

Annona muricata (Graviola): A Review of Its Traditional Uses and Pharmacological Activities

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Abstract: Traditional medicinal plants gained an enormous attention owing to the therapeutic effects as an alternative medicine in the treatment of various diseases. *Annona muricata*, also known as Graviola has traditionally been consumed to maintain health, but it is now considered for use in treating cancer patients. The objective of this review was to assess the potentials of *A. muricata* against many diseases. *A. muricata* particularly leaves, is found to contain biologically active constituents. More than 200 chemical compounds have been identified and isolated from this plant. Acetogenins are the most important phytoconstituent. *A. muricata*, have been reported to have positive properties against many diseases including inflammatory associated arthritis, diabetes, hypertension, parasitic infections, and cancer. Animal and human in vivo and in vitro studies were conducted to evaluate the effects of *A. muricata* leaves extract. *A. muricata* has antiproliferative and cytotoxic impacts on cancer cells, probably through apoptosis induction. Cancer remains the number one killer in the Western nations and most treatments for the disease rely on the use of chemotherapy that utilizes drugs that are also toxic against normal healthy cells. Thus, an alternative approach to anti-cancer therapies should involve the determination of novel drug targets that must be highly effective and specific against cancer development and growth, non-toxic to the host cells and affordable for the patients. However, these extracts and isolated compounds need to be further investigated to define the magnitude of the effects, optimal dosage, long-term safety, and possible side effects. Additionally, clinical studies are necessary to support the therapeutic potential of this plant.

Keywords: *Annona muricata*, Traditional Uses, Phytochemistry, Pharmacological Activities.

1. INTRODUCTION

Medicinal Plant extracts have been used for centuries by many cultures as a basis for treating various diseases having pivotal role in health preservation and care worldwide. Nowadays chronic degenerative diseases have reached epidemic proportions and are considered as a serious health problem. Therefore, the treatments of these diseases are of clinical importance [1]. Graviola *Annona muricata* L. is a fruit tree with many uses in traditional and alternative medicine. The fruits are widely used to make candies, syrups, ice creams, shakes and beverages. A wide array of medicinal activities is contributed to different parts of *A. muricata*. Locals in Africa and South America extensively use this plant in their folk medicine. Graviola, *Annona muricata* L. is a species of the Annonaceae family that has been widely studied in the last decades due to its therapeutic potentials.

2. BOTANICAL DESCRIPTION AND DISTRIBUTION

Taxonmy:

A. muricata is known as Soursop (English), Graviola (Portuguese), Guanábana (Latin American Spanish), Omusitafeli/Ekitafeli (Uganda), and other local names [2]. This plant is a species of the genus *Annona* with the following taxonomic classification. Kingdom: Plantae, Division: Angiosperms (Magnoliophyta), Class: Magnolids, Order: Magnoliales, Family: Annonaceae, Genus: *Annona*, Species: *A. muricata* L. The genus *Annona* comprises over 70 species among which *A. muricata* is the most widely grown [3].

Ecology:

The *A. muricata* tree is about 5–10 m tall and 15–83 cm in diameter with low branches [4, 5]. It tends to bloom and fruit most of the year [3]. It is widely distributed in the tropical regions of Central and South America, Western Africa, Central and Eastern Africa and Southeast Asia [3, 6] at altitudes below 1200 m above sea level, with temperatures between 25°C and 28°C, relative humidity between 60% and 80%, and annual rainfall above 1500 mm. The fruit is an edible collective ovoid berry, dark green in color with spiky skin. Its average weight is 4 kg in some countries [3], but in Mexico [4], Venezuela [7] and Nicaragua [5], it ranges between 0.4 kg and 1.0 kg. Each fruit may contain 55–170 black seeds [8] when fresh and they turn light brown when dry. The flesh is white and creamy with a specific aroma and flavor [3].

3. TRADITIONAL MEDICINAL USES

A. muricata is a potent medicinal plant with wide range of therapeutic activity. A number of medicinal uses have been reported across the globe for various parts of this plant ranging from the use of leaves, bark, roots, fruits to seeds of *A. muricata* [9]. Leaves and seeds were the major plant studied organs. The most widely used preparation in traditional medicine is the decoction of bark, root, seed or leaf. In the Brazilian Amazon the leaves were used to treat liver problems and the leaf extracted oil is believed to help with rheumatism, neuralgia and arthritis. In the Eastern Andes and Jamaica, the juice of Graviola was used to stop diarrhea, used as muscle relaxant and lower the intestinal acidity [10]. Lately, *A. muricata* leaves are employed to treat hypertension [11, 12], diabetes [9, 12] and cancer [12-17]. Moreover, ethnobotanical studies have indicated that *A. muricata* has been used as insecticide [18] and parasiticide [19]. Fruit juice and leaves or stems have been used to treat fever [20], sedative [21] respiratory illness [22, 23], malaria [24], gastrointestinal problems [20, 25, 26], liver, heart and kidney infections [9, 27, 28].

4. PHYTOCHEMISTRY

The phytochemical screening of the leaf extract was performed using aqueous and methanolic extracts have shown the presence of various phytoconstituents and compounds. Two hundred and twelve bioactive compounds had been reported to be found in *A. muricata* [2]. However, the predominant compounds are acetogenins (ACGs) followed by alkaloids, phenols and other compounds. The presence of different major minerals such as K, Ca, Na, Cu, Fe and Mg suggest the regular consumption of the *A. muricata* fruit that can help provide essential nutrients and elements to the human body [29]. ACGs and alkaloids are widely studied, due to their therapeutic potential versus neurotoxic activity.

Acetogenins (ACGs):

Annonaceous acetogenins are a unique class of secondary metabolites that are generally characterized as a family of natural products with antitumor activities. Due to the special structures and extensive biological activities, particular interest on ACGs has attracted scientific attention in recent years. ACGs are characterized by its unbranched C32 or C34 fatty acid with a γ -lactone at the end of the cytoskeleton [21]. More than 120 ACGs have been identified in ethanolic, methanolic or other organic extracts of different parts of *A. muricata* such as leaves, stems, bark, seeds [30], pulp [31], and fruit peel [2, 7]. Various biological activities have been reported for ACGs, including antimalarial, antiparasitic and pesticidal activities [32, 33]. However, the predominant biological activities of ACGs are depicted with toxicity against cancer cells and its mitochondrial related inhibitory effect. These ACGs demonstrated to be selective and toxic against various types of cancer cells without harming normal and healthy host cells [31]. Annonacin was the most abundant ACG reported in leaves, seeds, roots, peel and fruit [34, 35].

Alkaloids:

One of the most important characteristic of Annonaceae species is the presence of alkaloids [1]. Alkaloids are naturally occurring compounds containing basic nitrogen atoms. The higher alkaloid concentration found in leaves [36]. Several biological activities are related to alkaloids profiles. Alkaloids are a very diverse group of low-weighted secondary metabolites. While almost 46% of the alkaloids were reported in leaves, only 3.5% of them were obtained from seeds or roots. Previous studies have shown that alkaloids isolated from *Annona* species participate in dopamine biosynthesis [37]. Thus, it has been proposed that alkaloids derived from the *Annona* could induce antidepressant-like effects [37], and cytotoxic activity [38]. Neurotoxic effects have also been reported for some alkaloids, and suggested that neuronal death occurred by apoptosis [39].

Several pharmacological activities have been described for these compounds including anti acetylcholinesterase [40], antioxidant, antidepressant, antiepileptic [41], antimicrobial, antileishmanial [30], anti-*Trypanosoma*, antiplasmodial [42], antiproliferative, anti-ulcer [43], cytotoxic [44], immune-stimulant, larvicidal [45], and anxiolytic-like [46].

Phenolic Compounds:

Thirty-seven phenolic compounds have been reported to be present in *A. muricata*. The most important phenolic compounds found in *A. muricata* leaves include quercetin [47] and gallic acid [48]. The presence of flavonoids and lipophilic antioxidant compounds such as tocopherols and tocotrienols has been reported to be present in the pulp [48]. The most common medicinal use is aqueous infusion and the majority of phenols are soluble in water. Phenolic compounds are considered as the major phytochemicals responsible for the antioxidant activity [49]. Vitamins, carotenoids, amides, and cyclopeptides have also been identified in *A. muricata*. Vitamins and carotenoids have been found in leaves, seeds and fruit pulp [48]. On the other hand, 37 volatile compounds have been identified in the fruit pulp of *A. muricata* [50]. In addition, 80 essential oils, with parasitocidal, antidiarrheal, rheumatological, and antineuralgic properties [51], have been identified in the leaf [52].

5. PHARMACOLOGICAL ACTIVITIES

Gavamukulya et al. [53] reported that nearly 60% of the paper they reviewed related to in vitro studies, while 36% to in vivo studies in murine. Additionally, concerning the type of extracts used, about 85% corresponded to maceration of any part of the plant in organic solvents and 15% corresponded to aqueous preparations.

Antioxidant Activity:

Aqueous and methanolic leaf extracts of *A. muricata* revealed marked antioxidant activities of both extracts accompanied with DNA protective effects against H₂O₂-induced toxicity. However, aqueous extracts of the plant parts showed higher *in vitro* antioxidant potential compared to ethanol extracts [54, 55]. The seeds and leaves of the plant are reported to possess enzymatic antioxidants, including catalase and superoxide dismutase, and non-enzymatic antioxidants, including vitamin C and E [56].

Antihypertensive Activity (Hypotensive Effect):

The hypotensive effect of *A. muricata* leaves was evaluated. Aqueous leaf extract (9.17-48.5 mg/kg) was administered to normotensive Sprague–Dawley rats. The leaf extract significantly decreased blood pressure in a dose dependent manner without affecting heart rates. The hypotensive effects of *A. muricata* were mediated through peripheral mechanisms involving antagonism of Ca²⁺ [57].

Anti-inflammatory Activities (Hepatoprotective Activity):

The hepatoprotective effect of *A. muricata* leaves on extracellular matrix (ECM) accumulation, lysosomal membrane integrity, and liver damage has been evaluated in dimethylnitrosamine induced fibrotic rats by Usunobun and Okolie [58]. Simultaneous treatment with *A. muricata* leaf extract significantly reversed alterations in the biomarkers of liver damage, decreased synthetic ability, lysosomal membrane fragility and altered ECM function. *A. muricata* leaf extracts worked as a potent fibro suppressant. *A. muricata* leaves may reverse hepatic fibrosis probably through maintenance/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:

It has been shown that *A. muricata* possess anti-cancer properties on multi-drug resistant cancer cell lines. *A. muricata* has the ability for selective growth inhibition against a variety of cancer cells [61, 62]. Aqueous extract of commercial powder capsules containing leaf and stem of *A. muricata* also showed anti-tumorigenic and anti-metastatic activities on pancreatic tumors in murine models [13]. Breast tumor in rats was reduced by treatment for 5 weeks with *A. muricata* fruit extract [62].

The increasingly ethnobotanically popular use of *A. muricata* as an anticancer treatment may be related to its selective cytotoxic activity [63]. This bioactivity is considered selective as some of the extracts studied in vitro were shown to be more toxic to cancer cell lines than to normal cells. George et al. [63] reported that 1.6 mg/mL and 50 mg/mL from hydroalcoholic extract of *A. muricata* leaves increased the viability of non-cancerous cells, while 100 mg/mL did not alter their viability [47]. This selective activity has been reported to induce healing with minimum effects. The type of extract is critical in the results obtained while studying bioactivities of other compounds. Organic solvents, pentanoic and ethanolic, were the most active *A. muricata* extracts against cancer cells grown in vitro. For these extracts, activity has been reported to be 10 and 4.5 times higher, respectively, than the activity of the aqueous extract in the A375 cell culture [64], Table I.

TABLE I: Anticancer studies on *A. muricata*.

Plant Part	Subject of Study	Effect	Reference
water extract of the <i>A. muricata</i> leaves	benign prostatic hyperplasia (BPH-1) cell line and rats' prostates	a suppressive effect on BPH-1 cells with an IC50 value of 1.36 mg/mL after 72 h with through apoptosis. Decreased prostate size after 2 month 300 mg/mL.	[66]
ethanolic extract of <i>A. muricata</i> leaves	chemically-induced skin papillomagenesis in mice	able to suppress tumor initiation as well as tumor promotion even at lower dosage.	[67]
capsules consisted of 100% pure, finely milled Graviola leaf/stem powder	Pancreatic Cancer (PC) Cells <i>In Vitro</i> and <i>In Vivo</i>	induced necrosis of PC cells by inhibiting cellular metabolism inhibition of tumorigenic properties of PC cells.	[13]
extracts from <i>A. muricata</i>	HL-60 cells	antiproliferation potential, induce apoptosis through loss of membrane mitochondrial potential (MMP) and G0/G1 phase cell arrest. agent of chemotherapeutic and cytostatic activity.	[68]
<i>A. muricata</i> leaves ethyl acetate and methanol extract	lung cancer cells, A549	inhibited the proliferation of A549 cells cell cycle arrest and programmed cell death through activation of the mitochondrial-mediated signaling pathway.	[69]
ethyl acetate extract of <i>A. muricata</i> leaves	HT-29 colon cancer cell line	Annomuricin E inhibited the growth of HT-29 cells. G1 cell cycle arrest and early apoptosis induction in HT-29 cells. triggered mitochondria-initiated events. upregulation of Bax and downregulation of Bcl-2 at the mRNA and protein levels.	[70]
<i>A. muricata</i> crude extract	breast cancer cell lines	anti-metastatic features induced apoptosis in vitro and in vivo of the 4 T1 cells. decreased the level of nitric oxide and malondialdehyde. increased the level of white blood cell, T-cell, and natural killer.	[17]
ethanol extract of <i>A. muricata</i> leaves	cancer HepG2	induces HepG2 cell apoptosis through ROS pathway.	[15]
aqueous extract of <i>A. muricata</i> leaves	Huh-7 Human Liver Cancer Cells	antiproliferative and cytotoxic impacts on Huh-7 cells through apoptosis induction.	[16]

Many studies have reported the significant antiproliferative effects of different extracts of *A. muricata* and isolated ACGs towards various cancer cell lines [65]. However, few of these studies have illustrated the underlying mechanism of action.

6. MECHANISM OF ACTION OF *A. MURICATA*

ACGs are potent inhibitors of NADH (nicotinamide adenine dinucleotide phosphate-oxidase) of the plasma membranes of cancer cells. This molecular structure is a very potent compound against cancer as it deprives the highly energy demanding cancer cells from adenosine triphosphate (ATP) supply, with respect to normal cells, via the disruption of mitochondrial electron transport system, thus resulting in apoptosis [9, 25, 71]. In addition to the above, 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 causes depletion of mitochondrial membrane potential (MMP) leading to mitochondrial membrane permeability and the release of proapoptotic proteins, such as

cytochrome c from the mitochondria to the cytosol, resulting in the formation of the apoptosome and the activation of caspase 9 and caspase 3/7, which have been linked to the mitochondrial death pathway. Isolated Annonumuricin E was found to down regulate Bcl-2 proteins and up regulate Bax protein [69]. Asare et al. [72] demonstrated that *A. muricata* extracts suppressed phosphorylation of the key molecules, involved in the extracellular signal-regulated kinase (ERK) and the phosphatidylinositol 30 kinase (PI3 K/Akt) pathway, which play a crucial role in the proliferation and survival of pancreatic cancer cells [13].

7. CONCLUSION AND FUTURE PROSPECTS

The substantial anticancer and antitumor activities mentioned for *A. muricata* leaves led to tablet formulations of the ethyl acetate-soluble fraction of the leaves that can be used as a cancer adjuvant therapy. Furthermore, studies are required to verify the exact properties and the mechanisms of action. Even though several reports demonstrated positive actions of *A. muricata*, further strong and systematic clinical trials to test and verify its true validity and safety are necessary, in order to be confirmed as a therapeutic anti-cancer agent.

Conflict of Interest Statement: The author declares no conflict of interest.

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