

Cytotoxic and Apoptotic Effects of *Annona Muricata*: A Review of In Vitro Anticancer Studies

Swathi Rani SampathiRao¹, SPD Ponamgi², KantiPriya Kondala³,
Sujatha Peela⁴

^{1,3,4}Department of Biotechnology, Dr. B. R. Ambedkar University, Srikakulam, Andhra Pradesh, India

²Department of Biotechnology, Andhra University, Visakhapatnam, India

Coessponding Author: drpsujatha@gmail.com

Abstract:

Annona muricata L. (Annonaceae), known as soursop or graviola, is a tropical plant traditionally used to manage various ailments, including cancer. Numerous in vitro studies have demonstrated its potent cytotoxic and pro-apoptotic effects against diverse human cancer cell lines. This review summarizes current in vitro evidence on the anticancer properties of *A. muricata*, emphasizing its cellular and molecular mechanisms. Phytochemical analyses identify annonaceous acetogenins, alkaloids, and phenolic compounds as key constituents responsible for selective cytotoxicity. Mechanistic studies reveal that *A. muricata* induces apoptosis through mitochondrial membrane depolarization, reactive oxygen species (ROS) generation, caspase activation, and modulation of apoptosis-related genes such as Bax, Bcl-2, and p53. While results consistently support its anticancer potential, variations in extraction methods, dosages, and cell models limit direct comparison across studies. Overall, *A. muricata* shows promising in vitro antitumor activity, warranting standardized and mechanistically driven research to enable future clinical validation.

Keywords: *Annona muricata*, apoptosis, cytotoxicity, in vitro, anticancer activity, acetogenins.

1. Introduction:

Medicinal plants have long served as an indispensable source of bioactive compounds that play a crucial role in modern drug discovery and development. Approximately 60% of currently available anticancer drugs are derived directly or indirectly from natural sources, either as pure natural products or as synthetic analogues inspired by naturally occurring molecular scaffolds (1). Within this context, *Annona muricata* L. (family Annonaceae), commonly known as soursop or graviola, has gained increasing attention for its broad spectrum of pharmacological activities and extensive use in traditional medicine. This evergreen tropical tree, native to South and Central America and now cultivated widely across Africa and Southeast Asia, has been traditionally employed in folk medicine for the management of diverse ailments such as fever, inflammation, diabetes, hypertension, parasitic infections, and cancer (2,3).

Phytochemical investigations have revealed that *A. muricata* is rich in a variety of secondary metabolites, including alkaloids, flavonoids, phenolic compounds, and a distinctive group of long-chain fatty acid derivatives known as annonaceous acetogenins (4). Among these constituents, acetogenins have been identified as the principal bioactive components responsible for the plant's potent cytotoxic and antitumor properties. Mechanistically, these compounds exert their anticancer effects primarily through inhibition of the mitochondrial NADH-ubiquinone oxidoreductase (Complex I) enzyme, leading to impaired ATP production, increased oxidative stress, and activation of the intrinsic apoptotic signaling pathway (5).

In the past two decades, numerous in vitro studies have explored the cytotoxic and pro-apoptotic potential of *A. muricata* extracts and isolated acetogenins against a wide range of human cancer cell lines, including those derived from breast, colon, prostate, lung, and liver tissues (2,6,7). These studies consistently report significant antiproliferative activity, often associated with mitochondrial membrane potential disruption, caspase cascade activation, and modulation of key apoptotic regulatory genes such as Bax, p53, and Bcl-2. However, variations in extraction techniques, assay conditions, and cancer cell models have introduced inconsistencies across studies, making it difficult to establish standardized conclusions regarding efficacy and mechanisms of action.

2. Phytochemical Constituents and Mechanisms of Action

2.1 Major Bioactive Compounds:

The pharmacological activity of *Annona muricata* is primarily attributed to its rich composition of annonaceous acetogenins, a distinctive class of long-chain fatty acid derivatives (C_{35} – C_{37}), along with other phytochemicals such as alkaloids, flavonoids, and phenolic compounds (4,5). Annonaceous acetogenins—such as annonacin, annomuricin E, and bullatacin—have been identified as the principal bioactive constituents responsible for the plant's potent cytotoxic and antitumor effects. These compounds inhibit mitochondrial NADH-ubiquinone oxidoreductase (Complex I), thereby disrupting electron transport and ATP synthesis. The resulting energy depletion triggers apoptosis, particularly in highly metabolically active cancer cells, while often sparing normal cells with lower energy demands (8).

2.2 Cytotoxic Mechanisms:

A number of in vitro studies have demonstrated that *A. muricata* extracts exert significant, dose-dependent cytotoxicity against a variety of human cancer cell lines. Ethanolic extracts from the leaves, for example, exhibited pronounced cytotoxic effects against MCF-7 breast cancer cells with an IC_{50} value of approximately 5 μ g/mL, while showing minimal toxicity toward normal kidney epithelial cells (6). Likewise, acetogenin-enriched fractions derived from the seeds and fruit pericarp have been reported to inhibit the proliferation of colon (HCT-116, HT-29) and prostate (PC-3) carcinoma cell lines through mechanisms involving mitochondrial dysfunction, oxidative stress induction, and cell-cycle arrest at the G_1 phase (7). These findings collectively highlight the selective cytotoxic potential of *A. muricata*, suggesting its promise as a natural source of anticancer agents with lower systemic toxicity.

2.3 Induction of Apoptosis:

The induction of apoptosis is a central mechanism underlying the anticancer effects of *A. muricata*. Multiple studies have documented hallmark apoptotic features in treated cancer cells, including chromatin condensation, DNA fragmentation, phosphatidylserine externalization, and activation of the caspase cascade (3). Mechanistically, *A. muricata* extracts have been shown to modulate the intrinsic

apoptotic pathway by upregulating the expression of pro-apoptotic proteins such as Bax and tumor suppressor p53, while concurrently downregulating anti-apoptotic Bcl-2 expression (8). This molecular shift promotes mitochondrial membrane depolarization, leading to the release of cytochrome c and subsequent activation of initiator caspase-9 and effector caspase-3. Furthermore, increased generation of reactive oxygen species (ROS) has been identified as an upstream signaling event that amplifies mitochondrial dysfunction and apoptotic progression.

3. Summary of In Vitro Evidence:

A substantial number of in vitro studies have explored the anticancer properties of *Annona muricata* extracts and isolated acetogenins across various human cancer cell lines. These investigations consistently demonstrate cytotoxic and pro-apoptotic activities mediated through mitochondrial dysfunction, oxidative stress, and modulation of apoptosis-related genes.

Table.1 S ummarizes key findings from representative studies highlighting the cytotoxic and apoptotic mechanisms of *A. muricata* in different cancer models.

S.No	Cell Line (Cancer Type)	Extract/Compound	Observed Effects	Reference
1	MCF-7 (Breast carcinoma)	Ethyl acetate leaf extract	Significant cytotoxicity; caspase-3 activation; downregulation of Bcl-2 expression	Gavamukulya et al., 2014
2	HT-29 (Colon carcinoma)	Acetogenin-rich fraction	ROS generation; mitochondrial membrane potential (MMP) loss; G ₁ -phase arrest	Ilango et al., 2022
3	HL-60 (Human leukemia)	Methanolic leaf extract	Induction of apoptosis; chromatin condensation; DNA fragmentation	Moghadamtousi et al., 2016
4	PC-3 (Prostate carcinoma)	Crude leaf extract	Cell-cycle arrest; upregulation of Bax; downregulation of Bcl-2	Zeng et al., 2020

Conclusion:

In summary, *Annona muricata* demonstrates significant cytotoxic and pro-apoptotic effects in a wide range of in vitro cancer models, primarily mediated through mitochondrial dysfunction, oxidative stress, and regulation of apoptotic signaling pathways. The plant's bioactive compounds, particularly annonaceous acetogenins, show strong potential as selective anticancer agents with lower toxicity toward normal cells. Despite these promising findings, considerable variation in extraction methods, concentrations, and experimental conditions limits direct comparison across studies. Furthermore, the majority of available data remain confined to in vitro systems, with insufficient in vivo and clinical evidence to confirm safety, efficacy, and pharmacokinetics. Harnessing this plant's bioactivity could contribute to the development of effective, plant-derived anticancer therapeutics.

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