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Review Article

Therapeutic Potential of *Annona muricata* (Graviola) in Cancer Management: Current Evidence, Safety Considerations and Future Prospects

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ABSTRACT

Annona muricata L., colloquially designated as graviola or soursop, represents a tropical botanical species of significant pharmacological interest due to its diverse array of secondary metabolites and associated bioactivities. This narrative review critically evaluates the extant literature regarding its botanical taxonomy, phytochemical profile, preclinical oncological investigations, underlying molecular mechanisms, toxicological parameters, and current research constraints, while outlining strategic imperatives for future inquiry. Prominent analytical focus is directed toward annonaceous acetogenins —specifically annonacin and its structural analogues—alongside endogenous alkaloids, phenolic compounds, and flavonoids. Although *in vitro* and *in vivo* models demonstrate that these constituents modulate neoplastic cell viability, proliferative pathways, apoptotic biomarkers, cell-cycle checkpoints, and mitochondrial integrity, these preliminary outcomes remain strictly hypothesis-generating and do not constitute definitive evidence of clinical efficacy in human subjects. Comparative evaluation of the literature is profoundly challenged by systemic heterogeneities, including variations in anatomical plant parts, geographical provenance, extraction menstrua, processing methodologies, phytochemical yields, and experimental protocols. Furthermore, the potent mitochondrial disruption mediated by select acetogenins raises critical questions regarding cellular selectivity, suggesting that cytotoxicity may extend to non-malignant tissue. Concurrently, documented toxicological risks and unresolved questions surrounding prolonged exposure, potential neurotoxicity, standardized product quality, and herb-drug interactions necessitate pronounced clinical vigilance. While the reviewed data underscore the utility of authenticated botanical material and chemically profiled isolates as potential scaffolds for novel drug discovery, clinical advancement remains contingent upon strict analytical standardization, bioassay-guided isolation, comparative toxicity screening against normal cell lines, pharmacokinetic

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profiling, and comprehensive toxicological assays. Consequently, current empirical evidence is insufficient to validate *A. muricata* or its commercial derivatives as safe or effective antineoplastic modalities; thus, their use must not supplant, defer, or compromise standard, evidence-based oncological care. Any future translational evaluation demands chemically characterized matrices, a rigorous preclinical safety portfolio, and ethically approved clinical protocols.

INTRODUCTION

Rather than constituting a singular pathological entity, cancer encompasses a heterogeneous constellation of disorders characterized by acquired cellular aberrations that disrupt the homeostatic regulation of proliferation, survival, and architectural tissue organization. Depending upon the specific oncological malignancy, disease progression is driven by accelerated, unchecked proliferation, evasion of apoptotic pathways, metabolic reprogramming, neoangiogenesis, histopathological invasion, and metastatic dissemination to secondary organ systems. While modalities such as surgical resection, radiotherapy, cytotoxic chemotherapy, hormonal ablation therapies, molecularly targeted agents, and immunotherapy have significantly advanced clinical outcomes across numerous settings, the therapeutic efficacy of these approaches remains constrained by systemic toxicities, acquired drug resistance, disease recrudescence, and the critical imperative to personalize patient management[2,3,45,46].

Natural products have played an important role in pharmacological discovery because plants produce chemically diverse molecules with varied structural features. Natural-product research can identify compounds that affect cell signalling, energy metabolism, inflammation, oxidative balance, proliferation or regulated cell death. A candidate molecule must be identified chemically, tested in relevant biological systems, evaluated for selectivity and toxicity, and assessed through a development pathway appropriate to its intended use [1–4,46].

Annona muricata L.—commonly known as soursop, graviola, or guanabana—is a tropical plant from the Annonaceae family prized for its edible fruit and its long history in traditional medicine, where its leaves, bark, and seeds are frequently used. Because of this rich chemical diversity, researchers view the plant as a promising starting point for discovering new cancer treatments, rather than a proven cure in its own right[1,4].

However, the real scientific challenge isn't just showing that a soursop extract can kill cancer cells in a petri dish. The true test is whether a specific compound—or blend of compounds—can achieve a reliable, meaningful effect inside a living organism at a safe, realistic dose. Furthermore, simple cell culture tests cannot replicate how a living body absorbs, breaks down, distributes, and eliminates a compound, nor can they account for immune system reactions or the intricate environment of a real tumor[2,3,8,10–16].

This paper offers a narrative review of existing literature based on the accompanying reference list. Throughout the text, we explore the plant’s botanical identity, what causes its chemical makeup to vary, its primary phytochemical components, and its documented anticancer properties and mechanisms. Ultimately, our main goal is to deliver a fair, balanced academic overview that highlights both the exciting potential and the current boundaries of Annona muricata research.

2. Botanical Description and Taxonomy

Annona muricata L.—widely recognized as soursop, graviola, or guanabana—is a tropical evergreen tree belonging to the Annonaceae family. Highly adaptable, it thrives across various tropical and subtropical regions, producing a distinctive green fruit known for its soft, prickly skin, fleshy white pulp, and dark seeds. Crucially, researchers must not treat these different plant parts as interchangeable; each possesses a unique chemical footprint and can trigger entirely different biological reactions [1,4,39,40,44].

Accurately identifying a plant is the absolute foundation of any credible medicinal research. Scientists must verify the species using proper taxonomic methods and, ideally, store a voucher specimen in an official, recognized herbarium for future reference. Relying on a common name simply isn't enough to confirm a species' identity or guarantee what is inside a herbal preparation [1,4].

A plant's geographic origin and cultivation environment heavily dictate the chemical makeup of A.

muricata. Diverse factors—such as local climate, soil quality, the age of the plant, seasonal shifts, pest exposure, and specific harvesting techniques—all introduce significant variations in its secondary metabolites. Because these variables are so influential, researchers must provide meticulous methodological details to allow for any meaningful comparison between different studies [39,40].

For pharmaceutical research to be truly reliable, a plant's botanical identity must be tied to a traceable sample and a reproducible preparation process. Investigators need to clearly document the plant-to-solvent ratio, the exact time and temperature used during extraction, the solvent composition, the final yield, and the precise steps taken for filtration, concentration, and storage. This same rule applies to the market: two commercial products featuring the exact same botanical label can vary drastically in the actual concentration and balance of their active ingredients [7,39,40].

3. Phytochemical Constituents

Chemical analyses of Annona muricata have uncovered a diverse mix of secondary metabolites, featuring annonaceous acetogenins, alkaloids, phenolics, flavonoids, sterols, and terpenoids. The concentration of these compounds shifts dramatically based on the specific part of the plant used, its origin, and how it was processed in the lab. This internal complexity is incredibly important for both medical effectiveness and safety; a raw, unrefined extract contains a cocktail of multiple compounds that might work together, work against each other, or trigger entirely unrelated biological responses [1,3,4,17–30,39,40].

Among all the components of A. muricata, annonaceous acetogenins have easily received the most scientific attention. These unique molecules are derivatives of long-chain fatty acids, typically characterized by a terminal lactone ring and one or more tetrahydrofuran (THF) rings. Each specific acetogenin can differ dramatically in its therapeutic potency, selectivity toward cancer cells, chemical stability, and potential toxicity [17–30].

The primary pharmacological interest in acetogenins stems from their documented ability to block mitochondrial complex I, a key component of the electron transport chain required for oxidative phosphorylation. By interfering with this vital machinery, these compounds can severely deplete a cell's ATP (energy) production, crippling its basic energy-dependent operations. This underscores why therapeutic potency must always be evaluated alongside cellular selectivity and dose-dependent toxicity [2,3,8,9,48].

Phenolic compounds and flavonoids are also frequently featured in A. muricata research, primarily within studies evaluating antioxidant activity and inflammatory pathways. Additionally, alkaloids and terpenoids present in the plant may introduce further biological effects. To definitively pin down which components are responsible for an observed therapeutic effect, researchers must employ rigorous methodologies, including bioactivity-guided fractionation, precise chemical characterization, quantitative analysis, and meticulously controlled experiments [1,4,39,40].

Extraction conditions heavily dictate the exact chemical makeup of the material being tested. Solvents with different polarity levels—such as water, ethanol, methanol, or less polar alternatives—dissolve and recover vastly different proportions of plant compounds. Ultimately, a biological or therapeutic finding discovered using one specific preparation cannot automatically be generalized to all other leaf extracts, fruit preparations, or commercial supplements sold under the name graviola [4,39,40].

Analytical standardization serves as a vital safeguard in natural product research, relying on tools like chromatographic fingerprinting, reference standards, and the precise quantification of specific marker compounds. To build a comprehensive and truly useful product specification, researchers must also rigorously evaluate potential risks like residual solvents, microbial contamination, pesticide residues, and heavy metals, alongside testing for long-term stability and batch-to-batch consistency. Consequently, standardization is far more than a routine manufacturing requirement; it is an absolute necessity for accurately interpreting laboratory findings, comparing independent studies, and defining the exact level of chemical exposure to which safety and toxicity observations apply. [6,7,9].

4. Anticancer Potential

The anticancer potential of A. muricata has largely been studied through laboratory experiments and preclinical investigations. Researchers have evaluated crude plant extracts, partially purified fractions and individual compounds, particularly acetogenins, using different cancer-cell models. Although these findings suggest that the plant contains compounds worth investigating further, they do not confirm that A. muricata or products prepared from it can effectively treat cancer in humans [2–4,10–16,34–37].

Breast cancer is one of the areas explored in research on A. muricata. Dai and colleagues investigated the effects of graviola fruit extract in human breast cancer models and observed growth-inhibitory activity associated with reduced expression of the epidermal growth factor receptor [10]. The composition and concentration of compounds in laboratory extracts may differ considerably from those present in products used by consumers.

The possible effects of A. muricata have also been investigated in colorectal cancer models. Research using leaf preparations has reported changes in cell-cycle progression and effects associated with apoptosis in HCT-116 and HT-29 cancer cells. In patients, the disease is influenced by factors such as genetic differences, interactions with the immune system and variations in disease progression.

Studies have also examined the effects of graviola-derived preparations in pancreatic cancer models, focusing on their possible influence on tumour-cell metabolism, tumourigenicity and outcomes related to metastasis [11]. Researchers have further explored lung cancer models, prostate-related cell systems, hematological cancer cells and cancer-cell lines associated with multidrug resistance [14–16,34,36]. Differences in the extracts used, experimental methods, cell characteristics and outcome measurements also make direct comparisons between studies difficult.

An important consideration when evaluating the anticancer potential of A. muricata is whether its effects are selective for cancer cells. If a preparation damages normal cells at concentrations similar to those required to affect cancer cells, its usefulness as a potential treatment may be limited. Reporting both positive and negative findings is equally important for developing a balanced understanding of the evidence and avoiding exaggerated claims about the plant's anticancer activity [2,3,8,14].

At present, the available human evidence is insufficient to establish A. muricata as an effective cancer treatment. Personal accounts and uncontrolled observations cannot reliably demonstrate that a plant-based product caused a particular clinical outcome, especially when patients may also be receiving conventional cancer treatment or taking other supplements. It should not be described as a proven cancer cure or recommended as a replacement for evidence-based cancer treatment [3,4,50].

5. Mechanisms of Anticancer Action

Several mechanisms have been suggested to explain the biological activities of A. muricata preparations. These include disturbances in mitochondrial function, changes in proteins involved in apoptosis, cell-cycle arrest, alterations in inflammatory signalling and changes in factors associated with cell survival and migration. Therefore, these mechanisms should be considered potential explanations unless experimental studies have established a clear cause-and-effect relationship [2,3,8,10–16].

Mitochondrial energy production has received considerable attention because certain annonaceous acetogenins can inhibit mitochondrial complex I. This enzyme complex plays an important role in the electron transport chain and supports ATP production through oxidative phosphorylation. Therefore, a reduction in cell viability alone does not demonstrate that a preparation acts selectively against cancer cells [2,3,8,9].

To understand the role of mitochondria in the observed effects, researchers need to measure mitochondrial activity directly rather than depending entirely on general cell-viability tests. Useful measurements include oxygen-consumption rate, glycolytic activity, cellular ATP levels, mitochondrial membrane potential and selected indicators of cell death. Without pharmacokinetic data, the practical relevance and safety of these findings remain uncertain [2,3,8].

Apoptosis is a controlled form of cell death characterized by a series of biochemical and structural changes. Studies investigating A. muricata extracts and isolated compounds have reported alterations in caspases and proteins belonging to the BCL-2 family, suggesting that these preparations may influence pathways involved in apoptosis [12–15]. Suitable controls are also needed to distinguish apoptosis from necrosis and other forms of general cellular injury.

The cell cycle regulates the stages through which cells grow, replicate their DNA and divide. It consists of four main phases: G1, S, G2 and M. It is also important to determine whether cell-cycle arrest occurs at concentrations that do not cause extensive nonspecific cellular damage.

Inflammatory and cell-survival pathways, including NF-κB and PI3K/AKT/mTOR-associated signalling, have also been considered when examining the biological effects of natural compounds in cancer research [2,15,45]. These pathways participate in several normal cellular functions as well as disease-related processes, making it important to interpret changes in their activity carefully. However, these predictions need to be supported by experiments demonstrating direct target engagement, functional effects and reproducible findings in relevant biological models before a proposed mechanism can be considered well established [8,45].

6. Evidence from Experimental Studies

In breast cancer research, graviola fruit extract has been investigated using cell-based experiments and animal models. The findings indicated reduced cancer cell growth and a possible association with epidermal growth factor receptor expression [10]. However, results obtained in laboratory experiments cannot be directly applied to patients, nor do they establish that commercially available preparations are effective or safe for self-treatment.

In pancreatic cancer research, investigators have studied graviola-derived materials to understand their effects on cellular metabolism and tumour-related outcomes in preclinical models [11]. Research involving lung cancer cells has explored mitochondrial-mediated effects and signalling pathways associated with NF-κB. These findings should be interpreted in the context of the specific preparation, experimental conditions and methods used in each study rather than being considered evidence of a general anticancer effect.

A major challenge in translating laboratory findings into clinical applications is determining whether an effective concentration observed in a cell culture can be achieved safely in the human body. Some compounds may be poorly absorbed, rapidly metabolized, strongly bound to plasma proteins or unable to reach the tumour in sufficient amounts. Only after a specific candidate demonstrates consistent activity and an acceptable safety margin should it be considered for more advanced stages of development [2,3,6–8].

7. Safety and Toxicity

Safety evaluation is an important part of research on Annona muricata, as its potential pharmacological benefits may also be associated with certain health risks. Among its chemical constituents, annonaceous acetogenins, particularly annonacin, have received considerable attention because of their ability to inhibit mitochondrial complex I. However, the evidence currently available is not sufficient to confirm a direct causal relationship between exposure to these plant-derived compounds and neurological disorders in humans. [6,9,48].

The safety of Annona muricata preparations depends on several factors, not simply on the identity of the plant. The plant part selected, concentration of active constituents, preparation method, route of administration, dose and duration of use may all influence the potential risk. These uncertainties emphasize the importance of further research and systematic safety evaluation before the long-term use of such products can be considered acceptable [6,9].

The possible effects on the nervous system require particular attention because some acetogenins can interfere with mitochondrial function. Future studies should determine the levels of relevant acetogenins in the intended preparation and investigate their absorption, metabolism, distribution throughout the body and potential accumulation following repeated exposure. In addition, research evaluating the quality of commercially available A. muricata leaf products has identified

differences between preparations, indicating that the use of the same botanical name or product label does not necessarily guarantee a consistent chemical composition or level of exposure [7].

Other possible safety concerns also need further investigation. Research cited in this review has examined the blood-pressure-lowering effects of A. muricata in animal models, suggesting that its effects on blood pressure may be relevant when considering its use alongside prescribed medicines [38]. Findings from laboratory assays or animal experiments should therefore be regarded as preliminary indications that warrant further investigation rather than conclusive evidence of clinically significant interactions.

Patients undergoing cancer treatment may receive several medicines, including chemotherapy, endocrine therapy, targeted treatments, immunotherapy, antiemetics, analgesics and drugs for other health conditions. The use of a botanical preparation could potentially affect drug-metabolizing enzymes, transport proteins, blood pressure, glucose regulation or the occurrence of adverse effects. Such preparations should not be added to cancer treatment with the expectation that they will improve therapeutic outcomes or reduce treatment-related toxicity [6,7,50].

Before a potential Annona muricata-based medicinal product can be considered for further development, its safety should be investigated through a comprehensive toxicological assessment. This should include acute and repeated-dose toxicity, neurological effects, liver and kidney function, genotoxicity where appropriate, reproductive toxicity where relevant, and potential interactions with commonly used medicines. Until sufficient evidence establishes its safety and effectiveness, A. muricata should not be regarded as an established cancer treatment, and concentrated preparations should not be used as substitutes for standard medical care [3,6,7,50].

8. Limitations of Current Research

The available evidence has several limitations that make it difficult to draw firm conclusions about the anticancer potential of Annona muricata. One major concern is that the term “A. muricata extract” can refer to preparations with different chemical compositions. When studies do not provide details about botanical authentication, extraction yield and chemical composition, it becomes challenging to reproduce the findings or compare results across different investigations [1,4,39,40].

Another important limitation is that many reported anticancer effects have been observed in in-vitro experiments. Cell-culture studies are useful for identifying potentially active compounds and exploring their biological effects. Similarly, a reduction in cell viability does not necessarily explain how the cells were damaged or confirm the specific mechanism responsible for the observed effect [2,3,10–16].

Finally, the way experimental findings are reported and published may influence the overall interpretation of the available evidence. Studies reporting positive results may be more likely to appear in the published literature than those showing negative or inconclusive outcomes. Improving extract standardization, encouraging independent replication, making analytical data accessible and reporting negative findings are important steps towards producing more reliable evidence on the anticancer potential of A. muricata [6–8].

9. Research Gaps and Future Perspectives

Future work should begin with a clearly defined research material. Botanical authentication, a voucher specimen and complete reporting of collection and processing conditions should be paired with chemical fingerprinting and quantitative assays. This would help determine whether reported activity is associated with a particular plant part, extraction procedure or measurable constituent. Researchers should also establish whether a crude extract offers a reproducible advantage over purified compounds or whether its complexity introduces additional uncertainty [1,4,7,39,40].

Activity-guided fractionation may help identify molecules associated with a reproducible biological effect. Promising fractions should be chemically characterized, and candidate constituents should be evaluated using matched concentration ranges and appropriate controls. Tests should include multiple cancer models and relevant non-malignant cells. The objective should not be to find the material that kills cells most strongly, but to identify a candidate with a meaningful difference

between desired activity and toxicity. This distinction is especially important for compounds that interfere with mitochondrial energy metabolism [2,3,8,17–30].

Mechanistic studies should use a stepwise approach. After confirming a phenotype, researchers should test the proposed pathway directly and determine whether manipulating that pathway changes the outcome. For example, mitochondrial hypotheses could be examined using oxygen-consumption measurements, ATP assays, membrane-potential assessment and complementary cell-death endpoints. Apoptosis claims should rely on multiple validated methods. Direct target-engagement studies and independent replication would strengthen causal interpretation [8,12–15].

Pharmacokinetic and toxicological studies are essential before clinical translation. Investigators need to determine absorption, distribution, metabolism, elimination, protein binding, tissue exposure and the relationship between exposure and effect. They should assess whether concentrations associated with activity can be achieved without unacceptable neurological or systemic toxicity. Because some acetogenins have raised neurotoxicity concerns, neurological endpoints and cumulative exposure deserve particular attention. Product development should include evaluation of interactions with medicines likely to be used by the intended patient population [6–9,48].

Computational docking and network pharmacology may be useful for prioritizing compounds, targets or pathways, but their predictions should be treated as preliminary. They need confirmation through biochemical assays, cellular experiments and appropriate in-vivo models. Similarly, formulation research may eventually address solubility, stability, release and tissue distribution for a candidate compound. However, improving bioavailability can increase unwanted exposure as well as desired exposure; formulation cannot correct an intrinsically unacceptable toxicological profile [8].

If a candidate progresses, development should proceed through defined stages: reproducible manufacturing, a complete product specification, exposure-response assessment, structured preclinical toxicology and a defensible starting dose. Early clinical studies would primarily evaluate safety, tolerability, pharmacokinetics and interaction potential. The most realistic near-term contribution of this research may be the discovery and characterization of individual chemical leads rather than direct use of unstandardized plant preparations [3,6–8,50].

CONCLUSION

Annona muricata has gained considerable attention in scientific research due to its rich phytochemical composition, which includes annonaceous acetogenins, alkaloids, flavonoids and phenolic compounds. Preclinical investigations have indicated that extracts and bioactive constituents of this plant may influence several cancer-related cellular processes, such as cell survival, proliferation, apoptosis-associated signalling, cell-cycle regulation and mitochondrial activity. Studies conducted using breast, colorectal, pancreatic, lung, prostate and hematological cancer models have generated preliminary findings that support further investigation into its potential anticancer properties. [1–4,10–18,34–37].

Despite the encouraging findings, the available evidence regarding the anticancer potential of Annona muricata should be evaluated critically. Most reported results originate from in vitro studies and preclinical investigations, while variations in plant sources, extraction methods, phytochemical profiles, administered concentrations and experimental protocols make comparisons between studies challenging. At present, the limited availability of reliable clinical evidence prevents definitive conclusions regarding the therapeutic effectiveness of A. muricata in humans. [2–4,8,10–16].

Safety concerns are an essential part of the overall assessment. Some acetogenins, particularly annonacin, have been investigated in relation to mitochondrial inhibition and potential neurological toxicity. The available literature does not resolve every question about long-term human risk, but uncertainty should not be mistaken for proof of safety. Differences in the composition and quality of commercial products further complicate the assessment of exposure and risk. Possible interactions with conventional medicines also warrant evaluation, particularly for patients receiving cancer treatment [6,7,9,38,48,50].

Further progress will depend on authenticated plant material, reproducible extraction, chemical standardization, identification of active constituents, well-controlled mechanistic studies, pharmacokinetic assessment and comprehensive toxicological evaluation. Research should compare candidate activity in malignant and non-malignant cells, use appropriate exposure ranges, report negative findings and seek independent replication. Any future clinical investigation should use a defined preparation and follow accepted ethical and scientific standards.

In conclusion, A. muricata is best regarded at present as an investigational source of bioactive molecules, not as an established cancer treatment. Neither the plant nor commercial graviola products should replace or delay evidence-based oncology care. Only well-designed studies can determine whether any standardized constituent can provide a meaningful therapeutic benefit with an acceptable safety profile.

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