



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Review Article

Anticancer Potential of *Annona squamosa* L. With a Focus on Nanoparticle-Based Therapeutics: A Systematic Review

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ARTICLE INFO

Published: 17 July 2025

Keywords:

Anticancer, *Annona*
Squamous, Phytochemicals,
Nanoparticles, Acetogenins,
Cytotoxic effects

DOI:

10.5281/zenodo.16022650

ABSTRACT

Cancer is one of the most prevalent non-communicable diseases worldwide, contributing significantly to global morbidity and mortality. It results from a combination of genetic, environmental, and lifestyle factors that lead to abnormal cell growth. Natural products from medicinal plants have gained attention for their broad pharmacological potential and reduced side effects. *Annona squamosa*, commonly known as custard apple, has been traditionally used in various cultures for its therapeutic properties. According to the results, extracts from *Annona squamosa*, particularly the seeds and leaves, have strong cytotoxic effects on a variety of cancer cell lines. To further reduce systemic toxicity, integration with nanoparticle technologies (such as polymeric carriers, silver, or gold) has demonstrated improved bioavailability and selectivity towards cancer cells. The plant's bioactive compounds especially acetogenins, alkaloids, and phenolic compounds demonstrate significant cytotoxicity across a range of cancer types. Recent research indicates that in terms of pharmacokinetics, cellular absorption, and targeted distribution, the use of nanoparticles offers a significant improvement over the conventional administration of extracts. The therapeutic value of *Annona squamosa* is supported by this review, which also highlights the possibility of employing nanotechnology to provide more potent anticancer therapies. Nevertheless, additional clinical and scientific evidence is required to support these positive findings. Recent studies show that nanoparticle delivery improves pharmacokinetics, cellular uptake, and targeted delivery, offering a significant improvement over conventional extract administration. This review supports the therapeutic relevance of *Annona squamosa* and highlights the potential of integrating nanotechnology to develop more effective anticancer treatments. However, more standardized and clinical data are required to validate these promising findings.

INTRODUCTION

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



Cancer is a complex, multifactorial disease and become one of the leading causes of death worldwide over the past several decades. The challenging goal of cancer research continuously is discovering safe and effective new natural and synthetic products with new Anticancer effects. It arises from various contributing factors and is primarily characterized by uncontrolled cellular proliferation, resistance to programmed cell death, sustained angiogenesis, and the ability to metastasize. It constitutes one of the foremost causes of morbidity and mortality worldwide, accounting for approximately 10 million deaths annually, and this number is projected to rise to around 13.1 million by the year 2030, according to global health estimates. [1] Despite notable advancements in early detection and therapeutic modalities such as chemotherapy, radiotherapy, targeted therapy, and immunotherapy treatment outcomes remain suboptimal in many cases due to issues such as non-specific cytotoxicity, multidrug resistance, and disease recurrence. These challenges have prompted growing interest in the identification of novel therapeutic agents, particularly those derived from natural sources, which may offer enhanced safety profiles and multi-targeted anticancer activity. Many studies have reported the critical roles of natural plant extracts in the development of new anticancer drugs. They have emerged as potential compounds for use as adjuvant or complementary anti-cancer drugs with fewer side effects. [2]. Plants been one of the important sources of medicines since the beginning of human civilization. There is a growing demand for plant based medicines, health products, pharmaceuticals, food supplements, cosmetics etc.[3] The Annonaceae family, comprising flowering plants, includes approximately 2,300 to 2,500 species spread across more than 130 genera. This diverse group consists of trees, shrubs, and woody climbers (lianas). While the majority of these species are

native to tropical regions, only a few are found in temperate climates. Around 900 species are native to the Neotropical region, about 450 species belong to the Afrotropical zone, and the rest are distributed across the Indo-Malayan region. In India, members of the *Annona* genus are commonly found. Among them, *Annona squamosa* L. is recognized as the most drought-tolerant species, although it does not thrive in highly humid conditions.[4] The phytochemical investigation of this plant Genus has revealed the presence of acetogenins, alkaloids, essential oils, flavonoids, terpenoids, and other chemicals.[3,5] Acetogenins (ACGs) are the major constituents of the *Annona* S. and which found to possess a variety of pharmacological properties including as antitumor, Immunosuppressive, pesticidal, antiprotozoal, antimicrobial, antimalarial, anthelmintic, and antiviral agents, with some being commercially developed for the treatment of oral herpes and treating infestations of head lice, fleas, and ticks. [5] The development of novel nanoparticle-based formulations has become increasingly important in cancer therapy due to their potential to overcome several limitations of conventional treatments. One of the key advantages of nanoparticles is their ability to deliver drugs specifically to tumor tissues, thereby minimizing toxicity to healthy cells and enhancing therapeutic efficacy.[6] This review aims to systematically evaluate the anticancer potential of *Annona squamosa*, focusing on its bioactive constituents, mechanisms of action, and the enhancement of its therapeutic efficacy through nanoparticle-based delivery systems. [7]

Importance of Natural Products in Cancer Therapy

1. Therapeutic potential

Many natural products contain phytochemicals (e.g., flavonoids, alkaloids, terpenoids) with



proven anticancer properties, capable of inducing apoptosis, inhibiting angiogenesis, and suppressing tumor growth.

2. Multi-Targeted Mechanism of Action

Unlike synthetic drugs that often target a single pathway, natural compounds can modulate multiple signaling pathways involved in cancer progression.

3. Reduced Toxicity and Side Effects

Plant-based therapies generally show lower toxicity profiles compared to conventional chemotherapeutics, making them safer for long-term use.

4. Drug Resistance Management

Natural compounds can overcome or delay the development of resistance to conventional anticancer drugs by targeting alternative cellular mechanisms.

5. Cost-Effective and Accessible

Natural sources, especially medicinal plants, are often more affordable and accessible, particularly in developing countries.

6. Complementary to Conventional Therapies

Natural products are increasingly used as adjuvants to enhance the effectiveness of existing cancer treatments and reduce associated side effects.

7. Support for Combination Therapy

Natural agents can be used alongside conventional treatments to enhance efficacy and reduce adverse effects

Plant profile

The Annonaceae family, comprising flowering plants, includes approximately 2,300 to 2,500 species spread across more than 130 genera. This diverse group consists of trees, shrubs, and woody climbers (lianas). While the majority of these species are native to tropical regions, only a few are found in temperate climates. Around 900 species are native to the Neotropical region, about 450 species belong to the Afrotropical zone, and the rest are distributed across the Indo-Malayan region. In India, members of the *Annona* genus are commonly found. Among them, *Annona squamosa* L. is recognized as the most drought-tolerant species, although it does not thrive in highly humid conditions. [4]



Fig 1:- Annona Squamous (Custard Apple) - Fruits, Leaves, Seeds, Flower, etc

The phytochemical constitution present in the *Annona squamosa* Linn. shows that the presence of acetogenins, alkaloids, flavonoids, terpenoids, cardiac glycosides, essential oils, and other chemical constituents. [3,5] Scientifically, the acetogenins (acgs) are the main materials of all the *Annona* species which own a diffusion of medicinal properties including anticancer, immunosuppressive, pesticidal, antiprotozoal, antibacterial, antimalarial, anthelmintic, and antiviral agents, with a few being evolved for the treatment along with oral herpes and remedy the infestations of head lice, fleas, and ticks, and so on. [3].

Taxonomical Classification

***Annona squamosa* L.**

Kingdom: Plantae

Division: Magnoliophyta

Class: Magnoliopsida (Dicotyledons)

Subclass: Magnoliidae

Order: Magnoliales

Family: Annonaceae (Custard-apple family)

Subfamily: Maloideae

Tribe: Abreae

Genus: *Annona* L.

Species: *Annona squamosa* L.

Common name: Custard Apple, Sugar apple

Morphological Description of *Annona squamosa* Plant

A small, semi-deciduous tree with irregular branches reaches a height of approximately 5-10 m. The bark is light brown in color, featuring noticeable leaf scars and a surface that ranges from relatively smooth to mildly fissured into plate-like sections. The inner side of bark is pale yellow which taste slightly bitter. The twigs turn brown

and are marked with light brown speckles. [8] The leaves are greenish elliptical in shape with size between 5-15 cm long. The petals, which are also hairy on both sides, measure about 25×6 mm. The fruits are spherical, size 5-10 cm in diameter with

a waxy coating on the surface, turning yellowish-green when ripe with a white, powdery bloom. [9] Their Seeds are smooth, shiny, brownish black colour 1-1.5 cm long. In an average fruit there are 30-40 seeds. [10]

Table 1:- Phytochemical Constituents of Different Parts of *Annona squamosa*

Plant Part's	Phytochemical Class	Major Compounds Identified	Reported Activity	References
Leaves	Alkaloids	Anonaine, Liriodenine, Aporphine	Anticancer, Antioxidant	11
	Flavonoids	Quercetin, Kaempferol	Anti-inflammatory, Antioxidant	32
	Tannins, Saponins	-	Astringent, Antimicrobial	44
Seeds	Acetogenins	Squamocin, Bullatacin, Annonacin	Cytotoxic, Antitumor	35,11
	Alkaloids	Asimilobine	Anticancer	46
	Cyclopeptides	Cyclosquamosins A, squamin A and B, annosquamosin A	Anticancer	3, 5
Fruits pulp	Flavonoids	Rutin, Epicatechin	Antioxidant	45
	Tannins	-	Nutritional, Antioxidant	35,11
Bark	Alkaloids	Roemerine, Norushinsunine	Antifungal, antibacterial	47
	Terpenoids	-	Antimicrobial	11
Root	Acetogenins	Rolliniastatin, Annomontacin	Antitumor, Cytotoxic	35,44
Stem	Saponins, Flavonoids	-	Antimicrobial, antioxidant	44

Anticancer Activity

Cancer is a complex and multifactorial disease marked by uncontrolled cell growth, posing a significant global health burden. Researchers have emphasized on the anti-tumor Actions of seeds, pericarp and bark of herbs, and active plant Chemicals have been identified for their anti-cancer Properties. In previous studies, a research has been carried out on *A. squamosa* against anti-cancer related non-alkaloidal moieties particularly the Acetogenin. *A. squamosa* Yielded two benzyloquinoline alkaloids. The initial confirmation of anticancer activity was obtained

using the Microculture Tetrazolium (MTT) assay. Excellent activity for colon cancer cells (HTC116) and also for Human Breast cancer cells (MCF-7) which is due to the activity of Benzyloquinoline alkaloids in these cells. [12] In *Annona squamosa* seeds, the cytotoxic Acetogenins are present which are Squadiolins A and squafosacin B and C. Squadiolins A and B exhibit significant cytotoxic effect on MDA-MB-231 breast cancer cells. Squafosacin B is also significantly toxic to human Hep G2 and 3B hepatoma and MCF-7 breast cancer cells. [13] PLAT knockdown suppressed tumor proliferation in vivo. Additionally, it impaired mitochondrial function, triggered



caspase activation and cell cycle arrest, and activated TNF- α signaling, ultimately inducing apoptosis in gefitinib-resistant PC9 cells. Annosquacin A, B and C, squamostanin A and B, and Annosqatin A, B and D, Squamostolide, bullatacin with other Constituents which have antitumor properties. Historical and Clinical Relevance Several FDA-approved anticancer drugs (e.g., paclitaxel, vincristine, camptothecin) are derived from natural sources, validating their clinical potential. [14] The study investigated that the induction of apoptosis could be possible mechanism for antiproliferative activity of biosynthesized AgNPs. The dose dependent cytotoxic activity was observed in AgNPs treated MCF-7 cells. 50% of cell death, that shows the inhibitory concentration (IC₅₀) value of biosynthesized AgNPs against MCF-7 cells holds at 50 microgram/ml in 24 h and 30 microgram/ml in 48 h. Cell viability and proliferation assays, including colorimetric and fluorometric methods, are commonly used in vitro to assess cytotoxicity and provide initial insights into anticancer activity. These assays are cost-effective and easy to perform. [15]

Mechanism of Anticancer Action of *Annona squamosa*

Annona squamosa exhibits anticancer activity through various cellular and molecular pathways, primarily mediated by its bioactive constituents such as acetogenins, flavonoids, and alkaloids.

1. Induction of Apoptosis

Compounds from *A. squamosa* activate caspase-3 and caspase-9, upregulate pro-apoptotic Bax, and downregulate anti-apoptotic Bcl-2, leading to mitochondrial dysfunction and DNA fragmentation in cancer cells.

2. Cell Cycle Arrest

Extracts have been shown to induce cell cycle arrest at G₀/G₁ or G₂/M phases, thereby inhibiting uncontrolled proliferation of cancer cells. [16]

3. Generation of Reactive Oxygen Species (ROS)

Certain phytochemicals elevate intracellular ROS levels, causing oxidative stress that damages cellular components and triggers apoptosis. [17]

4. Inhibition of Angiogenesis

A. squamosa downregulates vascular endothelial growth factor expression and inhibits endothelial cell migration, thereby suppressing new blood vessel formation essential for tumor growth

5. DNA Damage and Genotoxicity

Some compounds directly interact with DNA or disrupt replication mechanisms, resulting in DNA strand breaks and cancer cell death. [17]

6. Anti-metastatic Effects

The plant's extracts inhibit matrix metalloproteinases (MMPs), enzymes involved in extracellular matrix degradation, thus reducing cancer cell invasion and metastasis. Apoptosis is the natural mechanism for programmed cellular damage. It is specially critical in lengthy-lived mammals it serves to do away with any needless or undesirable cells and is a distinctly regulated system. There are a wide kind of situations with a purpose to result in the apoptotic pathway turning into activated consisting of DNA damage or uncontrolled proliferation. The apoptotic pathway is activated with the aid of each intracellular and extracellular alerts each pathways that correlate with the signal kind. They're additionally known as the mitochondrial and dying receptor pathways, respectively [18]. The intrinsic cell death pathway is regulated by way of b-cell lymphoma-2 (bcl-2)

circle of relatives proteins, which have both antiapoptotic or proapoptotic features the anti apoptotic bcl-2 proteins inhibit apoptosis via inhibiting proapoptotic bcl-2 own family proteins bax and bak. On the other hand, the antiapoptotic BCL-2 proteins are themselves inhibited by the BH3-only proteins (BIM, BIK, NOXA, PUMA, BID, BAD, BMF) in response to an intrinsic signal. [19]. The pathway of the mitochondria usually contains the induction of a it's permeability transition and significantly release of cytochrome C. Procaspase-9, as apoptosomes. [20]. Caspase-nine is activated by means of binding to a complex containing APAF-1 and cytochrome C, influence

by stimuli, which includes DNA damage. [21]. Caspase-3 is an effector caspase that enters the nucleus after caspase-9 activation and at once interacts with its substrate, thereby promoting mobile apoptosis. [22] Annonacin may additionally deregulate the mobile cycle arrest checkpoint to allow a most cancers cellular to enter mitosis and go through apoptosis thru caspase-mediated DNA fragmentation and also lower bcl-2, which ultimately reduce cell proliferation of cancer cells. For this reason, it may be concluded that nanoparticles of annona squamosa are found to have anti-cancers property in opposition to the cancer cells.[23]

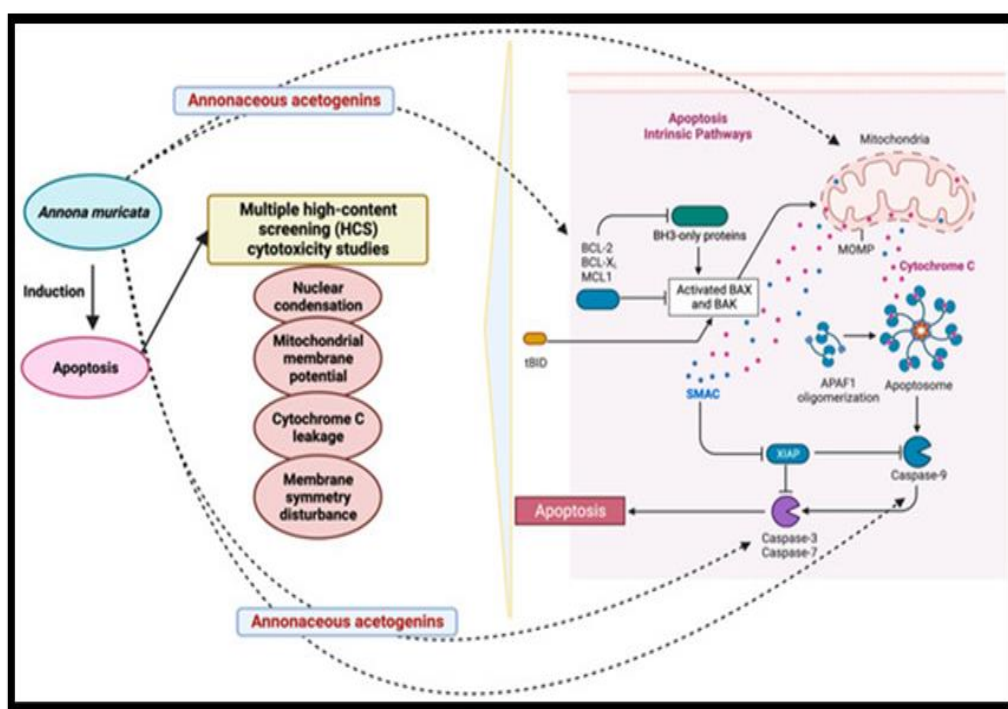


Fig 2:- Mechanism of Action of Annona Squamous L. in Apoptosis process. [25]

The presence of phytochemicals like terpenoids, flavonoids, glycosides, alkaloids and phenols have the Antioxidant property that they quench the free radicals and they work as cancer-preventive agents. Both in-vitro and in-vivo investigation showed that plant products had strong effects on stopping cell lines from multiplying and killing them. In-vivo studies showed that the extracts had

a big effect on the size of the tumors and the levels of proliferative and death markers. Developed NPS- A. squamosa leaves extract, a nanoparticle loaded with chitosan from colon cancer cells. [24] Due to the high surface area, efficient interaction nanoparticles can be utilised to target the delivery of therapeutic drugs. Nanoparticles can act as nanocarriers due to their low-cost, high surface

area, light weight, easily cross cell membrane and tissue barrier with stable and biodegradable properties. [25]

In-Vitro Anticancer Activity

In vitro studies have shown that annona squamosa seed extracts can inhibit the increase of diverse most cancers cellular strains including breast, prostate, colon, liver, and lung most cancers cells.[26] The cytotoxicity is performed at for different fractions containing the acetogenins and alkaloids, as they were which needs to be the most important lively metabolites of annona squamosa with regarded cytotoxic pastime the poisonous isolate become assayed for its anticancer activity which oppose to hela cells, which have been cultured in a medium. The number of cells are decreased. The cells have been trypsinized, harvested, and centrifuged to form layers, particularly, sediment and supernatant.[27] In a 96-well plate, accelerating development mcf-7, HepG-2, and HEK293 cells were seeded at a density of about 5×10^3 cells consistent with nicely. On the next day, cells have been treated with dose-established concentrations of agnps (5- eighty g for cancer mobile lines and 5 g to 2 hundred g for HEK 293). Coumarin (advantageous manipulate) turned into used for each cytotoxicity and pastime research. After 48hours, eliminated the supernatant. Then upload 20 μ l of mtt solution (5 mg/ml in pbs) to each properly, and incubated at 37 °c for 4 hours. Using an enzyme-linked immunoabsorbent assay (elisa) reader machine, mtt have been combined and read at 570 nm. All examined compounds' IC50 values had been assessed.[28] Finally, a hundred μ l of three-(four,five-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide (MTT) at a attention of 5 mg/ml became added at 37 °c. After 2 h of incubation in dark conditions, mtt became removed, accompanied via the addition of 100 μ l dimethyl sulphoxide to dissolve formazan crystals.

[29] This can estimate the potency of Annona Squamous silver nanoparticles to inhibit half of the percentage of the biological process in a cell. OD value was subjected to sort out percentage of viability by using the following formula

$$\text{Percentage of viability} = \frac{\text{OD value of san}}{\text{Mean OD value of control (untreated)}}$$

Mean OD value of control (untreated)

Where, OD is the mean optical density of the experimental group and control group

The results were presented as the mean $\pm$ standard deviation of three independent determinations. Statistical significance was evaluated using one-way analysis of variance (ANOVA), followed by a multiple comparison post-test to identify significant differences among groups.[30] The cell viability IC50 results are displayed as a mean $\pm$ standard deviations. Statistical significance was accepted at a level of $p < 0.05$. [31] The squadiolins A and B and squafosacin are known cytotoxic Acetogenins present in Annona Squamosa seeds exhibit cytotoxic effect on MDA-MB-231, HepG2, COLO-205 cancer cells.[32] The ZnONPs using bark of Annona Squamous has potential for breast cancer cell shows IC50 value of MCF-7 cells was estimated to be 53.10 microgram/ ml, which indicates the dose at which indicates the dose at which ZnO nanoparticles inhibit 50% of cancer cell proliferation. [33] The AgNPs using leaf of Annona Squamosa gives potential response IC50 value of hela cells was estimated to be 25 microgram/ml, represents the potency of As-AgNPs to inhibit half of the percentage of the biological process in a cell or enzyme. [31] Similarly, Annona squamosa fruits peel extract (40 ml) with SnO2 nanoparticles was evaluated for anti-tumour activity against HepG2 cell line using UV-visible spectroscopy, XRD, and TEM analysis. It was found that SnO2 nanoparticles inhibits the cell HepG2 cell line proliferation in a dose and time-dependent manner with IC50: 148



$\mu\text{g/ml}$, when compared with 5-fluorouracil which shows IC_{50} : $1.35 \mu\text{g/ml}$. [34] Using a green synthesis route, researchers have achieved IC_{50} s of 54 and 61.8 mg/L against lung cancer A-549 and colorectal cancer HT-29 cells by Cu_2O NPs, respectively. As suggested by the previous study, after the formation of reactive oxygen species (ROS), the CuNPs could promote the apoptotic activity of caspase-3 or directly attack the Cancer cells. [30] *Annona squamosa* had significant anti-tumor actions on Human epidermoid carcinoma cell line KB-3-1 and colon cancer cell line HCT-116. [32] Additional promising constituents, such as annosquacins A–D and annosquatin A and B, were isolated from the ethanol extract of *Annona squamosa* and exhibited notable anticancer activity against human tumor cells. [35] AnsTE and Ans-AgNPs exhibited the strongest cytotoxic effects on HeLa and SKOV3 cells, with IC_{50} values ranging from 0.001 ± 0.0001 to $1.6 \pm 0.1 \mu\text{g/mL}$, and the toxicity of Ans-AgNPs on PC3 cells, with

IC_{50} of 1.7 ± 0.4 . However, Ang-AgNPs demonstrated the strongest cytotoxic effect on PC3 and SKOV3 with IC_{50} 2.4 ± 0.3 and $2.8 \pm 0.23 \mu\text{g/mL}$. [36] The results revealed that the most toxic isolate, with an LC_{50} value of 100.00 ppm , exhibited potency comparable to that of an anticancer agent with an IC_{50} value of 70.9021 ppm . [27] The Study, the cytotoxic effect of the nano-ASLE against WiDr cells is investigated, Determined an IC_{50} value of $292.39 \mu\text{g/mL}$. The extracts were found to significantly increase the expression of caspase-3, Bax and bad genes, causing an arrested cell cycle at the G2/M phase and induction of WiDr apoptosis. [37] It might be caused by the particle size in form for optimizing activity of in vitro and increase the bioavailability of uncontrollable molecules. Releasing the bioactive compound with nanoparticles actually gives alternative therapeutic ways dropping the drug to specific target and decreases the toxicity effects. [16]

Table 2:- IC_{50} ($\mu\text{g/mL}$) value of *Annona squamosa* L. results different nanoparticle. [38]

Cell line	Seed (CH_2Cl_2 extract)	Leaves ($\text{C}_2\text{H}_5\text{OH}$ extract)	Pulp (50% $\text{C}_2\text{H}_5\text{OH}$ extract)	Cisplatin (Positive Control)
A549 (lung)	0.85 ± 0.00	2.40 ± 0.16	3.83 ± 0.44	0.09 ± 0.00
HCT-116 (colon)	0.33 ± 0.02	1.24 ± 0.02	1.65 ± 0.04	0.09 ± 0.11
MCF-7(Breast)	$68.4 \pm 1.6\%$	$61 \pm 1.1\%$	27.82 ± 5.50	0.09 ± 0.12

In-Vivo Anticancer Activity

In vivo studies have provided compelling evidence helping the anticancer capacity of *annona squamosa*, demonstrating its efficacy in decreasing tumor growth and improving survival prices in animal fashions. [26] 4t1 cells in logarithmic section had been suspended in rpmi medium with out fbs, and zero.2 ml cellular suspensions (1×10^7 cells/ml) have been inoculated by the subcutaneous route into the right axillary region of female BAL B/c mice. The mice had been fed in

the spf environment, and the boom of the tumor became carefully watched. While the tumor size reached approximately a hundred mm^3 , the mice had been randomly divided into four businesses ($n = 6$) as follows: regular saline (as terrible control), ptx injection (10 mg/kg , iv, as high-quality control), asso solution (one hundred thirty five mg/kg , ig), and asnps (15 mg/kg , iv). The bad manage group and the fantastic manage organization were injected via the lateral tail vein each different day 7 times. The asso solution group become orally administered every day five times,

stopped for 2 days, and then given each different day three instances. The asso-nps organization changed into given intravenously each different day three times, stopped for two days, and then given every different day three times. The volume of tumors and the mice weight have been measured every 2 days at some point of the experiment duration. The mice have been sacrificed with the aid of cervical vertebra dislocation and dissected 24 h after the final dose. The tir as equation (1), and the liver index or spleen index as equation was calculated (2).

$$\text{Tir (\%)} = (1 - w_e/w_n) \times \text{a hundred\%}. (1)$$

In which we and wn are respectively the mean tumor weight of the experimental institution and poor manage organization.

$$\text{Liver index or spleen index} = w_1/w_2. (2)$$

Wherein w1 is the imply liver or spleen weight of the experimental group, and w2 is the suggest mice weight of the poor manipulate organization. [39] The plant *Annona squamosa* traditionally known as custard apple possess potent bioactive principles in all its parts . The effect of aqueous and organic extract of seeds of plant was studied on rat histiocytictumor cell line AK- 5. [11]

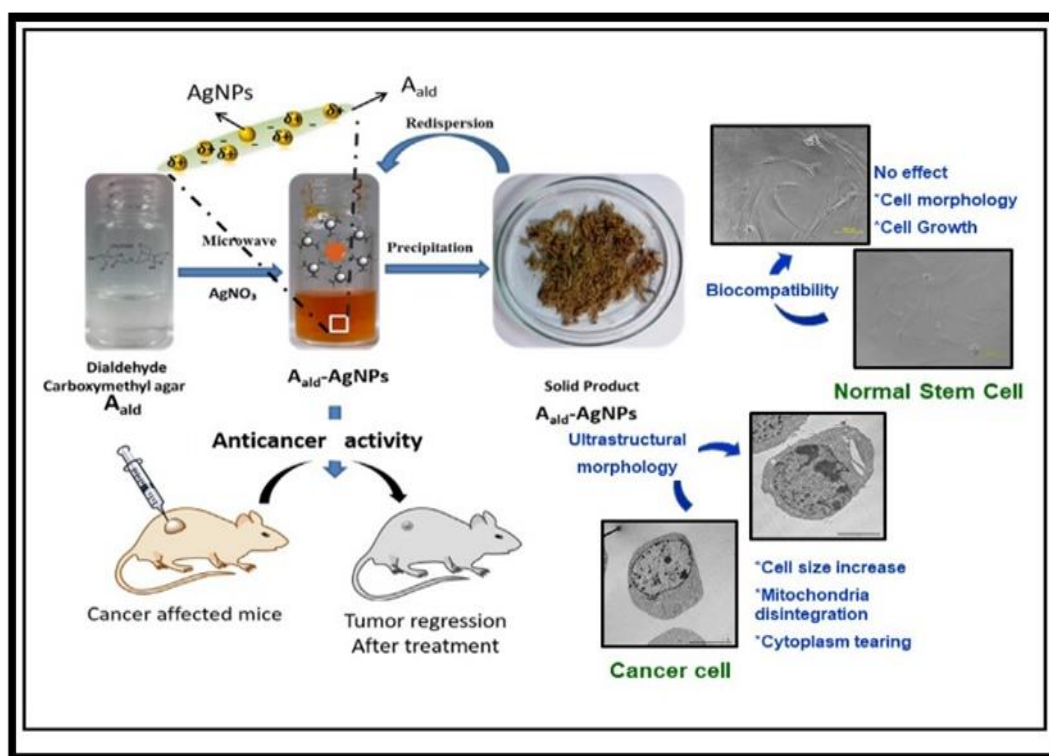


Fig3: - Representation of the IN-VIVO Anticancer Activity of AGNPS of *Annona Squamosa*

The study shows that both extract significant apoptoc tumor cell death with increase capscase - 3 activity . The extract downregulated genes Bcl-2 and Bclxi and increase generation of intracellular ROS, which corresponds perfect with decrease level of the intracellular GSH. [11] Oral administration of aqueous and ethanolic extracts at

a dose of 500 mg/kg b.w. and 300 mg/kg b.w reduced the total number of tumours and normalized the levels of Glycoconjugates in tumour-bearing animals. [40] Glycoproteins are major constituents of cell membrane, plays an important role in cell diffrentation, cell Proliferation, cell-cell interaction, carcinogenesis

and act as a receptor for many hormones and viruses measurement of serum glycoconjugates in oral pre-cancerous and cancerous lesions may be useful in the diagnosis of cancer patients and experimental animals. [41] In rats, *Annona* species leaves also showed chemo preventive potential against Azoxymethane-induced colonic aberrant crypt Foci. [42] The in vivo study confirmed that EST-bearing mice had higher levels of oxidative stress than normal mice, as indicated by increased lipid peroxidation products (MDA), decreased GSH level, and SOD activity in target tissues. In addition, loss of Mn-SOD activity or neutralization of superoxide in tumor cells and the decrease of mitochondrial number results in the decline in total SOD activity in the liver tissue of tumor-bearing mice. [43] In vivo assay showed that the asso-nps (15 mg/kg) had the very best tir of 69.Eight% have been and more than the asso answer (52.7%, one hundred thirty five mg/kg) in 4t1 tumor-bearing mice. Besides, asso-nps had terrific capacity as tumor-targeted transport automobiles. In vivo distribution facts confirmed that the rtti of (acgs and asso)-nps turned into 1.47-fold that of acgs added by myself. [39].

Future prospects

The exploration of *Annona squamosa* for its anticancer potential has gained considerable interest, particularly with the advent of green nanotechnology. The biosynthesis of silver nanoparticles (AgNPs) using *Annona squamosa* seed extract offers a sustainable and eco-friendly approach that combines the phytochemical richness of the plant with the enhanced therapeutic properties of nanomaterials. Future research should focus on the standardization of nanoparticle synthesis protocols, ensuring reproducibility in size, shape, and stability, which are critical for consistent biological activity. Advanced characterization techniques, including high-resolution electron microscopy and surface

plasmon resonance analysis, should be employed to better understand the physicochemical properties of these bio-nanoconjugates. Additionally, in-depth mechanistic studies are needed to elucidate how these silver nanoparticles exert cytotoxic effects at the molecular level—whether through ROS generation, DNA damage, mitochondrial disruption, or modulation of key signaling pathways involved in cancer progression. Another important area for future investigation is the in vivo efficacy and toxicity profiling of these nanoparticles. While in vitro results are promising, thorough preclinical testing is necessary to assess biocompatibility, biodistribution, and potential off-target effects. Finally, integrating computational modeling and systems biology can help predict nanoparticle interactions within biological systems, optimizing their design for maximum therapeutic benefit with minimal adverse effects.

CONCLUSION

The present review highlights the significant anticancer potential of *Annona squamosa*, attributed to its rich phytochemical composition, including alkaloids, acetogenins, flavonoids, and phenolic compounds. These bioactive constituents have demonstrated promising cytotoxic, pro-apoptotic, and anti-proliferative effects against various cancer cell lines in vitro, suggesting a strong foundation for further exploration.

Moreover, the integration of *Annona squamosa* in the green synthesis of silver nanoparticles presents an innovative and eco-friendly approach that enhances the plant's therapeutic efficacy. These biologically synthesized nanoparticles exhibit improved anticancer activity due to their unique physicochemical properties and ability to target cancer cells more effectively. Despite these encouraging findings, most studies remain confined to in vitro models, with limited in vivo and clinical data available. Therefore, further



research focusing on detailed mechanistic studies, standardized nanoparticle study, toxicity assessment, and clinical validation is imperative.

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HOW TO CITE: Vaishnavi Chaudhari*, Dr. Jyoti Wagh, Pratiksha Waghmare, Anticancer Potential of *Annona squamosa* L. With a Focus on Nanoparticle-Based Therapeutics: A Systematic Review, *Int. J. of Pharm. Sci.*, 2025, Vol 3, Issue 7, 2392-2406. <https://doi.org/10.5281/zenodo.16022650>

