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### **A Review on the Pharmacological Activities of *Annona muricata* Linn.**

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#### **ABSTRACT**

*Annona muricata* Linn, an evergreen natural species has been used traditionally for the treatment of various ailments. It has been reported to contain therapeutically valuable bioactive compounds. This plant has extraordinary medicinal potential which should be better explored to hit upon new chemical leads for pharmaceutical use. Extracts from this plant exhibit therapeutic properties like anticancer, anti-inflammatory, antiulcer, anthelmintic, antibacterial, antioxidant, anticonvulsant, antiarthritic, antiparasitic, hepatoprotective, antidiabetic and antimalarial. All these medicinal properties are validated using *in-vitro* and *in-vivo* studies. More than 150 compounds have been isolated from various parts of the plant like seeds, fruits, flowers, stem, barks, leaves and roots. A wide assortment of ethno medical uses is contributed by this plant. In view of the mammoth studies on *Annona Muricata* Linn, this review endeavors to pile up maximum information available regarding its studies on therapeutic potential.

**KEYWORDS:** *Annona muricata*; therapeutic potential; leaves; anticancer; extract

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## INTRODUCTION :

Plants have been used for medical purposes for several thousands of years. The number of higher plant species on earth is about 250,000. It is estimated that 35,000 to 70,000 species have been used for the treatment of various illnesses since before recorded history at one time or another. The relationship between food and medicine was quoted as “Let food be thy medicine and medicine be thy food”.<sup>1</sup> *Annona muricata* Linn, a valuable medicinal plant belongs to the family Annonaceae. *A. muricata* commonly known as Graviola or soursop is the most tropical semi deciduous tree possessing the largest fruits of the *Annona* genus. A large number of pharmacological activities of Graviola extracts in animals have been reported, including antiinflammation, antispasmodic, anticonvulsant, vasodilation, cardiodepressant and plasma glucose lowering activities.<sup>2,3,4</sup> It is widely used in the traditional treatment of cancer in many countries.<sup>5</sup> *A. muricata* contains anticancer annonaceous acetogenin compounds, therefore, leaf extracts from *A. muricata* are used in the studies for antitumor properties in various types of cancer cells.<sup>6</sup> Nutraceuticals derived from *A. muricata*, are commercially available in the market and are commonly used for therapeutic purpose. A majority of world's population in the developing countries still relies on herbal medicines to meet their health needs. Even in areas where modern medicine is available, the interest on herbal medicines and their utilization have been increasing rapidly in the recent years. The phytochemicals in plants are playing a pivotal pipeline for drug discovery. In order to support the readers who are interested to know the importance of Graviola, it is necessary to compile the reported bioactivities of this plant. In this review, we have described the various therapeutic uses of Graviola with special emphasis on the anticancer activity of *A. muricata* Linn.

## PHARMACOLOGICAL ACTIVITIES OF A. MURICATA:

### 1. Antileishmanial activity

Extracts (hexane, ethyl acetate and methanol) of *A. muricata* pericarp were effective *in-vitro* against *Leishmania braziliensis* and *L. panamensis* promastigotes and also against the cell line U 937, ethyl acetate extract was found to be more active than the reference substance used in the experiment. Three acetogenins namely annonacin, annonacin A and annomuricin A were isolated from the extract.<sup>7</sup>

### 2. Genotoxic effect

Acetogenins from *A. muricata* extract possess the capacity to reduce the mouse colon crypts that is induced by azoxymethane (Azo) and it showed 50% reduction in the amount of crypts in the

animals treated with acetogenin when compared with the levels determined in mice treated with azo.<sup>8</sup> This preliminary study indicates the genotoxic effect of the extract.

### 3. Antimicrobial activity

*A. muricata* extract contains a wide spectrum of activity against a group of bacteria that are responsible for the most common bacterial diseases. The antibacterial effect of the methanolic and aqueous extract of the leaves of *A. muricata* was tested against various bacterial strains such as *Staphylococcus aureus* ATCC29213, *Escherichia coli* ATCC8739, *Proteus vulgaris* ATCC13315, *Streptococcus pyogenes* ATCC8668, *Bacillus subtilis* ATCC12432, *Salmonella typhimurium* ATCC23564, *Klebsiella pneumonia* NCIM No.2719 and *Enterobacter aerogenes* NCIM No. 2340. Among the above organisms tested, *B. subtilis* and *S.aureus* was found to be the most susceptible gram positive bacteria while *K. pneumoniae* and *P. vulgaris* was found to be the most susceptible gram-negative bacteria, thus it proves that the plant possesses abundant antibacterial compounds.<sup>9</sup> Antibacterial activity of *A.muricata* was seen against several organisms namely *Pseudomonas*, *Staphylococcus*, *Klebsiella*, *Bacillus* and *E. coli*. The ethanol leaf extract showed maximum activity against *Pseudomonas* and *Staphylococcus*. The ethanolic bark extract showed maximum activity against *E. coli*.<sup>10</sup>

### 4. Antiarthritic activity

The antiarthritic potential of *A.muricata* was substantiated by the reports of Chan *et al* and Moghadamtousi *et al*.<sup>11,12</sup> An *in-vivo* study on different doses (3, 10, 30 and 100 mg/kg) of ethanolic extract from *A.muricata* leaves has showed prominent antiarthritic activity in complete Freund's adjuvant (CFA) induced arthritic rats. Oral administration of the extract reduced edema in a dose-dependent manner after two weeks of injection. Leaf extract of *A. muricata* at higher doses significantly suppressed TNF- $\alpha$  and IL-1 $\beta$  expression in local tissue, thus it is evident that the antiarthritic activity was due to the suppression of pro-inflammatory cytokines.

### 5. Anticonvulsant activity

Decoction of the *A.muricata* leaves is traditionally used to control fever and convulsive seizures. To validate the activity of the leaves in ethnomedicine, N'gouemo and colleagues investigated the effect of the ethanolic extract of the leaves against pentylenetetrazol-induced tonic-clonic seizures in mice.<sup>2</sup> The result showed that the plant extract significantly decreased the incidence, mortality rate of tonic seizures and also reduced the frequency of onset of clonic seizures.

## **6. Antidiabetic and hypolipidemic activity**

The parts of *A. muricata* are traditionally used in the management of diabetes. Adeyemi and colleagues reported that the methanol extract of *A. muricata* leaves significantly reduced the blood glucose concentration in diabetic rats.<sup>13, 14</sup> In addition to the antidiabetic activity, the investigators have also reported that the extract significantly decreased the serum total cholesterol, low-density lipoprotein, triglyceride and very low-density lipoprotein cholesterol.<sup>15</sup>

## **7. Anti-inflammatory and antinociceptive activity**

Anti-inflammatory activity exhibited by *A. muricata* leaf extract was investigated by Roslida *et al.*<sup>16</sup> They reported that the leaf extract significantly reduced carrageenan-induced edema in rat paws in a dose-dependent manner. They recognized that anti-inflammatory effect was accompanied by reductions in the leukocyte migration and exudate volume. Oral administration of the extract showed significant suppression of abdominal contortions induced with acetic acid (0.6% v/v) in mice, exhibiting a powerful antinociceptive activity. In addition, the formalin test, paw licking and hot-plate responses also substantiate the marked analgesic effect of the *A. muricata* leaves. The protective effect of *A. muricata* leaves against Complete Freund's Adjuvant (CFA)-induced arthritis in rats and xylene-induced ear edema in mice was associated with an attenuation in the TNF- $\alpha$  and IL-1 $\beta$  protein expression, demonstrating that the leaves could be used against both acute and chronic inflammation.<sup>17</sup> The same assays portrayed the anti-inflammatory and analgesic activities of *A. muricata* fruits, which were reported to be induced through the suppression of inflammatory mediators and interactions with the opioidergic pathway, respectively.<sup>18</sup> These results confirm the antiinflammatory and antinociceptive effects of *A. muricata*.

## **8. Antioxidant activity**

Both Aqueous and methanolic leaf extracts of *A. muricata* revealed marked antioxidant activity accompanied with DNA protective effects against H<sub>2</sub>O<sub>2</sub>-induced toxicity.<sup>19</sup> The seeds and leaves of the plant are reported to possess enzymatic antioxidants, catalase, superoxide dismutase and non-enzymatic antioxidants, vitamin C and E. Padma and colleagues showed that the ethanolic extract of the *A. muricata* stem bark caused a reduction in lipid peroxidation induced by cold immobilization stress in the brain and liver of rats, indicating the adaptogenic potential of this plant.<sup>20, 21</sup>

## **9. Antihypertensive activity**

The antihypertensive effect of aqueous leaf extract of *A. muricata* leaves was evaluated using Sprague-Dawley rats. The results confirmed that treatment of rats with the leaf extract significantly

decreased blood pressure in a dose-dependent manner without affecting heart rate. This effect was suggested to be induced through peripheral mechanisms involving the antagonism of  $Ca^{2+}$ .<sup>22</sup>

### **10. Antiparasitic activity**

Various pathogenic parasites have been subjected to *A. muricata* to determine its cytotoxic effects. The methanolic extract of *A. muricata* seeds showed significant antiparasitic activity against the infective larvae of *Molineriadesetae*.<sup>23</sup> The ethyl acetate leaf extract of *A. muricata* was assayed against three *Leishmania* species (PH8, M2903 and PP75) and *Trypanosoma cruzi*. Promising activity was reported with IC50 values lower than 25  $\mu\text{g/mL}$ .<sup>24</sup> An in-vitro investigation of *A. muricata* aqueous leaf extract was performed against *Haemonchus contortus*, a gastrointestinal parasite. The result showed 89.08% and 84.91% toxicity against larvae and eggs as assessed by larval motility and egg hatch tests. The immobilization of adult worms within 6 to 8 hours of exposure to different doses of the extract revealed a promising anthelmintic activity in the leaves.<sup>25</sup>

### **11. Antiplasmodial activity**

The pentane leaf extract of *A. muricata* was assayed against two strains of *Plasmodium falciparum*: the Nigerian chloroquine-sensitive strain and FcM29-Cameroon (chloroquine-resistant strain). A promising antiplasmodial effect was obtained with an IC50 value of 16 and 8  $\mu\text{g/mL}$  after 72 hours, respectively.<sup>26</sup> The leaf extract, at 20  $\mu\text{g/mL}$ , showed a 67% inhibition against an asynchronous F32 strain of *P. falciparum*.<sup>27</sup> Another study on different extracts of *A. muricata* leaves and stems also confirmed the reported cytotoxic effects against the chloroquine-sensitive (F32) and resistant (W2) *P. falciparum*.<sup>25</sup> These findings substantiated the traditional use of *A. muricata* as an antimalarial agent.

### **12. Hepatoprotective and bilirubin lowering activity**

*A. muricata* is traditionally employed to treat jaundice. A study was conducted to determine the in-vivo bilirubin lowering potential of the aqueous extract of *A. muricata* leaves. Direct and total bilirubin was measured in phenyl hydrazine-induced jaundiced adult rats, treated with oral doses 50 and 400 mg/kg of the extract, which showed a significant reduction in bilirubin levels at both low and high doses.<sup>28</sup> In addition, the hepatoprotective effect was also reported for the aqueous extract of the leaves against carbon tetrachloride and acetaminophen-induced liver damage. Pretreatment with different concentrations of the extract (50, 100, 200, and 400 mg/kg) for 7 days prior to liver damage restored liver function towards normal, which was assessed by biochemical and histological analyses.<sup>29</sup> Therefore, these findings substantiate the traditional use of *A. muricata* as a potential hepatoprotective agent and against jaundice.

### 13. Insecticidal activity

Mosquito-controlling activity of both the aqueous and oil extracts of *A. muricata* seeds against the larvae and adults of *Aedes albopictus* and *Culex quinquefasciatus* demonstrated promising bioactivity with lethal concentration 50 (LC50) values ranging from 0.5% to 1% for larvae and 1% to 5% for adults.<sup>30</sup> In another study, this activity for the ethanolic extract of the leaves against *C. quinquefasciatus* was also reported with an LC50 value of 20.87µg/mL after 24 hours.<sup>31</sup> In addition, the larvae of the *Aedes aegypti* mosquito, the transmitters of dengue fever, elicited high susceptibility to the ethanolic extract of the seeds with the LC50 of 224.27 ppm.<sup>32</sup> *A. muricata* seeds showed more than five times synergistic larvicidal activity when combined with ethanolic extract of *Piper nigrum* fruit (*A. muricata* 90:10 *P. nigrum*).<sup>33</sup> The fractionation analysis of the extract showed that *n*-hexane is the most active fraction with an LC50 of 73.77 ppm. The leaf extract of *A. muricata* also showed a time-dependent toxicity against the larvae of *Anastrepha ludens* (Mexican fruit fly) with a mortality rate of 63% to 74%. Leatemia et al. 2012 investigated the growth inhibition potential of the ethanolic seed extracts of *A. muricata* isolated from different locations against polyphagous lepidopteran *Spodoptera litura*. The surprising result showed significant differences for the growth inhibition based on the isolated locations ranging from 18% to 96% compared with the control (ethanol).<sup>34</sup> The ethanolic leaf extract (1.0 g/L) showed 40%, 80% and 98% mortality against *Callosobruchus maculatus* (Fabricius) after 24, 48 and 72 hours post-treatment, respectively. At the same concentration, the extract significantly decreased the ovi position of *C. maculatus* and appeared to be a promising protectant against the respective insect in stored cowpea.<sup>35</sup> This growing body of experimental evidence supports the idea that *A. muricata* exhibits insecticidal activity against assorted types of insects.

### 14. Wound healing activity

Moghadamtousi and colleagues (2015) investigated the wound healing activity of the ethyl acetate extract of *A. muricata* leaves against excisional wound in rats.<sup>12</sup> Topical administration of the extract for 15 days demonstrated significant wound healing potential. The antiinflammatory effects of the extract were also verified during the healing process as shown by the up-regulation of Hsp70 by immunohistochemical evaluation. The wound healing activity of alcoholic extract of stem and bark of *A. muricata* was tested in the albino rats and it showed a marked reduction in area of the wound.<sup>36</sup>

### **15. Gastroprotective activity**

Gastroprotective activity of *A. muricata* leaves was examined against ethanol-induced gastric injury. The results of the oral administration of the ethyl acetate extract (200 and 400 mg/kg) showed significant antiulcer potential, which was mediated through protective effects against gastric wall mucosal damages.<sup>17</sup> Immunohistochemical staining demonstrated that the leaf extract decreased the Bax protein expression and elevated the Hsp70 protein expression. The effect of extract on the gastric tissues was accompanied with augmentation in the activity of enzymatic antioxidants.<sup>37</sup>

### **16. Antiviral activity**

*A. muricata* extract was effective against Herpes simplex virus-1 (HSV-1) and clinical isolate (obtained from the human keratitis lesion) and they inhibit the cytopathic effect of HSV-1 on vero cells. This identifies the anti-HSV-1 potential of *A. muricata* extract. The minimum inhibitory concentration of ethanolic extract was found to be 1 mg/ml which shows that the *A. muricata* could be used as the potential antiviral drug.<sup>38</sup>

### **17. Molluscicidal activity**

To establish plant-derived molluscicides for the vector control of schistosomiasis, different parts of the *Annona* species were tested against *Biomphalaria glabrata*, both in egg masses and adult forms. Dos and colleagues demonstrated that the leaves of *A. muricata* possess significant toxicity against adult worms with an LD90 value of 8.75 ppm. Additional toxicity of the *A. muricata* leaves against snail egg masses was markedly noted among different *Annona* species.<sup>39</sup> A bioassay-guided investigation on the cytotoxicity of the ethanolic extract of *A. muricata* leaves against the larvae of the brine shrimp *Artemia salina* and the snail *B. glabrata* showed the potent molluscicidal activity of this plant.<sup>40</sup>

### **18. Anticancer activity**

The increasing use of herbal medicine has increased the concerns as it has been alleged that the herbal medicines are safe and free from adverse effects, because they are of natural origin.<sup>41</sup> Secondary metabolites in the herbal products are capable of modulating the physiological action through synergistic or antagonistic effects. So it is the need of the hour to discern the anticancer effect of *A. muricata*.





### 1. *Annona muricata* depiction

It has been declared that the Graviola extracts have significant anticancer effects in a number of cancer cell lines both *in-vitro* and *in-vivo*.<sup>42</sup> Graviola extract acquire selective inhibition of breast cancer cells via epidermal growth factor receptor EGFR down regulation, a rational target for breast cancer therapy development. Graviola fruit extract selectively inhibited the growth of EGFR-over expressing human breast cancer (MDA-MB-468) cells but not in non-tumorigenic human breast epithelial cells (MCF-10A).<sup>43</sup> They concluded that Graviola has selective antigrowth effects between cancer and non-cancer cells. Ko *et al* supported that Graviola promotes apoptosis in breast cancer cells by decreasing MCF-7 tumor growth while inhibiting ER-cyclin D1 and Bcl-2 protein expressions in nude mice.<sup>44</sup> Minari *et al* demonstrated the preventive measure against 7, 12-dimethyl benzene anthracene DMBA-induced breast cell proliferation in the breast tissues of female albino mice.<sup>45</sup>

Graviola promotes necrosis in prostate cancer cell lines (PC-3) through inhibition of tumor mobility and cellular metabolism by *in-vitro* and *in-vivo* model. Further they demonstrated the down regulation of expression of hypoxiarelated factors and glycolytic factors following treatment in prostate cancer cells with Graviola (i.e. HIF-1 $\alpha$ , NF- $\kappa$ B, GLUT1, GLUT4, HKII, and LDHA).<sup>46</sup> Reports of an animal study by Yang *et al*, also confers that the leaves of *Annona muricata* is protective against prostate cancer.<sup>47</sup>

In colon cancer cells, Graviola leaves also has significant effects on cell survival potential via mitochondrial-mediated apoptosis associated with the G1 cell cycle arrest. Graviola induces apoptosis by generating reactive oxygen species ROS and down-regulating the antiapoptotic Bcl-2 protein, while up-regulating pro-apoptotic Bax protein. These processes subsequently leads to the attenuation of mitochondrial membrane potential (MMP) and cytochrome c release. Release of cytochrome c activates apoptosome and the intrinsic caspase cascade that triggers execution of apoptosis through DNA fragmentation.<sup>48</sup>

Graviola has also been reported to have antiproliferative effects of HL-60 cells via loss of cell viability, loss of MMP, G0/G1 phase cell arrest and morphological apoptotic changes. These results



substantiate and confirm that Graviola does indeed have antiproliferative and cytostatic activity in HL-60 cells.<sup>49</sup> Herbal medicines are often used to provide first-line and basic health service, both to people living in remote areas where it is the only available health service and to the poor people, where it offers the only affordable remedy.

Gonzalez *et al* reported the *in-vivo* as well as *in-vitro* effects of Graviola extract on Lewis lung carcinoma (LLC) tumor cell lines and also supported the antitumor activity of Graviola against lung tumors.<sup>50</sup> Studies also indicated the anticancerous and cytotoxic mechanisms of action of Graviola that affected NADH oxidase inhibition in cancer cell lines, down regulation of the P-glycoprotein pump via ATP depletion and cell cycle arrest at S-phase progression.<sup>51,52</sup> *In-vivo* (GLE) pharmacokinetics of Graviola leaf extract and *in-vitro* absorption kinetics showed inhibitory effect on prostate cancer proliferation, viability and clonogenic colonies. Oral administration of extract showed tumor growth inhibition in human prostate tumor in xenografts studies.<sup>3</sup> Yang *et al* demonstrated the synergy among the constituents of Graviola leaf extract (GLE) compared to its flavonoid enriched (FEF) and acetogenin enriched (AEF) fractions for its anticancer effect.<sup>47</sup>

The important class of medicinal components found in Graviola is acetogenins. More than 120 acetogenins have been identified from the leaves, stems, bark, seeds, pulp, and fruit peel of *A. muricata*, and currently around 46 acetogenins have been analyzed from the leaves.<sup>53</sup> Preliminary research showed that acetogenins block production of adenosine triphosphate, which inhibits the pump that removes cancer drugs from the cell, allowing chemotherapy to be more effective. Furthermore, research suggested that acetogenins may have chemotherapeutic potential, especially against cancer that resistant to multiple drugs.<sup>54</sup> Parkinson like symptoms may occur on oral ingestion of Graviola.<sup>46</sup> Some specific acetogenins have been reportedly identified to be toxic for various cancer cell lines like lung solid human-breast cancer, tumor carcinoma, pancreatic carcinoma, prostatic adenocarcinoma, colonic adenocarcinoma, human lymphoma, liver cancer, and multiple-drug resistant human breast adenocarcinoma.<sup>55</sup> Torres *et al* reported that Graviola extract inhibited multiple signaling pathways that regulate metabolism, cell cycle, survival, and metastatic properties in pancreatic cancer cells.<sup>6</sup> Despite the lack of human data, many websites promote Graviola to cancer patients based on traditional use and on the *in-vitro* studies. Caution is, however, required as there is no evidence of safety or efficacy in this regard.<sup>43</sup>

## CONCLUSION

Medicinal plants were the persuasive resource of health due the presence of highly active metabolites. These metabolites are the novel leads for drug discovery and they are also responsible for significant pharmacological actions. Research works done on this plant divulge its valuable application in the field of pharmacy. This review possibly demonstrates the reported pharmacological activities of *A. muricata* as per documentation. However, there are gaps in the reported studies, which needs further attention by the research scientists to explore the full therapeutic potential of this plant. Therefore, new drugs that include bioactive natural molecules from *Annona muricata* need to be developed for the benefit of the health care system. Further detailed study may still be necessary to elucidate the molecular mechanism behind the therapeutic action of this plant and it paves the pathway for novel research.

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