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Annona Muricata: Unveiling its Potential as a Complementary and Alternative Cancer Therapy

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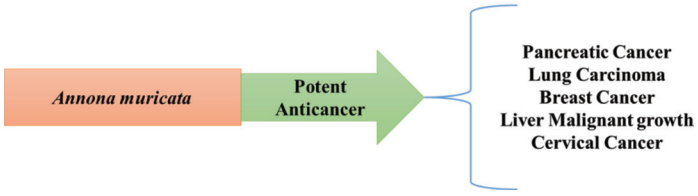
ABSTRACT

Background: Soursop (Annona muricata) is a tropical fruit that has recently been under scrutiny for its supposedly appreciable health benefits. The plant is rich in phytochemicals and the medicinal value of the fruit has been under study in treating cancer, diabetes, oxidative stress, hypertension, haemorrhagic disease, and reduction of bad cholesterol.

Purpose: The review serves to discuss the potential use of the Annona muricata in nutraceutical and pharmaceutical development. The discussion below is based on the use of soursop pulp, seeds, and leaf extracts as functional ingredients in food products and their implications for pharmaceutical industries.

Methods: Recent literatures have been surveyed from PUBMED, GOOGLE SCHOLAR, etc. like search engines, for summarising detailed ongoing research on Annona muricata, which could be used in complementary and alternative cancer therapy.

Conclusion: The high nutritional value and pharmacological potential of Annona muricata turn it into a very good candidate for different health-related applications. There exist promising benefits of phytochemicals present in soursop for the treatment and prevention of a number of health conditions, underscoring its importance in functional foods and medicines development.



Graphical abstract: Annona muricata as a potent anti-cancer plant

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1. Introduction

Malignant growth is the subsequent driving reason for death around the world. In excess of 6 million individuals kick the bucket and in excess of 10 million new malignant growth patients are analyzed every year. Around 12% of all passing's overall are ascribed to this. By 2020, there will be more than 15 million new cases analyzed yearly, addressing a 70% expansion in the number of new cases throughout the following 20 years. Cancer-causing agents, diseases, chemicals, resistant circumstances, and the reception of social and dietary gamble factors like smoking, less than stellar eating routine, idleness, and ecological contaminations are contributing variables to this quick ascent. Additionally, contributing elements are a maturing and growing populace. Risk variables can act freely or together to cause a typical cell transformation (Kciuk *et al.*, 2024b; Mattiuzzi & Lippi, 2019). Uncontrolled cell division and malignant growth are brought about by a lot of people of these changes, which modify significant quality items' demeanour or capability. Medical procedure, radiation-based treatment, chemotherapy, quality treatment, or potentially hormonal treatment are presently the most well-known malignant growth therapy choices,

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either exclusively or in the mix (Zugazagoitia *et al.*, 2016). Antimetabolites, DNA-associating specialists, anti-tubulin specialists, chemicals, and sub-atomic focusing on specialists are the chemotherapy medicates that are utilized the most often. They all attempt to slow the development of malignant cells or dispose of them. Conflictingly, most cytotoxic medications hurt both solid and harmful cells, bringing about after effects like going bald, concealment of bone marrow, drug opposition, gastrointestinal sores, neurologic brokenness, and heart poisonousness. In this way, the improvement of novel anticancer meds with expanded selectivity, viability, and negligible to no secondary effects is a first concern (Bhattacharya *et al.*, 2022; Goodman, 1989; Kumar *et al.*, 2020).

Starting from the start of medication, regular items, especially those got from plants, have been utilized to keep up with well-being. Plant phytochemicals play had a huge impact in the improvement of new drugs over the course of the last hundred years. Because of their importance in both farming and medication, researchers are especially keen on the organic exercises of plant dynamic fixings (Ahmed *et al.*, 2023; Kishore *et al.*, 2014; Rubio-Melgarejo *et al.*, 2020). Plants that have been utilized for quite a while in ethnomedicine are a rich wellspring of dynamic phytoconstituents in a drug scene. These phytoconstituents offer restorative or medical advantages against different sicknesses and infections. Bioactive mixtures and optional metabolites found in restorative plants have been displayed to have hostile to malignant growth properties in examinations. Most of these natural mixtures restrain the beginning, development, and movement of malignant growth by influencing cell multiplication, separation, apoptosis, angiogenesis, and metastasis (Goyal *et al.*, 2017).

In the relentless pursuit of novel and effective therapeutic agents against cancer, the exploration of natural sources has emerged as a promising avenue. Among the myriads of botanical treasures, Annona muricata, commonly known as soursop or graviola, has captivated the attention of researchers and herbalists alike for its purported anti-cancer properties. This review delves into the wealth of scientific evidence surrounding the remarkable anti-cancer potential inherent in Annona muricata, offering an insightful synthesis of the current knowledge and highlighting the various bioactive compounds that contribute to its pharmacological prowess (Table 1).

Annona muricata Linn is the name of a swamp tropical organic product-bearing tree in the Annonaceae family (Table 2). Annona muricata is otherwise called guanabana, soursop, and graviola. The prepared kind of enormous soursop organic product gives it its name. The Asimina triloba incorporates the cherimoya, A. squamosa, and paw, which are all connected species (Moghadamtousi *et al.*, 2015). A tropical natural product that fills in the Caribbean, Focal and South America, and southern Florida is the soursop. From ocean level to 1150 meters above ocean level, it is currently filled broadly in tropical locales everywhere, including Southeast Asia and southern Florida. Soursop is a typical Caribbean therapeutic plant. The organic product's mash is eaten and utilized in many dishes and beverages. The plasma layer catalyst NADH oxidase (nicotinamide adenine dinucleotide phosphate-oxidase), which is important for the improvement of various kinds of malignant growth, is actually restrained by acetogenins. Due to its financial worth, the natural product is filled in huge amounts and devoured as food. A portion of the plant's vitally pharmacological impacts incorporate cytotoxicity, antileishmanial movement, wound mending, and antimicrobial action. Natural cures are produced using all elevated pieces of the plant Annona muricata, otherwise called Graviola. This plant's concentrates have shown guarantee as restorative specialists. It likewise has anticarcinogenic and genotoxic properties (Dhankhar *et al.*, 2024a; Mittal *et al.*, 2023; Moghadamtousi *et al.*, 2015; Narwal *et al.*, 2023; Panchal *et al.*, 2024). Recent scientific investigations have provided compelling evidence to support the traditional claims of Annona muricata's anti-cancer potential. The plant is rich in bioactive compounds such as acetogenins, alkaloids, and polyphenols, each contributing to a diverse pharmacological profile with anti-inflammatory, antioxidant, and anti-cancer properties. The selective cytotoxicity exhibited by certain acetogenins derived from Annona muricata against cancer cells has ignited a fervent interest in exploring its therapeutic applications. This review comprehensively synthesizes findings from in vitro and in vivo studies, clinical trials, and epidemiological observations, aiming to elucidate the molecular mechanisms underpinning the anti-cancer effects of Annona muricata. As we navigate through the intricate web of cellular signalling pathways and interactions, a clearer understanding of the plant's impact on cancer cells and its potential as an adjuvant therapy emerges. While the promising anti-cancer attributes of Annona muricata hold immense potential, it is crucial to critically evaluate the existing literature, addressing gaps in knowledge, and identifying areas for further research. As we embark on this exploration of nature's gift, the hope is to contribute to the ongoing dialogue surrounding Annona muricata as a potent anti-cancer plant, fostering a deeper appreciation for the intricate relationship between traditional wisdom and modern scientific inquiry.

Table 1: Phytochemical properties

Compound	Part of fruit
Anomuricine	Leaf, root, stem
Anomurine	Leaf, root, stem
Annonaine	Fruit, leaf

Annonamine	Leaf
Asimilobine	Fruit
Atherospermine	Stem

Table 2: Scientific classification

Scientific classification	
Kingdom	Plantae
Division	Spermatophyte
Subdivision	Angiospermae
Class	Dicotyledonae
Order	Polycarpiceae
Family	Annonaceae
Genus	Annona
Species	Annona municata L.

2. Anticancer Action of A. Muricata on Various Cancers

It has been exhibited that framework metalloproteinases (MMPs) like MMP-2 and MMP-9, which are fundamental for the improvement of disease, can be hindered by extricates from the natural product, stem, seeds, and twigs of A. muricata (Gavamukulya *et al*., 2017). The human leukaemia cell line HL-60 had the option to quit developing when separate from the leaves, twigs, and roots upset MMPs, receptive oxygen species (ROS), and the G0/G1 cell cycle capture (Hasmila *et al*., 2019; Kciuk *et al*., 2024a; Rohilla *et al*., 2023).

2.1. Pancreatic Cancer

The world's deadliest and fourth most normal malignant growth, pancreatic malignant growth seems to have a 5-year endurance pace of just 8%. The high death pace of patients who are analyzed past the point of no return is exacerbated by the shortfall of early clinical side effects. Late findings, protection from flow chemotherapy therapies, and the forceful way of behaving of the disease have all ignited innovative work of chemopreventive and chemotherapy specialists as well as new early location markers (El Tawiil *et al*., 2020). Pancreatic cell development inhibitors are created by hindering the ERK and PI3K pathways, which are important for the endurance of pancreatic disease cells. The cortical actin and microtubule network affect malignant growth cells' portability and relocation. Mitotic capture is likewise remembered to be brought about by actin redesign in the cytoskeleton and a respite in microtubule elements, the two of which have been connected to cell ATP exhaustion. The concentrates of A. muricata disturb the cortical actin organization, keeping malignant growth cells from moving (Prasad *et al*., 2019).

2.2. Lung Carcinoma

A. muricata leaf separate causes cell cycle capture at the G0/G1 stage and apoptosis when tried in vitro on human lung adenocarcinoma cell lines A549 with IC50 upsides of 21, 42, and 100 g/mL, individually. The separated acetogenins cis-gigantetrocinone and trans-gigantetrocinone, cis-isoAnnonacin and trans-isoAnnonacin, and squamolone have ED50 upsides of 3.39 102, 9.74 103, 4.42 105, and 10 against the A549 cell lines, individually (Rethinam & Sundararaj, 2016). A muricata leaf ethyl acetic acid derivation removal (AMEAE) with an IC50 worth of 5.09 0.41 g/mL prompted apoptosis in the A549 cell line following 72 hours of treatment. In the A549 cell line, the concentrate of graviola expands the Bax/Bcl-2 proportion interceded hindrance of mitochondrial layer potential, actuates cytosolic cytochrome c, and restrains atomic variable B (NF-B) flagging (Ahmed *et al*., 2023; Dhankar *et al*., 2024c).

2.3. Breast Cancer

Breast malignant growth is the most widely recognized kind of disease among ladies. It is feasible to treat the beginning phase of bosom malignant growth; the disease that is progressed can't. We critically require new chemopreventive and chemotherapeutic prescriptions to stop the development of cancers and decrease the related horribleness. Notwithstanding the way that a few regular synthetic substances have been demonstrated to be more secure and less hurtful than manufactured synthetic compounds in vitro tests, their absence of clinical viability has forestalled their interpretation (Moghadamtousi *et al*., 2015). Late exploration shows that A. muricata has powerful antiproliferative and antitumor properties. The morphology of the disease cells that were presented to the ethyl acetic acid derivation division and A. muricata leaf remove proposed apoptosis, a cycle described by the breakdown and loss of the cell layer. MCF7 cells' cytotoxic movement is principally prompted by raised caspase-9 and caspase-3 articulation notwithstanding diminished Bcl-2 and PARP-1 articulation. Furthermore, xenograft cancers express Bcl2, emergency room, and cyclin D1 less when anonacin (0.1 M) is directed. Following 48 hours of therapy with anannomycin (0.5-1 M), the MCF breast cancer cell line passed on (Dhankar *et al*., 2024d; Hadisaputri *et al*., 2021; Saharan *et al*., 2024; Samrat Chauhan, 2015).

MDA-MB-468 cells showed critical downregulation of EGFR mRNA articulation, cell cycle capture, and apoptosis (IC50 = 4.8 g/mL), yet MCF-10A cells didn't. In the

xenograft mouse model, MDA-MB-468 growth articulation of EGFR, p-EGFR, and p-ERK was decreased by 56-32.5% following 5-week dietary treatment with organic product removal (200 mg/kg diet) (Naik & Sellappan, 2020). MDR is the most well-known way that disease cells foster helpful opposition, which brings about treatment disappointment and cancer development. By diminishing ATP content, the MCF-7/ADR bosom disease cell line is cytotoxic to ACG bullatacin (1 g/mL). ACGs from A. muricata are especially compelling against MDR bosom growths, while ACGs from Annona Squamosa seeds modify mitogen-enacted protein kinase (MAPK) flagging and cause apoptosis in MCF-7/ADR cells. As well as causing apoptosis in MCF-7/ADR cells, annosquacin B (Abdominal muscle) likewise expanded caspase-3, caspase-9, Bax/Bcl-2, p-p38 MAPK, and p-JNK (IC50 esteem: 14.69 M) (Dhankhar *et al.,* 2024b; Fidianingsih & Handayani, 2014).

2.4. Liver Malignant Growth

The likelihood that the plant concentrates could be utilized as a therapy for liver disease is raised by the way that it has been shown that they cytotoxically affect hepatic malignant growth cells. Subsequent to being presented to an ethanol concentrate of A. muricata, it was found to restrain the HepG2 cell line's development and practicality; The LD50 values were 180 and 80 g/mL, individually, after 24 and 48 hours (Dhankar *et al.*, 2024d; Dhankhar *et al.*, 2023; Tejasari *et al.*, 2018).

2.5. Cervical Cancer

Different leaf extricates in solvents had the option to advance antiproliferative action in HeLa cervical malignant growth cells. It was exhibited that A. muricata methanol leaf removal represses the expansion of the HEp-2 (laryngeal disease) cell line using the 3-[4, 5-dimethylthiazol-2-yl]-2, 5-diphenyltetrazole (MTT) decrease technique. Afterwards, it was found that HEp-2 was really a defiled HeLa cell line (Hasan *et al.*, 2022).

3. Contraindications

Graviola ought not to be utilized during pregnancy because of its shown uterine energizer action in rodents. Graviola has been displayed in creature studies to have hypotensive, vasodilator, and cardio-depressant properties, so it ought not to be taken by individuals with low circulatory strain. Individuals on antihypertensive prescriptions ought to converse with their primary care physicians prior to taking graviola, and their pulse ought to be checked in like manner (as meds might be changed) (Sawant & Dongre, 2014). Chronic use of Graviola has powerful antimicrobial properties in vitro. Because of its antimicrobial properties, utilizing this plant routinely and for a drawn-out timeframe may bring about the demise of gainful intestinal system microbes. In the event that this plant is consumed for over 30 days, probiotics and stomach-related chemicals ought to be added to the eating regimen (Nayak & Hegde, 2021).

4. Toxicology

A. muricata's anonacin is neurotoxic at nanomolar fixations. The plant's acetogenins may assume a part in parkinsonism since they are likewise powerful mitochondrial harms. At the point when guinea pigs are presented with watery concentrates of the products of the soil that contain high convergences of annonacin, which effectively crosses the blood-cerebrum hindrance, their basal ganglia may deteriorate (Badrie & Schauss, 2010; Rehni *et al.*, 2008; Rehni *et al.*, 2010). Seven different acetogenins were tested for neurotoxicity using rat striatal neuronal cells, mesencephalic dopaminergic neurons, and laboratory rats, and the results showed that A. muricata's most prevalent acetogenin (annonacin) and alkaloid (reticuline) were neurotoxic. However, studies on the neurotoxicity of annonacin suggest that prolonged exposure to this molecule is required in order to evaluate the effect in mouse models, and pharmacokinetic studies also predicted that this compound had a low degree of bioavailability.

5. Conclusion

This current review highlights the anticancer potential and other health advantages of A. muricata by offering insights into its bioactive chemical components. The organic product›s helpful, viable, and dietary advantages have altogether expanded its worldwide fame lately. Soursop has been demonstrated to be a decent natural substance for the handling of an assortment of useful and esteem-added food items because of its high mash extraction, extensive variety of fragrant parts, and thickness. Alkaloids, coumarins, tannins, flavonoids, phenols, terpenoids, and saponins are among the pharmacologically dynamic mixtures tracked down in the leaves, seeds, and different pieces of soursop. As our understanding of the molecular mechanisms of different components of graviola extract that regulate metastasis, proliferation, apoptosis, and cell signaling grows, so does the allure of the concept of employing these components in a tailored method to strengthen our arsenal against cancer. Soursop is one of the natural products with the best business and monetary potential on account of its charming smell and flavour. All in all, the soursop products of the soil parts can be utilized to make a large number of superior grades,

helpful food sources and prescriptions in the food and drug ventures.

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Shinam Bakshi: Writing original draft; Sanchit Dhankar: Conceptualization and methodology; Samrat Chauhan: Supervision; Shushank Mahajan: Review and editing; Abhinav Yadav: Formal analysis and data collection; and Deepak Singla: Editing.

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Conflict of Interest

There is no conflict of interest.

Ethical approvals

This study does not involve experiments on animals or human subjects.

Declaration

It is an original article and has neither been sent elsewhere nor published anywhere.

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