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Review Article

Review of Phytochemical and Medical Applications of *Annona Muricata* Fruits

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Abstract:
Cancer disease is increasing annually worldwide, creating some concerns regarding the efficacy of the present treatment options. This has caused patients to seek alternatives to complement the chemotherapy, radiotherapy, and surgery. *Annona muricata* (family annonaceae) is a medicinal plant and is a fruit tree with a long history of traditional use. *Annona muricata* contains significant anticancer agents which called acetogenins play an important role in several cancer types. *Annona* Muricate has specific bioactive constituents responsible for the major anticancer, antioxidant, antimicrobial, anti-inflammatory and other health benefits of graviola include different classes of annonaceous acetogenins (metabolites and products of the polyketide pathway), alkaloids, flavonoids, sterols, and others. This review focuses on the phytochemistry, biological activities, medicinal are used as anti-cancer and antibiotic, also focuses on the mechanisms of action for the fruit extracts and acetogenins, in order to stimulate additional studies on the fruit pulp used for human consumption.

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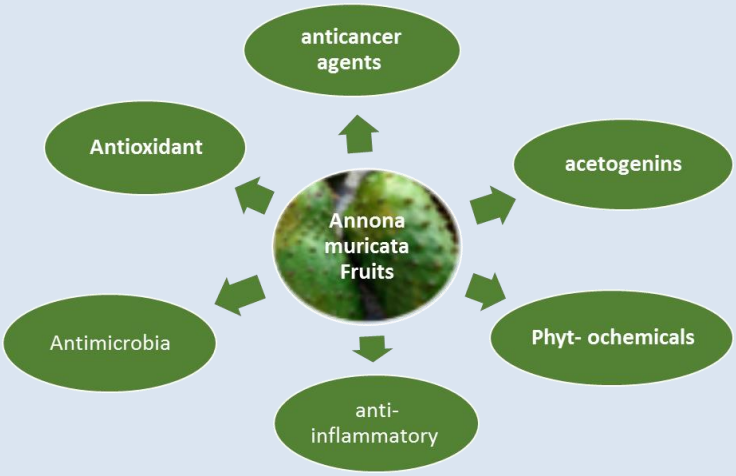
Keywords: *Annona muricata* fruits; Annonaceous acetogenin compounds (AGEs); Phytochemical compounds; Antibacterial; Cancer diseases

Graphical Abstract:



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1. Introduction

Caner has been considered as the major cause of mortality and morbidity globally as estimate world health organization [1]. According to global cancer statistics in 2012, nearly 14.1 million new cases of cancer were diagnosed, and the cancer mortality rate was 8.2 million worldwide [3]. Globally, lung and breast cancer have been the most prevalent cancers. It is worth mentioning that the importance of a healthy diet has been proven in cancer prevention and control; however, whether using dietary supplements during cancer treatment to be effective are still unclear [4]. There are many treatments for cancer including, chemotherapy, radiotherapy, DNA-interacting agents, and molecular targeting agents, and all of them are used to destroy cancerous cells and limiting their proliferation [5]. In contrast, most cytotoxic drugs have disadvantages such as effecting both cancerous and healthy cells, and therefore elicit side effects such as hair loss, bone marrow suppression, drug resistance, gastrointestinal lesions, neurologic dysfunction, and cardiac toxicity [5].

These issues have created a significant distrust towards cancer management procedures in hospitals, caused patients to seek treatment elsewhere, especially from traditional medications, whether as a complementary treatment alongside conventional medications or to improve their health without needing to use chemotherapy [6]. Natural products, especially phytochemicals, have been used to help mankind sustain health as the dawn of medicine [7]. Recently, phototherapy (also called herbalism or herbal medicine) has provided remedies for ailments, including cancer [8]. In this review, we explore some benefits of complementary and alternative medicines (CAMs), particularly *Annona muricata*, as potential treatment agent against breast cancer and other forms of cancer [6]. It is worth mentioning that the herbal medicine acts as the representative of the most significant fields of conventional medicine. The research on the medicinal plants is important to promote the suitable use of herbal medicine to define their potential as a source of the alternative drugs [6]. Medicinal plants are used for the treatment of some disease since before recording history. The sacred Vedas dating back between 3500 B.C and 800 B.C gives several references of the use of the therapeutic plants [6]. For example, “Virikshayurveda” is one of the remotest works in the traditional herbal medicine, which had compiled even earlier, the beginning of the Christian era. In addition, “Rig Veda” is considered to be one of the oldest literatures which was written around 2000 B.C., presented the use of Cinnamon (Cinnamomum verum), Ginger (Zingiber officinale), Sandalwood (Santalum album) not only in the religious ceremonies but also in the medical preparations [9]. Muricata is a species in the *Annonaceae* family that obtained much interested in the last decades due to its pharmaceutical potential. Previously, many studies reported on the medicinal use of the *Annonaceae* family, since then, the bioactivity and toxicity of this species attracted the attention of several researchers [10,11].

2. Taxonomy, Ecology, and Physiology of *A. muricata*

A. muricata, commonly is known as soursop, graviola, guanabana, paw-paw and sirsak. It is a member of the Annonaceae family comprising approximately 130 genera and 2300 species [12, 13]. *A. muricata* is native to the warmest tropical areas in South and North America and recently it is widely distributed

throughout tropical and subtropical parts of the world, including India, Malaysia and Nigeria [14]. *A. muricata* is an evergreen, terrestrial, erects tree reaching 5–8 m in height and 15-83 cm in diameter with low branches [15], roundish canopy with large glossy, dark green leaves. The edible fruits of the tree are large, heart-shaped and green in color, and the diameter varies between 15 and 20 cm (Figure 1) [15]. Each fruit contains about 55-170 black seeds when are fresh [15, 16].

Figure 1. A. muricata, tree (A), leaves (B), flowers (C) and fruits (D) [7].

Soft, curved spines cover the leathery skin of the fruits, each of which may contain 55–170 black seeds distributed in a creamy white flesh with a characteristic aroma and flavor [11,17]. All portions (leaves [18-23], pericarp [24-26] fruits [7,27,28], seeds [28,29], and roots [30]. The roots *A. muricata* has been used in traditional medicine, while the most widely used in the preparations of traditional medicinal decoctions are stem barks, roots, seeds, and leaves [31,32]. Furthermore, Coria-Téllez *et al.* [11], have reported 212 bioactive compounds in A. muricata extracts [11]. Most parts of the plant are used in traditional medications in treating various diseases and ailments (Figure 1), including inflammation [33], rheumatism [12], diabetes [7], hypertension [34] and parasitic infestation [35]. The seed is extracted and used to fight against worms, while the fruits are used traditionally to cure arthritis and fever. Both seeds and fruits are also used to treat parasitic infections. In the same hand, the leaves are used as a traditional medication that is considered to be very active against collapses [36], hypoglycemia, inflammation and as a relief medication against spasms [12]. Moreover, the leaf of the plant has been nicknamed "the cancer killer" and, as the name suggests, is also used in conventional medicine for cancer treatment. [37,38]. It is well known that the plant has been used widely as a source of chemically active metabolites as result to their various curative properties [37]. For this reason, plants are considered as a good candidate to be used as a complementary medicine. In the same way, a phytochemical composition analysis of *A. muricata* by Gavamukulya [39] indicated that extracts from the plant contain a high concentration of secondary class metabolite compounds, such as alkaloids, saponins, terpenoids, flavonoids, coumarins and other lactones, anthroquinones, tannins, cardiac glucosides, phenols and phytosterols [39]. These compounds are called Annonaceous acetogenins (AGEs), which were shown to induce cell cytotoxicity by inhibiting the mitochondrial complex I [40]. Other studies have also suggested the presence of compounds such as megastigmanes [41], cyclopeptides and essential oils [42,43], as well as essential minerals, such as K, Ca, Na, Cu, Fe, and Mg [44].

3. Phytochemicals as Bioactive Metabolites

Phytochemicals are constitutive metabolites that are produced using different parts of plants *via* their primary or secondary metabolism, which have essential functions in the plant for general growth and defense against animals, insects, microorganisms, and abiotic stress [45, 46]. Also, primary metabolites such as carbohydrates, lipids, and proteins have a direct relationship to the growth and metabolism of the plant. While, secondary metabolites, are biosynthetically derived from primary metabolites, which are not necessary for survival, but are involved in significant

functions in the plant, such as protection, competition, and species interactions [47,48]. These can be classified into three major groups based on their biosynthetic origins, phenolic compounds, terpenoids, and nitrogen/sulfur-containing compounds [49]. These compounds have been investigated for use in carcinomatous-related diseases and revealed various anti-cancer properties including, anti-proliferation and apoptotic cell death activity. In this review, we categorize the plant metabolites according to their structure and discuss their anti-cancer activity. In addition, extensive phytochemical evaluations on different parts of the *A. muricata* plant have shown the presence of various phytoconstituents and compounds, including alkaloids (ALKs) [13,50], megastigmanes (MGs) [45], flavonol triglycosides (FTGs) [51], phenolics (PLs) [52], cyclopeptides (CPs) and essential oils (Table 1 and Figure 2) [46,47]. In contrast,*Annona* species, including *A. muricata*, have been shown to be a generally rich source of annonaceous acetogenin compounds (AGEs) [53]. The presence of different main minerals such as K, Na, Ca, Cu, Fe, and Mg propose that regular consumption of the *A. muricata* fruit can help provide essential nutrients and elements to the human body [44].

Table 1. Chemical compounds isolated from *Annona muricata*. ALK: alkaloid; AGE: annonaceous acetogenin; MG: megastigmane; FTG: flavonol triglycoside; PL: phenolic; CP: cyclopeptide

Entry	Plant part	Compound	Class	Biological activity	References
1	Fruits	Annonaine	ALK	Anti-depressive	[54, 55]
2	Fruits	nornuciferine	ALK	Anti-depressive	[54, 55]
3	Fruits	asimilobine	ALK	Anti-depressive	[54, 55]
4	Fruits	epomusenin-A	AGE	-	[56]
5	Fruits	epomusenin-B	AGE	-	[56]
6	Fruits	epomurinin-A	AGE	-	[56]
7	Fruits	epomurinin-B	AGE	-	[56]
8	Fruits	*cis*-annoreticuin	AGE	-	[57]
9	Fruits	muricin J	AGE	toxicity against prostate PC-3 cancer cells	[58]
10	Fruits	muricin K	AGE	toxicity against prostate PC-3 cancer cells	[58]
11	Fruits	muricin L	AGE	toxicity against prostate PC-3 cancer cells	[58]
12	Fruits	cinnamic acid derivative	PL	-	[52]
13	Fruits	coumaric acid hexose	PL	-	[52]
14	Fruits	5-caffeoylquinic acid	PL	-	[52]
15	Fruits	dihydrokaempferol-hexoside	PL	-	[52]
16	Fruits	*p*-coumaric acid	PL	-	[52]
17	Fruits	caffeic acid derivative	PL	-	[52]
18	Fruits	dicaffeoylquinic acid	PL	-	[52]
19	Fruits	feruloylglycoside	PL	-	[52]
20	Fruits	4-feruloyl-5-caffeoylquinic acid	PL	-	[48]
21	Fruits	*p*-coumaric acid methyl ester	PL	-	[52]
22	Fruits	sabadelin	AGE	-	[57,59]

NBE: near-band-edge emission (nm), FE: Fluorescence emission, D: crystallite size (nm)

4. Annonaceous Acetogenins

A. muricata has shown to be the most abundant source of the annonaceous acetogenin compounds (AGEs). For instant, researchers have identified more than 120 acetogenins from methanolic, ethanolic or another organic extract of different part of *A. muricata* like leaves, seeds, bark, stems, pulp, and fruit peel [57,60]. AGEs are the main bioactive compounds of the Annonaceae family [15]. Since 1982 when Jolad *et al.* [61] discovered uvaricin from *Uvaria accuminata*, more than 500 AGEs have been identified from several parts of plants in the Annonaceae family [61]. In recent years, many scientific studies focused on AGEs because of their unusual structures and extensive biological activities. Some studies have shown that

AGEs are more cytotoxic than alkaloids and rotenone [12]. The biological activities of AGEs, are known as anticancer are initially by inhibiting the complex I mitochondrial of the cell (mitochondrial NADH: ubiquinone oxidoreductase) [62]. Biological studies and phytochemical investigations of the *A. muricata* fruit brought a wide range of AGE compounds. The general structure of acetogenins is depicted in Figure 2.

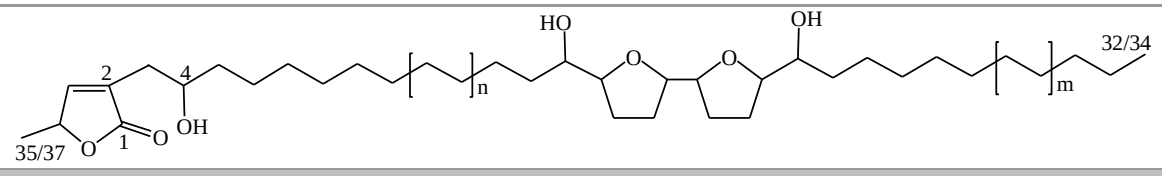

Figure 2. General structure of acetogenins

Chemical structures of the essential AGEs extracted from *A. muricata* fruit are demonstrated in Figure 3. Many mechanisms of action of the cytotoxicity of *A.muricata* were suggested including the inhibition of multiple signaling pathways, metastasis, cell cycle arrest and induction of necrosis [63,64]. Ko and co-workers also reported that bullatacin extracted from *A.* Many mechanisms of action of the cytotoxicity of *A. muricata* at doses of 0.4 g/kg could reduce a tumor induced in rodents 300 times better than the drug Taxol (paclitaxel) [65]. Meanwhile, Wang and co-workers reported that annonacin decreased tumor size in murine models at doses of 0.01 mg/kg compared to the commercial drugs such as adriamycin and cisplatin [66].

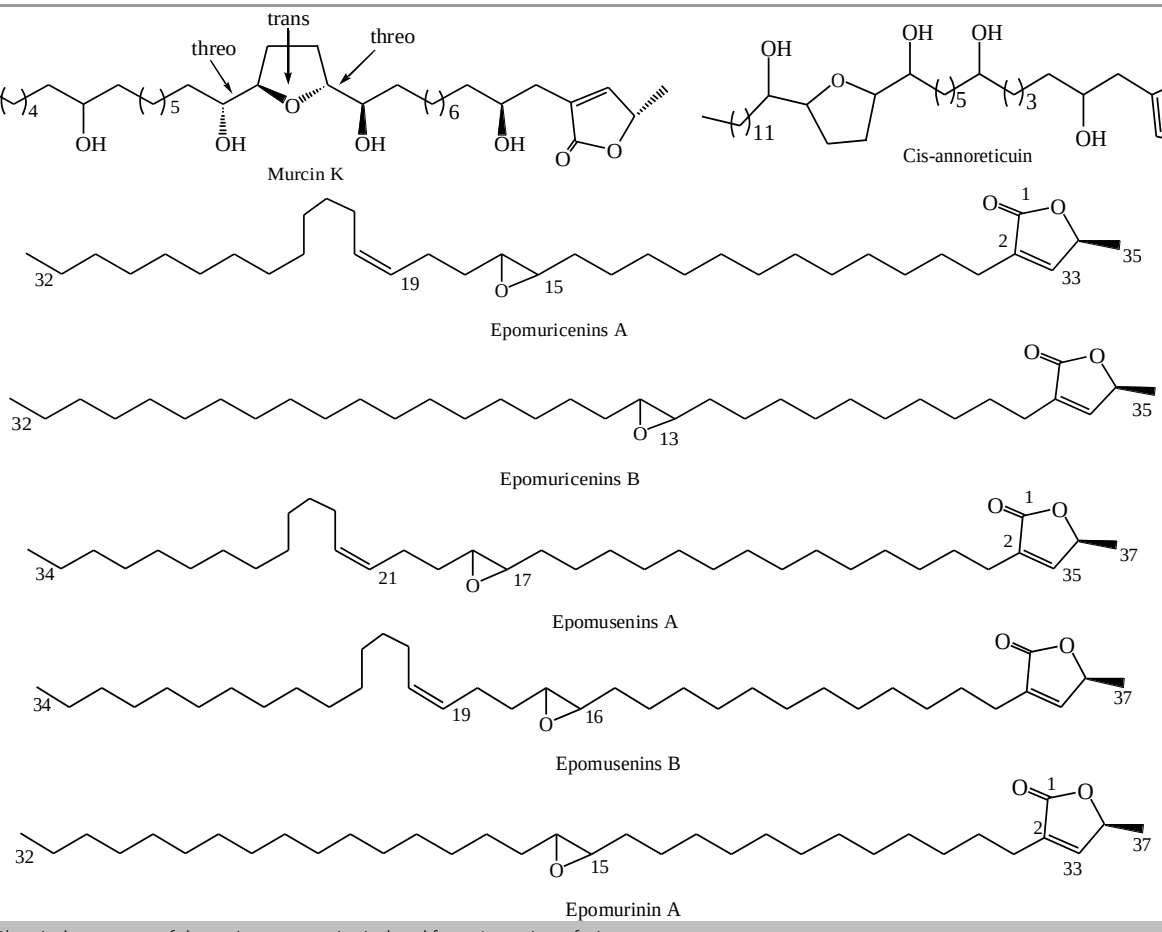

Figure 3. Chemical structures of the major acetogenins isolated from *A. muricata* fruit.

Although there are many AGEs isolated and identified from *A. muricata* fruit, there is insufficient understanding of its mechanisms of action in reducing tumor or cancer cells [57,60]. Therefore, more study is needed to understand how AGEs work entirely. These significance anticancer and antitumor activities selected for A. muricata is due to the active compounds, especially AGEs that can be utilized as a cancer adjuvant treatment [67]. Total of 31 compounds were identified with δ-cadinene (22.58%) and α-muurolene (10.64%) being the most plentiful, two compounds were identified in the fruit pulp essential oil with Ç-sitosterol (19.82%) and 2-hydroxy-1-(hydroxymethyl) ethyl ester [68].

5. Anti-Microbial Activity

Antibacterial effect of the extract of the leaves of *Annona muricata* including methanolic and aqueous was tested against the Gram-positive bacteria and Gram-negative bacteria including Escherichia coli ATCC8739, Staphylococcus aureus ATCC29213, Proteus vulgaris ATCC13315, Bacillus subtilis ATCC12432, Streptococcus pyogenes ATCC8668, Salmonella typhimurium ATCC23564, Enterobacter aerogenes NCIM No. 2340, and Klebsiella pneumonia NCIM No.2719 [68]. It is noted that, B. subtalis and S.aureus have shown noticeable biological activities and found to be the most sensitive Gram-positive bacteria whereas K. pneumoniae and P. vulgaris as Gram-negative bacteria were found to be more sensitive from other kinds of bacteria. Furfurole, *Annnona muricata* leaf extraction is used in the treatment of different bacterial infectious diseases based on the kind of solvent used in the extraction [69, 15]. These extractions are including pneumonia, urinary tract infections, diarrhea, liver diseases, and skin diseases. For example, *Annona muricata* extract contains a wide range of activity compounds against a several types of bacteria. The mechanism of action is suggested as result to synergism of these compounds. For example, phenylphenol is described to bind to membrane protein with vital proteins like microbial enzyme causing to change their function and inhibition of bacterium growth [15]. Due to increase kinds of bacteria that are responsible for many bacterial diseases which illustrates its importance to be used as anti-bacterial agent due to its possesses an abundance of antibacterial compounds [69] and that may encourage scientist to use this plant instead of tradition antibiotics to reduce the unwanted side effects of drugs [69].

6. Annona muricata for Cancer Diseases

As mentioned early, the *Annona muricata* extracts have shown a significant bioactivity based on some studies *in vitro* which were demonstrated the toxic of this plant to cancer cell lines without making any damage to the normal cells [11]. Similarly, in the other study of biological activities, the type of extract is crucial in the results obtained. For instance, organic solvents such as pentanoic and ethanolic, were found the most active A. muricata extracts against cancer cells growing in vitro. Where in these extracts, the activity was reported to be 10 and 4.5 times higher respectively in comparison with the aqueous extract activity in A375 cell culture [11].

In the same hand, the hexane extract of leaves found to be had the highest flavonoid content and the most effective inhibition of cell proliferation than other solvents extract such as methanol or chloroform [70]. The mechanism of the cytotoxic action of the A. muricata extracts are the inhibition of the mitochondrial complex I, and the inhibition of ubiquinone linked NADH oxidase in the plasma membranes of tumorous cells leading to apoptosis. Moreover, based on recent findings, it proposes that A. muricata extracts causing apoptosis via (ROS) Reactive Oxygen Species [70].

According to the literature, it is reported that 1.6 μg/mL and 50 μg/mL from hydroalcoholic extract of A. muricate leaves led to increase the viability of non-cancerous cells however 100 μg/mL did not change their viability [11,51]. As well as, according to results reported in 2015 the *A. muricata* hexane and commercialized extracts led to induce mild cytotoxicity in human pancreatic cancer cells (Capan-1) in vitro [70].

7. Conclusions

This review demonstrated that, *Annona muricata's* can be used as a nature therapy with the potential of being anticancer and other health-related benefits by providing insights into its bioactive chemical constituents. Annona muricata, a traditional medicinal plant was investigated and showed that the phytochemical constituents and the bioactive compounds possess the medicinal properties which makes them to be a potential species in the family of Annonaceae and this can be play a significant role in treatment of serious diseases nowadays, such as cancer. Finally, more clinical studies are required to verify and validate the plant extracts safety, to be adopted as a therapeutic anticancer agent.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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