

MIRACULOUS *ANNONA MURICATA* LINN. (GRAVIOLA/SOURSOP): A HOLISTIC APPROACH OF ITS COMPREHENSIVE REVIEW ON TRADITIONAL USES, PHYTOCHEMISTRY, PHARMACOLOGICAL ACTIVITIES AND MECHANISMS OF ACTION INVOLVEDRavi Sharma¹, Lakha Ram², Ashok K. Kakodia³, Upma Singh⁴, Bina Rani⁵ and Raaz K. Maheshwari^{6*}¹Department of Chemistry, Jai Narain Vyas University, Jodhpur (Rajasthan) India.²Department of Chemistry, JNMP Govt PG College, Phalodi, Jodhpur (Rajasthan) India.³Department of Chemistry, SGG Govt PG College, Banswara, (Rajasthan) India.⁴Department of Humanities & Applied Sciences, IIMT College of Engineering, Greater Noida, Gautam Buddha Nagar (UP) India.⁵Department of Applied Chemistry, School of Vocational Studies & Applied Sciences, Gautam Buddha University, Greater Noida, Gautam Buddha Nagar (UP) India.⁶Department of Chemistry, SBRM Govt PG College, Nagaur (Rajasthan) India.***Corresponding Author: Dr. Raaz K. Maheshwari**

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The use of anti-inflammatory natural products for cancer prevention and therapy is an appealing area of interest in the last decades. *Annona muricata* L. is one of the many plant extracts that have been explored owing to their anti-inflammatory and anticancer effects. The leaves of the plant have been extensively investigated for its diverse pharmacological aspects and found eminent for anti-inflammatory and anticancer properties. In this comprehensive review, all significant findings from previous investigations till date on the leaves of *A. muricata*, specifically on their anti-inflammatory and anticancer activities have been compiled. Annonaceous species, have been extensively investigated for and antioxidant properties. Phytochemical studies have identified the acetogenins, a class of bioactive polyketide-derived constituents, from the extracts of Annonaceous species, and dozens of these compounds are present in different parts of graviola. More than 100 annonaceous acetogenins have been isolated from leaves, barks, seeds, roots and fruits of *A. muricata*. This review summarizes current literature on the therapeutic potential and molecular mechanism of these constituents obtained from *A. muricata*.

KEYWORDS: Ehanomedicinal, Acetogenins, Chemopreventive Phytochemistry, Anticancer, Anti-inflammatory, polyketide.

INTRODUCTION

Natural products, especially those derived from plants, have been used to help mankind sustain its health since the dawn of medicine. Over the past century, the phytochemicals in plants have been a pivotal pipeline for pharmaceutical discovery. The importance of the active ingredients of plants in agriculture and medicine has stimulated significant scientific interest in the biological activities of these substances.^[1,2] Despite these studies, a restricted range of plant species has experienced detailed scientific inspection, and our knowledge is comparatively insufficient concerning their potential role in nature. Hence, the attainment of a reasonable perception of natural products necessitates comprehensive investigations on the biological activities of these plants and their key phytochemicals. In a pharmaceutical landscape, plants with a long history of use in ethno medicine are a rich source of active

phytoconstituents that provide medicinal or health benefits against various ailments and diseases. *Annona muricata* Linn. is a lowland tropical fruit-bearing tree (Fig. 1,2 & 3) in the Annonaceae family.^[3,4]

Annona muricata is also commonly known as Graviola or Soursop or Gunbanana. Soursop also known as Hanuman Phal/Laxman Phal in Hindi is a fruit that has its origin in the forests of South America, Africa and Southeast Asia. This is an evergreen broad leaved tree whose every part is useful and has medicinal properties. This fruit is extremely delicious with a sharp aroma and a sweet-sour taste which is basically a combination of the taste of pineapple and strawberry. The name soursop is due to sour and sweet flavour of its large fruit. This small evergreen tree with large glossy dark green leaves grows to a height of 5-6 meters. The edible fruit is heart shaped, yellow green in color and white inside.^[5-9]



Fig. 1, 2 & 3 A lowland tropical fruit-bearing *Annona muricata* Linn. Tree.

Graviola has gained much importance because of acetogenins, a group of potential anti-cancer agents, found in this plant. This reputation of *A. muricata* as a versatile medicinal plant has attracted considerable interest such that a number of studies have been done through the years to evaluate the claims of medicinal potential of this plant. According to multiple publications discussed in this paper, there are significant evidences to back the therapeutic potential of *A. muricata* against diabetes and several types of cancer such as breast, pancreatic, lung, liver, prostate and colon cancer.^[10-15] Based on available data, there is good evidence that these long-used plants could have both chemopreventive and therapeutic potential. In view of the immense studies on *A. muricata*, this review strives to unite available information regarding its phytochemistry, traditional uses and biological activities.^[16-18]

Active compounds such as acetogenins have been identified and characterized. However, large-scale animal and human trials are still lacking which are necessary to firmly establish the anti-diabetic and anti-cancer properties of *A. muricata* to be able to proceed

with developing *A. muricata*-based interventions. This reputation of *A. muricata* as a versatile medicinal plant has attracted considerable interest among the members of the general public as well as the scientific community.^[19-21] Therefore, a number of studies have recently been done to prove or disprove these claims of healing potential of *A. muricata*. This paper explores the medicinal properties of *A. muricata*, with an emphasis on cancer and diabetes, as evidenced by scientific research and publications.^[22-24]

Pharmacology and Phytochemistry of Graviola

The composition of graviola (soursop) fruit by weight is edible pulp (67.5%), peel (20%), seeds (8.5%) and core (4%). Most of the edible pulp is made up of water (80-81%) and the rest are carbohydrate (18%) and protein (1%). Other minerals and nutrients found in soursop fruit at low concentrations include Ca, P, Fe, β -carotene, thiamine, riboflavin, niacin, ascorbic acid, tryptophan, methionine and lysine. The seed and seed coat contain the following toxicants: tannin, phytate and cyanide.^[25-30]



Fig. 4-7 Folk Medicine prepared from leaves of Graviola.

Compounds that have been extracted in soursop include alcohols, aldehydes, esters, ketones and terpenes. A wide

array of ethnomedicinal activities is contributed to different parts of *A. muricata*, and indigenous

communities in Africa and South America extensively use this plant in their folk medicine (Fig. 4-7). Numerous investigations have substantiated these activities, including anticancer, anticonvulsant, anti-arthritis, antiparasitic, antimalarial, hepatoprotective and antidiabetic, analgesic, hypotensive, antiinflammatory, and immune enhancing effects. Phytochemical studies reveal that annonaceous acetogenins are the major constituents of *A. Muricata*.^[31-36] More than 100 annonaceous acetogenins have been isolated from leaves, barks, seeds, roots and fruits of *A. muricata*. In view of the immense studies on *A. muricata*, this review strives to unite available information regarding its phytochemistry, traditional uses and biological activities.^[37]

There has been an enormous interest in the literature that phyto-compounds have therapeutic and beneficial effects in various diseases including inflammatory associated arthritis, diabetes, hypertension, parasitic infections, and cancer. The leaves from the tropical tree *Annona Muricata*, have been reported to have positive and effective properties against many of the above mentioned diseases. Graviola (*Annona muricata*) is commonly called as soursop or Brazilian paw paw and belongs to the Annonaceae family, scientifically known

as *Annona muricata*.^[7] The bark, leaves, roots, fruits, and seeds have their own unique uses and specific properties.^[38] Ethnomedicinal practices in Africa and South America exploit this plant's extracts in their conventional and alternative medicine. The anti-convulsant, anti-parasitic, anti-arthritis, anti-malarial, anti-diabetic, hepatoprotective and anti-cancer properties of this plant are well established. Biological and biochemical characterization of the extracts indicate that annonaceous acetogenins are the main ingredients of graviola. Principally, graviola plays a predominant role in promoting anticancer activity.^[19-21]

The fruits of Graviola are extensively used to make candies, syrups, ice creams, shakes^[7-10] and beverages. A wide range of ethno-medicinal activities in Africa and South America extensively use this plant in their conventional medicine. A number of laboratories have reported Graviola's for its beneficial actions against anticonvulsant, antiparasitic, anti-arthritis, antimalarial, antidiabetic hepatoprotective and cancer activities. Biological and chemical characterization studies indicate that annonaceous acetogenins are the main ingredients of Graviola.^[21,22]



Fig. 7-8 Shake prepared from pulp of Graviola.

Nowadays more than 100 annonaceous acetogenins that are generally characterized as a family of natural products with antitumor activities, from roots, leaves, barks, fruits and seeds of Graviola have been widely used in alternative medicine for many purposes. In the Peruvian Andes for example, the Graviola leaves are used to combat parasites and treat diabetes. 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, Haiti the juice of Graviola was used to stop diarrhea, used as muscle relaxant and lower the intestinal acidity.^[24-27]

Other reports have demonstrated that Graviola has a number of biological activities such as antifungal, anti-bacterial, anti-malarial and antioxidant. Furthermore, it has been showed to have anti-cancer properties on multi-drug resistant cancer cell lines.

The fruit is of economic value and hence cultivated and used widely as an edible food. The plant possess the major pharmacological activities includes cytotoxic, antileishmanial, wound healing, antimicrobial activity. It also has the anticarcinogenic and genotoxic effect. Phytochemical analysis of the plant revealed the presence of tannins, steroids and cardiac glycosides which are the major phytochemical compounds. Recently,

it has gained attention and popularity due to its natural cancer cell killing properties. Apart from its anti-cancer properties, it has several other medical benefits. Soursop leaves are the most beneficial parts of this tree. They have the Acetogenin containing compounds namely bulatacin, asimisin and squamosin. Acetogenin acts as an anti-feedent. Thus, they are often used in killing insects and pests which die by consuming these leaves even in small amounts.^[27-29]

Scientific research conducted by The National Cancer Institute has proved that Soursop leaves can effectively attack and destroy cancer cells. In addition to this, they are also used in the treatment of several other diseases. Soursop leaves are rich in several compounds including protein, calcium, fructose, fat, vitamins A and B and the like. Thus, the leaves have excellent medicinal properties making them usable as an ingredient in several herbal health products.^[28]

Chemical composition of graviola.

S.No.	Constituents	Quantity
A.	Fruit flesh	
1	Water	80%
2	Carbohydrate	18%
3	Protein	1%
4	Vitamin B	Traces
5	Vitamin B2	Traces
6	Potassium	Traces
7	Dietary fiber	Traces
B.	Fruit pulp	
1	2-hexenoic acid methyl ester	23.9%
2	2-hexenoic acid methyl ester	8.6%
3	2-hexenoic acid ethyl ester	5.4%
4	2-octenoic acid methyl ester	2.4%
5	2-butenic acid methyl ester	12.7%
6	β -caryophyllene	9.9%
7	1,8- cineole	7.8%
8	linalool	2.8%
9	α -terpineol	2.2%

The compound annonacin, which is contained in the seeds of soursop, is a neurotoxin associated with neurodegenerative disease and research has suggested a connection between consumption of soursop and atypical forms of Parkinson's disease due to high concentrations of annonacin. Tea (Fig. 8) made from Graviola leaves has long been used in the Amazon region to treat liver and stomach disorders. A tea made from the bark, leaves, and roots are used as a sedative, antispasmodic, to calm the nerves, to reduce high blood pressure. Unripe fruit has been used to treat diarrhea and dysentery. The leaves, roots, and stems have been shown clobber in bacteria grown in laboratory culture. Seeds are known to be send parasites packing. Roots bark has been used to tame raging fevers. A leaf extract stood its ground against malaria. The fruit used as a natural medicine for arthritic pain, Neuralgia, Arthritis, Diarrhea, Fever,

Malaria, Rheumatism, Skin rushes and worms and also to elevate a mother's milk after childbirth.^[29-32]

They have the Acetogenin containing compounds namely bulatacin, asimisin and squamosin. Acetogenin acts as an anti-feedent. Thus, they are often used in killing insects and pests which die by consuming these leaves even in small amounts. Scientific research conducted by The National Cancer Institute has proved that Soursop leaves can effectively attack and destroy cancer cells. In addition to this, they are also used in the treatment of several other Soursop leaves are rich in several compounds including protein, calcium, fructose, fat, vitamins A and B and the like. Thus, the leaves have excellent medicinal properties making them usable as an ingredient in several herbal health products.^[33]

Soursop leaves can inhibit cancer cells and cure cancer more quickly and effectively than chemotherapy which results in several side effects besides being expensive. In fact, research has proved that soursop has an active ingredient that is 10000x stronger than chemotherapy in fighting cancer cells. Thus, soursop leaves can treat different types of cancers including prostate, lung and breast cancers.^[34-37] The nutrient content of soursop leaves is believed to boost the immune system and avoid infections in the body. In addition to the benefits mentioned above, soursop leaves are extremely effective in inhibiting the growth of bacteria, virus, parasites and tumor development. Their healing properties make them capable of being used as an anti seizure medication. They are also capable of reducing fever and lowering high blood pressure.



Fig.11 Tea Prepared from Graviola Leaves.

Soursop leaves can treat eczema in a natural way. Leaves are used for headaches and insomnia. The leaves also contain antioxidants known to fight inflammation and insomnia. Cooked leaves, applied topically, fight rheumatism and abscesses. In certain regions of Brazil, the oil of the leaves and unripe fruit is mixed with olive oil and used externally for neuralgia, rheumatism and arthritis pain. The fruit and fruit juice are used as deworming and antiparasitic agents, as an astringent for diarrhea and dysentery, to cool fevers and to increase mother's milk after childbirth. Graviola has been found to be beneficial in cases of diabetes. Studies have shown Graviola to be a hypotensive (reduces blood pressure),

vasodilator (widens the blood vessels) and cardio depressant (decreases heart rate).^[38]

CONCLUSION

Plant-derived natural products and their derivatives have historically been used to treat various diseases, including cancer. Several leading chemotherapeutic agents are directly or indirectly based on botanical natural products. Beyond these important drugs, however, a number of crude herbal or botanical preparations have also shown promising utility for cancer and other disorders. One such natural resource is derived from certain plants of the family Annonaceae, which are widely distributed in tropical and subtropical regions. Among the best known of these is *Annona muricata*, also known as soursop, graviola or guanabana. Graviola has been purported to have a number of uses, especially therapeutic and pharmacological activities. Leaves, seeds, bark, fruits and roots are the traditionally used parts of this tree. *A. muricata* leaf and its secondary metabolites produce anti-inflammatory, anti-cancer and other immune system related effects. Isolates from the leaf of *A. muricata*, consisting mainly of annonaceous acetogenins, alkaloids, and phenolic compounds are identified and reported in literature. This review summarizes the recent findings on the effects of Graviola tree extract as a novel anti-cancer agent for the treatment and prevention of cancers; a possible natural anti-cancer candidate agent in line with all the attributes pointed above.

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