

# Graviola

*Annona muricata*

Monograph 03/01/04

**Family:** Annonaceae

**Synonyms:** *Annona macrocarpa*, *A. bonplandiana*, *A. cearensis*, *Guanabanus muricatus*

**Standard Common Name:** Soursop - North American (Herbs of Commerce, 2<sup>nd</sup> edition)

**Other Common Names:** Graviola, guanábana (Herbs of Commerce, 2<sup>nd</sup> edition)

**Additional Common Names:**

Graviola -	Brazil	Huanaba -	Spanish
Guanábana -	Spanish	Toge-Banreisi -	Taiwanese
Guanábano -	Spanish	Durian benggala -	Indian
Guanavana -	Spanish	Nangka blanda -	Indian
Guanaba -	Spanish	Cachiman épineux -	French
Corossol -	French	Sauersack -	German
Epineux -	French	Stachelannone -	German

## Overview

### Botanical Description

Graviola is a small, upright tropical evergreen tree, 5-6 m high, with large, glossy, dark green leaves. It produces a large, heart-shaped, edible fruit that is 15-23 cm in diameter, is yellow-green in color and has white flesh inside. The fruit is popular in South America.

### Ethnobotanical Uses

All parts of the graviola tree have been used medicinally in traditional herbal medicine. Traditional herbal medicine practitioners have attributed graviola with the following properties and actions: anthelmintic, antiparasitic, antipyretic, sedative, antispasmodic, nervine, hypotensive, anticonvulsant and digestive.

The traditional use of graviola has been recorded in herbal medicine systems in the following countries: Amazonia,<sup>1</sup> Barbados,<sup>2</sup> Borneo,<sup>3</sup> Brazil,<sup>4-8</sup> Cook Islands,<sup>9</sup> Curacao,<sup>10</sup> Dominica,<sup>11</sup> Guatemala,<sup>12</sup> Guam,<sup>13</sup> Guyana,<sup>14</sup> Haiti,<sup>15,16</sup> Jamaica,<sup>17,18</sup> Madagascar,<sup>19</sup> Malaysia,<sup>20,21</sup> Peru,<sup>22,26</sup> Suriname,<sup>27</sup> Togo<sup>28</sup> and West Indies.<sup>29,30</sup>

### Summary of Traditional Uses of Graviola:<sup>31</sup>

Flower: Bronchitis, cough.

Fruit: Colitis, diarrhea, dysentery, fevers, hydropsy, juice, lactogogue, mouth sores, parasites, tranquilizer.

Seeds: Astringent, carminative, emetic, head lice, insecticide, parasites, skin parasites, worms.

Bark: Asthenia, asthma, childbirth, cough, diabetesgrippe, heart tonic, hypertension, nervine, parasites, sedative, spasms.

Leaf: Abscesses, arthritis pain, asthenia, asthma, astringent, bronchitis, catarrh, colic, cough, diabetes, diuretic, dysentery, edema, fever, gallbladder disorders, grippe, heart, hypertension, indigestion, infections, intestinal worms, lactogogue, liver disorders, malaria, nervine, nervousness, neuralgia, palpitations, parasites, parturition, rashes, rheumatism, ringworm, sedative, skin disorders, spasms, styptic, tonic, tranquilizer, tumors, ulcers, worms.

Root: Diabetes, sedative, spasms.

Rootbark: Calmative, diabetes, spasms.

### Primary Uses in Traditional Herbal Medicine Systems

#### Internal

Graviola is primarily employed in traditional herbal medicine systems for parasitic infections and cancer.<sup>22,25,32,33,24</sup> It has also been used in some herbal medicine systems for its sedative and antispasmodic properties.<sup>24</sup>

### Chemistry

Phytochemically graviola is rich in miscellaneous lactones and isoquinoline alkaloids. The leaf, stem, bark and seeds of graviola contain varying amounts of a novel group of chemicals believed to be biologically active, called Annonaceous acetogenins. The annonaceous acetogenins in graviola include: annocatalin, annohexocin, annomonacin, annomontacin, annomuricatin A & B, annomuricin A thru E, annomutacin, annonacin, annonacinone, annopentocin A thru C, cis-annonacin, cis-corossolone, cohibin A thru D, corepoxylone, coronin, corossolin, corossolone, donhexocin, epomuricenin A & B, gigantetrocin, gigantetrocin A & B, gigantetrocinone, gigantetronenin, goniothalamycin, iso-annonacin, javoricin, montanacin, montecristin, muracin A thru G, muricapentocin, muricatalicin, muricatalin, muri-catenol, muricatetrocin A & B muricatin D, muricatocin A thru C muricin H, muricin I, muricoreacin, murihexocin 3, murihexocin A thru C, murihexol, murisolin, robustocin, rolliniastatin 1 & 2, saba-delin, solamin, uvariamicin I & IV, xyломaticin.<sup>31</sup>

Various acetogenins in graviola have been documented with the following biological activity:

#### ***In vivo***

##### Cytotoxic Activity

10 mg/kg of annonacin was given intraperitoneally in mice with Lewis lung cancer; a 57.9% inhibition was seen.<sup>34</sup>

#### ***In vitro***

##### Cytotoxic Activity

*In vitro* studies are numerous. Following are select *in vitro* studies where acetogenins were utilized against various cell lines:

- Human hepatoma hep G(2), 2, 2, 15 cell lines. A CC50=49.5 mcg/ml was seen in one study.<sup>35-38</sup>
- Six human tumor cell lines.<sup>39-41</sup>
- Prostate adenocarcinoma PC-3.<sup>39,40</sup>
- Pancreatic carcinoma PACA-2.<sup>39,40</sup>
- Murine leukemia L1210 and P388 leukemia.<sup>30,42,43</sup>
- Human breast adenocarcinoma MDA-MB231 and carcinoma MCF-7.<sup>40,42,44</sup>
- Human tumor multidrug-resistant SW480 (P-glycoprotein+, Pgp+) tumor cells.<sup>45</sup>
- Human lung carcinoma A-549.<sup>44</sup>
- Human colon cancer HT-29.<sup>44</sup>
- Various cancer cell lines; growth was inhibited 50% at concentrations of <10-12 ug/ml.<sup>46</sup>
- Adriamycin resistant tumor cells (M17/adr breast cancer cells); Non-adriamycin resistant tumor cells.<sup>47</sup>
- Annonacin was able to kill various cancer cell lines at an IC50=<4 ug/mL.<sup>48</sup>

##### Cytostatic Activity

Acetogenins have shown inhibition of tumor cell growth towards adriamycin resistant human mammary adenocarcinoma MCF-7/Adr cells.<sup>43,49</sup>

## Neurological Activity

In a 2002 study cultured mesencephalic dopaminergic neurons were exposed to total alkaloids from graviola rootbark, or two of the most abundant alkaloids coreximine and reticuline. After 24 hours 50% of dopaminergic neurons degenerated with 18 mcg/ml of total extract, 4.3 mcg/ml of coreximine or 100 mcg/ml reticuline. GABAergic neurons were also affected. Neuronal death, occurring by apoptosis, was attenuated by increasing the concentration of glucose in the culture. Toxin withdrawal after short-term exposure arrested cell death.<sup>50</sup> Chronic exposure to these alkaloids may be an etiological factor in atypical Parkinson's disease.<sup>51</sup>

In a recent 2003 study one of the main acetogenins in graviola, annonacin, was added to mesencephalic cultures for 24 hours. It had an ED50 of 0.018 microM, killing dopaminergic neurons. Toxic effects were seen at lower concentrations when incubation time was extended over several days. Withdrawal of the toxin after short-term exposure arrested cell death. Annonacin also reduced the survival of non-dopaminergic neurons. Increasing glucose or mannose concentrations, along with the presence of annonacin, prevented neuronal death.<sup>52</sup>

Acute treatment of mesencephalic dopaminergic neurons and GABA neurons *in vitro* with a rootbark extract of coreximine or reticuline reversibly inhibited dopamine uptake without causing neuronal death. GABA uptake was not affected.<sup>51</sup>

## Insecticidal

The acetogenins (such as squamocin) have shown activity against the following insects: *M. sanborni*, *L. decemlineata*, *M. persicae*, *Blatella germanica*.<sup>53-55</sup>

## ***In vivo* and *In vitro* Research and Pharmacological Actions**

### **Anticancerous Activity**

#### Cytotoxic Activity

The leaf, seed, stem and bark have all been documented with *in vitro* cytotoxic activity utilizing various extracts including ethanol and water:

- Ethanol leaf extract showed activity against human hepatoma hep G 2,2,15.<sup>37</sup>
- Leaf extract showed activity against human kidney carcinoma CA-A498. IC50=0.67 mcg/ml seen.<sup>56</sup>
- Ethanol leaf extract showed activity against human breast carcinoma MCF-7. ED50=1.9 mcg/ml.<sup>57</sup>
- Ethanol leaf & stem extract showed activity against human oral epidermoid carcinoma CA-9KB. ED50=<20 mcg/ml.<sup>3,32</sup>
- Ethanol leaf extract showed activity against bovine kidney cell line MDBK. IC50=2 mcg/ml.<sup>58</sup>
- Hexane, ethyl acetate and methanol extract showed activity against human histiocytic lymphoma U-937.<sup>59</sup>
- Leaf & twig showed activity against human tumor cell lines.<sup>33</sup>

#### Cytostatic Activity

The leaf inhibited tumor cell growth including adriamycin resistant human mammary adenocarcinoma MCF-7/Adr cells *in vitro*.<sup>43,49</sup>

#### Antitumor Activity

Ethanol and chloroform extracts of the seed and leaf have shown antitumor activity *in vitro*.<sup>60,61</sup> The leaf had an LC50=0.17 mcg/ml, demonstrated through the *in vitro* anticrustacean assay system.<sup>61</sup>

### **Uterine Stimulant Activity**

Water and ethanol extracts fed orally to rats at 0.033 ml/L had uterine stimulant activity.<sup>62</sup>

## Cardioactive and Hypotensive Activity

In one study 1 ml/L water extract of the leaf fed intravenously to rats resulted in a reduction in blood pressure by more than 30%.<sup>63</sup> This activity may be due to the *in vivo* hypotensive activity of the leaf and stem.<sup>62</sup> A water extract of the bark exhibited a cardiodepressant effect in rabbits.<sup>64</sup>

## Antispasmodic and Muscle Relaxant Activity

Ethanol and water extracts of the leaf and stem fed at 0.033 ml/L to guinea pigs had antispasmodic activity. In rabbits an ethanol extract at 3.3 ml/L relaxed smooth muscle; 2.2ml/L of a water extract had the same effect.<sup>62</sup>

## Neurological Activity

100 mg/kg of an ethanol leaf extract given intraperitoneally to mice had anticonvulsant activity.<sup>65</sup>

Extracts of the fruit, leaf and seed have shown serotonin receptor binding activity *in vitro*.<sup>66</sup>

Alcoholic extracts of the stem bark was administered to rats intragastrically at 100 mg/kg. One hour after administering the extract the rats were stressed by cold immobilization (placing animals in a restrainer for 3 hours at 4 C). Following is the effect of graviola on brain neurotransmitters versus controls:<sup>67</sup>

Treatment Group	Noradrenaline (ng/gm)	Dopamine (ng/gm)	5-Hydroxytryptamine (ng/gm)	5-Hydroxy Indole-acetic acid (ng/gm)	Monoamine oxidase units/mg protein
Normal Control	445.99 ± 22.53	892.02 ± 32.19	679.22 ± 59.53	533.38 ± 59.53	5.00 ± 0.28
Restraint Control	376.30 ± 29.19	699.77 ± 72.66	750.10 ± 67.12	731.43 ± 19.72	4.24 ± 0.37
Graviola treated	588.99 ± 62.34*	930.82 ± 13.32	402.76 ± 22.24	588.24 ± 47.25	8.10 ± 0.15

\* p<0.01 compared to restraint control

## Antimicrobial and Antiprotozoal Activity

### Antiparasitic

Methanol, hexane and ethyl acetate extracts of the seed, stem, bark and pericarp have demonstrated *in vitro* antiparasitic activity against *E. histolytic*, *N. brasiliensis*, *M. dessetae*, *A. salina*, *Leishmania trypanosoma*, *L. braziliensis*, *L. panamensis* and *L. promastigotes*.<sup>34,59,68</sup>

### Antimalarial

Ethanol leaf extracts have shown *in vitro* antimalarial activity against *Plasmodium falciparum* D-6 & W-2 at IC50=20 - 63 mcg/ml.<sup>3,28,69</sup>

### Antibacterial

Leaf, stem and bark water, acetone, methanol and ethanol extracts have demonstrated *in vitro* antibacterial activity at concentrations of 2-3 mcg/plate to 1 mg/disc. Organisms the extracts are active against include: *E. coli*, *P. aeruginosa*, *S. flexneri*, *S. spp.*, *S. marcescens*, *S. aureus*, *S. albus*, *S. newport*, *B. subtilis*.<sup>70-72</sup>

### Antiviral

A water soluble fraction from the stem had an antiproliferative effect on HIV-infected cells *in vitro* at IC50=<2mcg/ml.<sup>73</sup> The stem and bark in an ethanol extract at 1 mg/ml had *in vitro* activity against herpes simplex 1, while the root had activity against herpes simplex type 2 *in vitro* at CC50 and EC50=0.5 mcg/ml.<sup>38,74</sup>

### Molluscicidal

Stem, bark and leaf ethanol extracts have demonstrated *in vitro* activity against *B. glabrata* at LD50-0.97-20.26 ppm.<sup>6,75</sup>

### Insecticidal

The leaf had activity against the following insects *in vitro*: *M. sanborni*, *L. decemlineata*, *M. persicae*, *Blatella germanica*.<sup>53-55</sup>

### **Antiulcer Activity**

Stem and bark ethanol extracts at 100 mg/kg intragastrically in rats had antiulcer activity.<sup>76</sup>

### **Antioxidant Activity**

Stem and bark ethanol extracts at 100 mg/kg intragastrically in rats had antioxidant activity.<sup>77</sup>

### **Antihepatotoxic Activity**

A leaf decoction reduced ASAT leakage by hepatocytes *in vitro* at 1 mg/plate.<sup>78</sup>

### **Patents Pending / Filed**

Numerous patents have been filed on various acetogenins which are found in graviola and other plant members of the Annonaceae family.

### **Mechanism of Action**

### **Anticancerous Activity**

#### Cytotoxic Activity

Anticancerous and cytotoxic effects of graviola are attributed to the annonaceous acetogenins which have a number of mechanisms including:

- Inhibition of NADH oxidase in the plasma membranes of cancer cells. This enzyme is only transiently expressed in 'normal healthy' cells. By inhibiting this enzyme cellular ATP is depleted.<sup>46,79,80</sup>
- Inhibition of complex I (NADH:ubiquinone oxidoreductase) in mitochondrial electron transport systems, inhibiting oxidative phosphorylation and resulting in lower ATP levels, hence inhibiting cancer cell growth.<sup>46,80-83</sup>
- Inhibition of cancer cells that are multidrug resistant. Increased expression of a plasma membrane pump, P-glycoprotein, is a contributor to multidrug resistance. The pump ensures elimination of the anticancer compound before it can have its effect on the cancer cell. Two intracellular ATP-binding sites are found on P-glycoprotein, and the pump activity requires ATP. The acetogenins, through depletion of ATP, can reduce the activity or shut down the P-glycoprotein pump.<sup>46,80,84</sup>
- Cancer cells at the S phase of their cell cycle are more vulnerable to the acetogenin annonacin. Annonacin is able to arrest the cell cycle in the G1 phase, and inhibit the S phase progression. In addition p53 and p21, cell cycle checkpoint proteins, were enhanced by annonacin.<sup>48</sup>

- The acetogenin annonacin is able to induce apoptotic cell death. It enhanced the expression of Bax and Bad, but not Bcl-2 or Bcl-xL.<sup>48</sup>

Through the above mechanisms of action the acetogenins are able to decrease oxidative phosphorylation and cytosolic ATP production. Deprivation of the cancer cells ATP results in apoptosis of the cancer cell.<sup>46,80</sup>

### **Neurological Activity**

Antidepressant, sedative and tranquilizing properties of graviola may be due to the ability of certain alkaloids to have agonistic properties towards 5-HT<sub>1A</sub> receptors in calf hippocampus.<sup>85</sup>

Cold immobilization stress in rats causes depletion of norepinephrine and dopamine levels in the brain. It also decreases MAO (monoamine oxidase) activity which leads to increases in 5-HT and 5-HIAA levels. Pre-treatment with graviola prevented the stress-induced depletion of norepinephrine and dopamine, helping the organism cope better during stress. In addition pre-treatment with graviola reduced the stress-induced rise in brain 5-HT and 5-HIAA, and increased MAO activity. It was concluded that graviola had a normalizing effect in rats against a variety of stressors, indicating it had adaptogenic potential.<sup>67</sup>

The potential neurotoxic effect of the seeds, root and rootbark is discussed under Chemicals.

### **Antimicrobial Activity**

Graviola has insecticidal activity which is attributed to the acetogenins. They are suggested for use in the control of insect pests such as cockroaches. Pest ingestion of the acetogenins produces mortality in both susceptible and insecticidal/pesticidal-resistant cockroaches. The effectiveness of the acetogenins against insecticidal/pesticidal-resistant insects suggests that pesticide-resistance is associated with ATP-dependent factors.<sup>46,83</sup>

### **Overall Activity**

The activity of graviola is mainly attributed to the acetogenins, which are mitochondrial respiratory chain complex I inhibitors.<sup>52</sup>

<b>Dosage</b>
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Internal

Crude Preparations, Leaf and Stem

2 grams three times daily

Infusion: 1 cup (150 ml) boiling water poured over approximately 2 grams of dried leaf and stem and steep, covered, for 5-10 minutes, 3 times daily between meals

Tincture: Of a 1:2 tincture take 2-4 ml three times daily

<b>Duration of Administration</b>
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Internal

Long-term administration (6 months) with no health complaint may deplete healthy cells of ATP. Duration of administration varies per complaint and individual.

## Contraindications

Pregnancy and Lactation: Graviola has documented uterine stimulant activity in an animal study (rats) and should not be used during pregnancy.<sup>62</sup>

Graviola has demonstrated hypotensive, vasodilator, and cardiodepressant activities in animal studies and is contraindicated for people with low blood pressure.<sup>63</sup>

## Drug Interactions

Graviola may potentiate antihypertensive and cardiac depressant drugs.<sup>63,64</sup>

It may potentiate antidepressant drugs and interfere with MAO-inhibitor drugs.<sup>66,67</sup>

Co-enzyme Q10 may reduce the activity of graviola. Coenzyme Q10 is required for the function of the ubiquinone oxidoreductase, which graviola has been shown to inhibit.<sup>46,80-83</sup>

## Side Effects

Graviola has demonstrated emetic properties in one animal study with pigs. Large single dosages may cause nausea or vomiting.<sup>31</sup>

## Safety Rating

Not rated.

Alcohol extracts of graviola leaf showed no toxicity or side effects in mice at 100 mg/kg intraperitoneally; however, at a dosage of 300 mg/kg, a reduction in explorative behavior and mild abdominal constrictions was observed.<sup>65</sup>

Alkaloids in the rootbark, root and seed of graviola have been linked to a levodopa-resistant parkinsonism. *In vitro* studies show they cause DNA damage and apoptosis of dopaminergic cells and GABAergic neurons.<sup>50</sup> Excessive consumption of these parts of the plant should be avoided.

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