

The type of extract is critical while studying bioactivities of other compounds. Pentanoic and ethanolic organic solvents of the *A. muricata* extracts have been identified as the most active against cancer cells in vitro. The activity of these extracts in A375 cell culture was reported to be 10 and 4.5 times higher, than that of the aqueous extract [64].

**Table 1. Variou Studies on Anticancer *A. muricata* Activities**

Part of the plant	Topic of study	Result	Reference
Aqueous extract (Leaves)	Benign prostatic hyperplasia in vitro and in vivo	A suppressive influence on the cell line BPH-1 with apoptosis. Diminished prostatic hyperplasia	[66]
Ethanol extract. (Leaves )	Papilloma in mice	Suppress of tumor initiation at lower dose.	[67]
Capsules made up of 100% Graviola leaf/stem powder	In vitro and in vivo pancreatic cancer	Inhibition of cellular metabolism and necrosis stimulation of pancreatic cancer cells	[13]
<i>A. muricata</i> extracts	HL-60 cells	Induced apoptosis, and arrested mitosis	[68]
Ethyl acetate and methanol extract (Leaves)	In vitro Lung cancer	Inhibited proliferation of lung cancer cells, cell cycle arrest and apoptosis.	[69]
Ethyl acetate extract (Leaves)	In vitro Colon cancer	Inhibition of colon cancer cells growth cell cycle arrest and apoptosis initiation. Upregulation of Bax and downregulation of Bcl-2 at the mRNA and protein levels.	[70]
<i>A. muricata</i> crude extract	breast cancer in vitro	Anti-metastatic activity Induced apoptosis in vitro and in vivo. Increased the level of white blood cell, T-cell, and natural killer.	[17]
Ethanol extract. Leaves	cancer HepG2	Induced apoptosis through ROS pathway.	[15]
Aqueous extract. (Leaves)	In vitro Liver Cancer Huh-7 Human	Anti-proliferative and toxic effect by inducing apoptosis.	[16]

Although numerous studies have reported the significant anti-proliferative effect of various extracts of *A. muricata* and isolated ACGs against different cancer cell lines [65], very few studies have explained the mode of action.

### Mechanism of Action of *A. muricata*

ACGs are effective blockers of NADH (nicotinamide adenine dinucleotide phosphate-oxidase) of cancer cells plasma membranes. The effect of ACGs accomplished by depriving cancer cells from adenosine triphosphate (ATP) supply, without affecting the normal cells. Disruption of mitochondrial electron transport system, results in apoptosis [9, 25, 71]. In addition, plant extract inhibited the expression of glucose transporter and glycolytic enzymes, all of which lead to the reduction of glucose uptake and ATP production by pancreatic cells [13]. Annomuricin E depletes the mitochondria membrane's potential leading to membrane permeability and liberation of proapoptotic proteins, such as cytochrome c into the cytosol. This is followed by the formation of apoptosome and activation of caspase 9 and caspase 3/7, which interrelated to mitochondria pathway of death. The Bcl-2 protein is down regulated and the Bax protein is up regulated by the isolated Annomuricin E. [69]. Asare et al. [72] proposed that *A. muricata* extracts inhibited the growth of pancreatic cancer cell by inhibiting the phosphorylation of the molecules involved in extracellular signal-regulated kinase and the phosphatidylinositol 30 kinase pathway, that play a key role in the proliferation and viability of pancreatic cancer cells [13].

## II. CONCLUSION

Researchers are seeking alternative treatment methods for cancer. The substantial work on the activities of anticancer and antitumor of *A. muricata* leaves led researchers to produce tablet formula that can be used as an adjuvant therapy for cancer.

Although several studies reported the selective cytotoxic activities of *A. muricata* on cancer cell, more studies are needed to explore the potential activities of it and further clinical trials are crucial to verify the safety of *A. muricata* to be approved as anti-cancer therapeutic agent.

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