RESEARCH PAPER

An Integrative Review of *Annona squamosa*: From Ethnomedicinal Knowledge to Phytochemical Characterization and Modern Pharmacological Validation

[1]Brijesh Kumar Saroj*, [2]Peeyush Kumar Sharma, [3]Kaneez Fatima, [4]Ambrish Kumar Singh

[1]Research Scholar, Faculty of Pharmacy, Maulana Azad University, Bujhawar, Luni, Jodhpur, Rajasthan. 342001
Email- brijeshkumarsaroj9@gmail.com

[2]Professor in Pharmaceutics, Faculty of Pharmacy, Maulana Azad University, Bujhawar, Luni, Jodhpur, Rajasthan. 342001
Email- pharmacy.mau@gmail.com

[3]Associate Professor, Ayesha College of Pharmacy, Gulbarga , 585104, Karnataka.

[4]Faculty of Pharmacy, Institute of Medical Sciences, Rajeev Gandhi South Campus, Banaras Hindu University, Barkachha, Mirzapur - 231 001, India

Corresponding Author
[1]Brijesh Kumar Saroj*,
[1]Research Scholar, Faculty of Pharmacy, Maulana Azad University, Bujhawar, Luni, Jodhpur, Rajasthan. 342001
Email- brijeshkumarsaroj9@gmail.com
Orcid:- 0009-0005-9577-7051

Abstract

Annona squamosa L., commonly known as custard apple or sugar apple, is a tropical medicinal plant widely used in traditional systems of medicine for the treatment of infections, inflammation, metabolic disorders, and neurological conditions. In recent decades, scientific investigations have validated many of its ethnomedicinal claims, revealing a diverse phytochemical composition rich in acetogenins, alkaloids, flavonoids, phenolic compounds, and terpenoids. These constituents exhibit significant antioxidant, antimicrobial, antidiabetic, anti-inflammatory, anticancer, and neuroprotective activities. Despite promising pharmacological evidence, translational research remains limited, and challenges related to standardization, toxicity, and clinical validation persist. This review critically compiles botanical, phytochemical, pharmacological, and toxicological data on *Annona squamosa*, emphasizing its therapeutic potential and research gaps. The review further discusses pharmaceutical and nutraceutical applications and highlights future research directions necessary to develop standardized phytopharmaceuticals from this plant. The integration of traditional knowledge with modern pharmacology suggests that *Annona squamosa* represents a valuable candidate for novel drug discovery and functional health products.

Keywords: *Annona squamosa*; phytochemistry; antidiabetic activity; antioxidant mechanism; medicinal plant pharmacology

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1. Introduction

Medicinal plants continue to serve as a foundational resource for drug discovery and public health, particularly in regions where traditional medicine remains the primary healthcare system. Approximately 80% of the global population relies on plant-derived remedies, underscoring the importance of ethnopharmacological knowledge as a guide for modern therapeutic innovation. Among these medicinal plants, species belonging to the Annonaceae family have attracted considerable attention due to their unique bioactive metabolites, especially annonaceous acetogenins, which demonstrate potent biological activities (Anand et al., 2022; Banerjee et al., 2018; Kasote et al., 2017; Malik et al., 2022; Mulat et al., 2019; Singh & Bharadvaja, 2021; Srivastava et al., 2018).

Annona squamosa L. is one of the most widely cultivated and medicinally significant species of the genus *Annona*. It is

**Author for Correspondence:*

valued both as a nutritional fruit and as a therapeutic plant. Traditional medical systems across Asia, Africa, and South America have used different parts of the plant-including leaves, bark, seeds, and roots, for treating fever, dysentery, diabetes, inflammation, parasitic infections, and nervous disorders. These long-standing uses have stimulated pharmacological investigations that confirm a broad spectrum of bioactivities (Abd-Elghany et al., 2022; Harahap et al., 2022; Lele et al., 2025). The renewed scientific interest in *Annona squamosa* arises from three major factors. First, the global burden of chronic diseases such as diabetes, cancer, and neurodegenerative disorders necessitates safer and more effective therapies. Second, plant-derived compounds often exhibit multi-target mechanisms, making them attractive candidates for complex disease management. Third, advances in phytochemical analysis and biotechnology allow precise identification and standardization of bioactive constituents (Abd-Elghany et al., 2022; Leite et al., 2020; Qi et al., 2025; Rangel et al., 2026; Shi et al., 2025; T et al., 2025). This review aims to provide a comprehensive and updated synthesis of the botanical characteristics, ethnomedicinal relevance, phytochemistry, pharmacological evidence, safety considerations, and therapeutic prospects of *Annona squamosa*. By integrating traditional knowledge with modern research findings, this article identifies opportunities and limitations in translating this plant into evidence-based pharmaceutical and nutraceutical applications.

2. Botanical Description and Taxonomy

Annona squamosa belongs to the family Annonaceae, a group of flowering plants known for aromatic and bioactive species. The plant is a small deciduous tree or shrub that grows up to 6–8 meters in height. It is widely cultivated in tropical and subtropical climates and thrives in well-drained soils with moderate rainfall (Bisht et al., 2025; Can-Cauich et al., 2025; Lele et al., 2025; Li et al., 2024; Mobasher et al., 2024; Rodrigues et al., 2024; T et al., 2025). The leaves are simple, oblong-lanceolate, and aromatic when crushed. Flowers are greenish-yellow and pendulous, with three outer fleshy petals. The fruit is a segmented aggregate berry with a characteristic scaly appearance, containing sweet pulp and numerous black seeds. The seeds are toxic and contain bioactive acetogenins with insecticidal properties (Bisht et al., 2025; Can-Cauich et al., 2025; Lele et al., 2025; T et al., 2025).

Table 1. Taxonomic Classification of *Annona squamosa*

Rank	**Classification**
Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Magnoliales
Family	Annonaceae
Genus	*Annona*
Species	*Annona squamosa* L.

The plant is known by various vernacular names including custard apple, sugar apple, sharifa, and sitaphal. Its widespread cultivation has contributed to its integration into multiple traditional healthcare systems (Dey et al., 2023; Di Giulio et al., 2023; Ko et al., 2020; Leite et al., 2020).

Figure 1. Botanical morphology of *Annona squamosa* showing leaves, flowers, and fruit structure.

3. Ethnomedicinal Uses

The ethnomedicinal relevance of *Annona squamosa* is deeply rooted in traditional healthcare systems across Asia, Africa, and Latin America, where the plant has been valued as both a therapeutic and nutritional resource. Indigenous knowledge systems have preserved extensive practical experience regarding the medicinal utility of its leaves, bark, roots, fruit, and seeds. These uses were not random but developed through generations of empirical observation, reflecting an early understanding of plant bioactivity that modern pharmacology has begun to validate (Abd-Elrazek et al., 2021; Ansari et al., 2020; Ma, Chen, et al., 2017; Patle et al., 2021; Vikas et al., 2019). The leaves are among the most frequently used medicinal parts. Traditional healers commonly prepare leaf decoctions for external application in wounds, ulcers, abscesses, and inflammatory skin conditions. Poultices made from crushed fresh leaves are applied directly to affected areas to reduce swelling and accelerate healing. In some communities, leaf infusions are consumed to manage fever, digestive disturbances, and mild infections. The anti-inflammatory and antimicrobial reputation of the leaves is widely recognized in folk medicine (Y. Miao et al., 2016; Y. J. Miao et al., 2016; Tu et al., 2016).

The fruit pulp is consumed not only as food but also as a restorative tonic. It is traditionally given to individuals recovering from illness to improve strength and digestion. In

tropical cultures, the fruit is considered cooling and nourishing, supporting hydration and gastrointestinal health. Its use as a convalescent food highlights the overlap between nutrition and medicine in traditional systems (Baker et al., 2017; Bonneau et al., 2017; Chai et al., 2017; Chatatikun & Chiabchalard, 2017). Bark and root extracts occupy a distinct role in internal medicine. Decoctions prepared from bark are used in treating fever, diarrhoea, and parasitic infections. Root infusions are employed in dysentery and intestinal disorders, suggesting antimicrobial and astringent properties. Some traditional practitioners also use bark preparations for managing toothache and inflammatory pain (Anuragi et al., 2016; Santos et al., 2016; Tu et al., 2016).

Seeds represent a unique case within the ethnomedicinal profile of *Annona squamosa*. Despite their known toxicity, traditional medicine has utilized powdered seeds as a topical insecticide and anti-parasitic agent. They are applied externally for treating lice infestations and skin parasites. Importantly, indigenous medical traditions strongly caution against internal consumption of seeds, demonstrating early awareness of their toxic potential (Chel-Guerrero et al., 2018; Chen et al., 2016; Silva & Sirasa, 2018). In Ayurvedic medicine, *Annona squamosa* is described as cooling in nature, digestive, and restorative. It is believed to balance bodily humors and support general vitality. Southeast Asian folk medicine attributes additional roles to the plant in diabetes management and nervous system disorders, where leaf extracts are consumed to stabilize blood sugar and calm neurological agitation. These uses align with contemporary pharmacological findings suggesting antidiabetic and neuroprotective activity (Chel-Guerrero et al., 2018; Chen et al., 2016; Silva & Sirasa, 2018).

Ethnobotanical surveys across different geographic regions reveal consistent patterns of application, reinforcing the credibility of traditional knowledge. The convergence of uses, particularly in inflammation, infection, digestive disorders, and metabolic regulation, indicates a broad therapeutic spectrum that attracted scientific investigation. Many modern pharmacological studies have indeed confirmed the antioxidant, antimicrobial, anti-inflammatory, and hypoglycaemic effects of leaf and seed extracts, validating centuries of empirical practice.

Table 2. Traditional Uses of Different Parts of *Annona squamosa*

Plant Part	**Traditional Use**	**Preparation Method**
Leaves	Wounds, inflammation, ulcers	Decoction / paste
Bark	Fever, diarrhoea	Boiled extract
Roots	Dysentery	Infusion
Fruit pulp	Nutritional tonic	Fresh consumption
Seeds	Insecticidal / anti-parasitic	Powdered application

These ethnomedicinal records provided the foundation for modern pharmacological investigations, many of which confirmed the biological activity of leaf and seed extracts. The continuity between traditional practice and laboratory validation underscores the importance of ethnopharmacology as a guide for drug discovery (Leite et al., 2020; Quílez et al., 2018).

4. Phytochemical Profile

The therapeutic versatility of *Annona squamosa* is closely linked to its rich and chemically diverse secondary metabolite composition. Extensive phytochemical investigations over the past several decades have revealed that the plant contains multiple bioactive compound classes with distinct pharmacological properties. These compounds are distributed unevenly across plant parts, with leaves and seeds being particularly rich in pharmacologically active constituents. The synergy between these phytochemicals is believed to contribute to the plant's broad-spectrum biological activity (Aati et al., 2025; Can-Cauich et al., 2025; Kifle et al., 2025; Leite et al., 2020; Rangel et al., 2026; Yassin et al., 2025). Among the identified metabolites, annonaceous acetogenins are the most characteristic and chemically distinctive constituents of the Annonaceae family. These compounds are long-chain fatty acid derivatives typically containing tetrahydrofuran or tetrahydropyran rings and terminal lactone groups. Structurally, they are highly lipophilic and exhibit strong biological activity through inhibition of mitochondrial complex I, leading to disruption of cellular ATP production. This mechanism explains their cytotoxic effects against tumor cells as well as their pesticidal and insecticidal properties. Compounds such as squamocin, annonacin, and bullatacin have attracted considerable interest as lead molecules in anticancer research due to their selective toxicity toward rapidly dividing cells (Aati et al., 2025; Can-Cauich et al., 2025; Kifle et al., 2025; Leite et al., 2020; Rangel et al., 2026; Yassin et al., 2025).

Alkaloids represent another important phytochemical group in *Annona squamosa*. Isoquinoline and aporphine alkaloids such as anonaine, liriodenine, and norcorydine have been isolated from leaves and bark. These nitrogen-containing compounds exhibit antimicrobial, analgesic, and neuroactive effects. Some alkaloids demonstrate central nervous system activity,

suggesting potential roles in neuroprotection and modulation of neurotransmitter pathways. Their antimicrobial activity supports traditional use in treating infections and inflammatory conditions (Can-Cauich et al., 2025; Kifle et al., 2025). Flavonoids and phenolic acids are abundant in the leaf extracts and contribute significantly to antioxidant and anti-inflammatory activity. Quercetin derivatives, kaempferol glycosides, and catechin-like compounds neutralize reactive oxygen species and protect cellular membranes from oxidative damage. Phenolic acids such as gallic acid and chlorogenic acid act as free radical scavengers and metal chelators, further enhancing antioxidant defence. These compounds are particularly relevant in chronic disease prevention, where oxidative stress plays a central pathogenic role (Aati et al., 2025; Qi et al., 2025; Rangel et al., 2026; Rangel et al., 2025).

Terpenoids and essential oils constitute another class of bioactive metabolites present in the aerial parts of the plant. Monoterpenes and sesquiterpenes isolated from leaf oil exhibit antimicrobial and anti-inflammatory properties. Although present in smaller quantities compared to phenolics and acetogenins, terpenoids contribute to the plant's aroma and therapeutic potential. Some terpenoid fractions also demonstrate insect-repellent activity, complementing the pesticidal role of seed acetogenins (Al Kazman et al., 2023; Ma et al., 2024; Ma et al., 2019). Modern analytical technologies have enabled precise characterization of these compounds. High-performance liquid chromatography (HPLC) is widely used for quantitative profiling of flavonoids and phenolics. Liquid chromatography–mass spectrometry (LC–MS) provides structural identification of acetogenins and alkaloids, while gas chromatography–mass spectrometry (GC–MS) is particularly effective for volatile terpenoid analysis. Spectroscopic techniques such as NMR and FTIR further support structural elucidation. These tools have facilitated the development of phytochemical fingerprints that are essential for standardization and quality control of herbal preparations (Ma, Wang, et al., 2017; Ma et al., 2019; Y. Miao et al., 2016). The phytochemical complexity of *Annona squamosa* suggests that its therapeutic effects arise not from a single compound but from a multi-component system acting through complementary mechanisms. This chemical diversity supports its use in traditional medicine and positions the plant as a valuable resource for drug discovery, nutraceutical development, and phytopharmaceutical standardization.

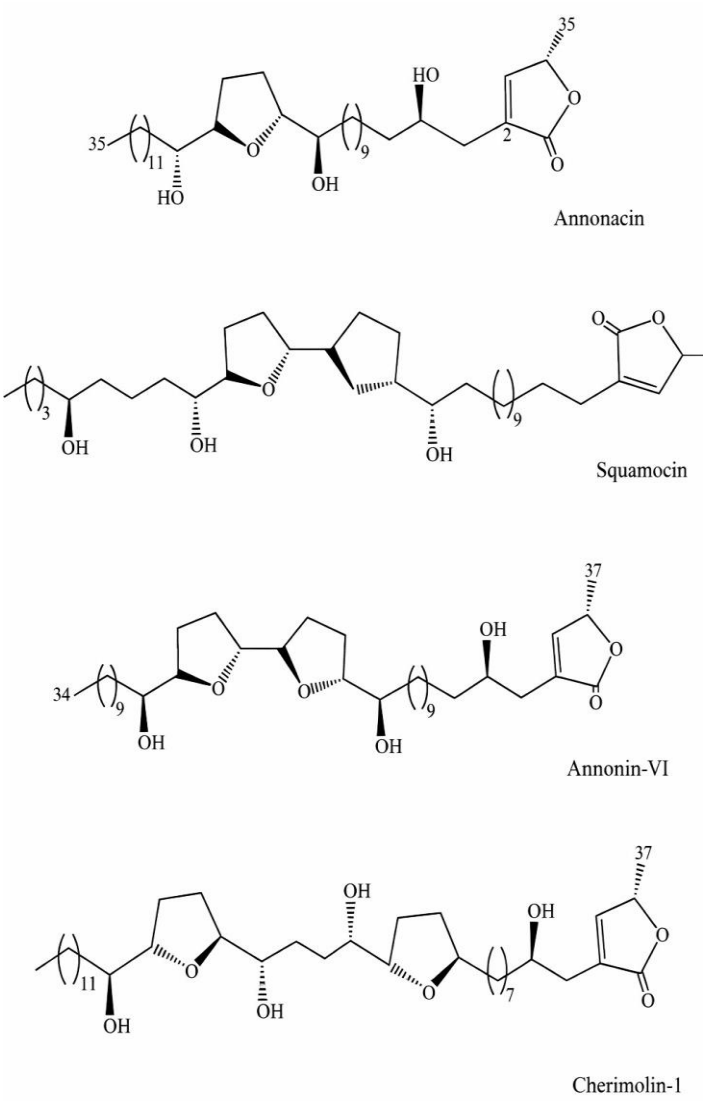

Figure 2. Chemical structures of key acetogenins and flavonoids isolated from *Annona squamosa*.

Table 3. Major Phytochemical Classes in *Annona squamosa*

Phytochemical Class	Representative Compounds	Reported Activity
Acetogenins	Squamocin, annonacin	Anticancer, insecticidal
Alkaloids	Anonaine, liriodenine	Antimicrobial
Flavonoids	Quercetin derivatives	Antioxidant
Phenolics	Gallic acid	Anti-inflammatory
Terpenoids	Essential oils	Antimicrobial

The identification of these phytochemical classes has provided a mechanistic basis for the pharmacological activities reported in experimental studies, reinforcing the scientific validity of traditional medicinal applications.

5. Pharmacological Activities

5.1 Antioxidant Activity

Oxidative stress is implicated in aging, cancer, diabetes, and neurodegenerative diseases. Extracts of *Annona squamosa* leaves demonstrate strong free radical scavenging activity in DPPH, ABTS, and FRAP assays. The antioxidant capacity correlates with total phenolic and flavonoid content. Animal studies suggest that leaf extracts enhance endogenous antioxidant enzymes such as superoxide dismutase and catalase (Almarri et al., 2023; Leite et al., 2021).

Table 4. Antioxidant Studies on *Annona squamosa*

Extract Type	Model Used	Key Findings
Methanolic leaf extract	DPPH assay	High radical scavenging activity
Aqueous extract	FRAP assay	Strong reducing power
In vivo rat model	Oxidative stress model	Increased antioxidant enzymes

5.2 Antidiabetic Activity

Several studies report hypoglycaemic effects of *Annona squamosa* leaf extracts in diabetic animal models. Mechanisms include enhanced insulin secretion, inhibition of carbohydrate-digesting enzymes, and improved glucose uptake. Flavonoids are believed to contribute to pancreatic protection and insulin sensitization (Ansari et al., 2020; Kumar et al., 2021; Moussa et al., 2024).

5.3 Antimicrobial Activity

Microbial resistance to conventional antibiotics has intensified interest in plant-derived antimicrobials. Extracts of *Annona squamosa* demonstrate broad-spectrum antimicrobial activity against Gram-positive and Gram-negative bacteria as well as fungal pathogens. Methanolic and ethanolic leaf extracts exhibit inhibitory effects against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida albicans*. The antimicrobial mechanism is believed to involve disruption of microbial cell membranes and interference with enzymatic pathways (Khan et al., 2024; Mokhtar et al., 2022). Seed extracts show particularly strong pesticidal and antiparasitic effects due to acetogenins, which inhibit mitochondrial complex I in target organisms. This bioactivity supports the plant's traditional use as an insecticidal agent (Alaqeel et al., 2023; Ma et al., 2024).

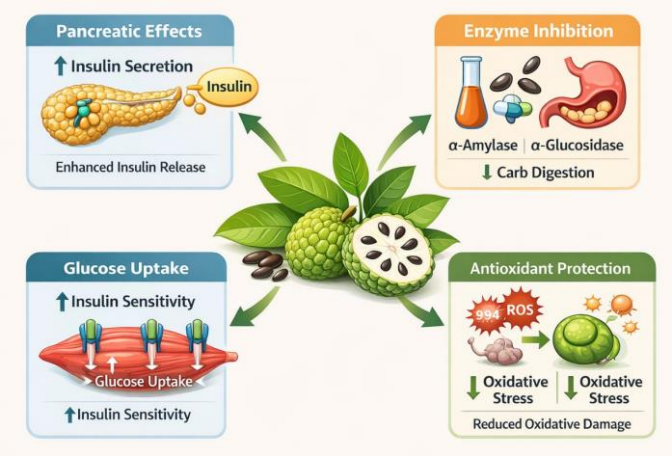

Figure 3. Proposed mechanisms of antidiabetic action of *Annona squamosa* phytochemicals

5.4 Anti-inflammatory Activity

Inflammation is a central component of many chronic diseases. Experimental models demonstrate that *Annona squamosa* leaf extracts significantly reduce edema, leukocyte migration, and inflammatory cytokine production. Flavonoids and phenolic compounds inhibit cyclooxygenase (COX) and lipoxygenase pathways, thereby suppressing prostaglandin synthesis (Al-Zubaidi et al., 2025; Li et al., 2024). In vivo studies using carrageenan-induced paw edema models confirm dose-dependent anti-inflammatory activity comparable to standard non-steroidal anti-inflammatory drugs. These findings align with ethnomedicinal use in treating swelling and inflammatory wounds (Abd-Elrazek et al., 2021; Ito et al., 2024; Vibhute et al., 2023).

5.5 Anticancer Activity

The anticancer potential of *Annona squamosa* is primarily attributed to annonaceous acetogenins. These compounds exhibit selective cytotoxicity against tumor cells by inhibiting mitochondrial respiration and inducing apoptosis. In vitro studies demonstrate strong activity against breast, liver, colon, and lung cancer cell lines (Alaqeel et al., 2023; Balkrishna et al., 2023; Shehata et al., 2021; Swantara et al., 2022). Mechanistic investigations reveal activation of apoptotic pathways, disruption of ATP synthesis, and inhibition of tumor cell proliferation. Importantly, some acetogenins show higher toxicity toward malignant cells than normal cells, suggesting therapeutic selectivity (Al-Ghazzawi, 2019; Fadholly et al., 2019; Vikas et al., 2019).

Table 5. Summary of Pharmacological Activities of *Annona squamosa*

Activity	Plant Part Used	Experimental Model	Key Outcome
Antioxidant	Leaves	In vitro assays	High radical scavenging

Antidiabetic	Leaves	Diabetic rat model	Reduced blood glucose
Antimicrobial	Leaves, seeds	Bacterial cultures	Growth inhibition
Anti-inflammatory	Leaves	Paw edema model	Reduced inflammation
Anticancer	Seeds, leaves	Cancer cell lines	Cytotoxic activity

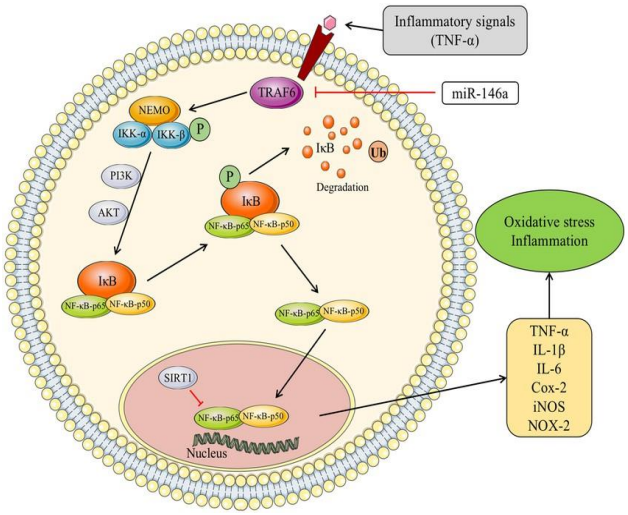

Figure 4. Integrated pharmacological pathways of *Annona squamosa* bioactive compounds in oxidative stress, inflammation, and metabolic regulation.

5.6 Neuroprotective Activity

Neurodegenerative diseases are often associated with oxidative stress and neuroinflammation. Preliminary studies indicate that *Annona squamosa* extracts protect neuronal cells from oxidative damage and improve cognitive performance in animal models. Alkaloids and flavonoids may contribute to cholinesterase inhibition and neuroprotection (Kazman et al., 2020; Leite et al., 2021; Li et al., 2024; Tundis et al., 2017). However, caution is warranted because certain acetogenins have been linked to neurotoxicity in excessive exposure. This dual nature underscores the importance of dose standardization and safety evaluation.

5.7 Hepatoprotective and Cardioprotective Effects

Leaf extracts exhibit hepatoprotective effects against chemically induced liver injury by reducing lipid peroxidation and restoring antioxidant enzymes. Similarly, cardioprotective activity has been observed through lipid profile modulation and reduction of oxidative stress markers. These effects suggest potential benefits in metabolic syndrome and cardiovascular disorders (Ma, Chen, et al., 2017; Zahid et al., 2020).

Table 6. Comprehensive Evidence Matrix of Experimental Studies on *Annona squamosa*: Extract Type, Model, Mechanism, and Key Outcomes.

Study Focus	Plant Part	Extract / Compound	Experimental Model	Dose / Concentration	Mechanism Proposed	Key Findings	Therapeutic Implication
Antioxidant	Leaves	Methanolic extract	DPPH, ABTS, FRAP assays	50–500 µg/mL	Phenolic radical scavenging	Strong dose-dependent antioxidant activity	Potential anti-aging and oxidative disease protection
Antioxidant (in vivo)	Leaves	Aqueous extract	Rat oxidative stress model	200 mg/kg	Upregulation of SOD & catalase	Reduced lipid peroxidation	Organ protection under oxidative stress
Antidiabetic	Leaves	Hydroalcoholic extract	Streptozotocin diabetic rats	250 mg/kg	Enhanced insulin secretion	Significant blood glucose reduction	Adjunct diabetes therapy
Antidiabetic	Leaves	Flavonoid fraction	Enzyme inhibition assay	IC50 < 100 µg/mL	α-amylase inhibition	Reduced carbohydrate digestion	Glycaemic control

Antimicrobial	Leaves	Ethanolic extract	Bacterial cultures	25–200 µg/mL	Membrane disruption	Inhibited *S. aureus*, *E. coli*	Natural antimicrobial agent	Neuroprotective	Leaves	Alkaloid fraction	Memory impairment model	100 mg/kg	Cholinesterase inhibition	Improved cognitive performance	Alzheimer's adjunct therapy
Antifungal	Seeds	Acetogenin-rich fraction	*Candida albicans* culture	50 µg/mL	Mitochondrial inhibition	Strong antifungal activity	Antifungal drug candidate	Hepatoprotective	Leaves	Aqueous extract	CCl4 liver injury model	200 mg/kg	Antioxidant enzyme restoration	Reduced liver damage markers	Liver protective agent
Anti-inflammatory	Leaves	Methanolic extract	Paw edema model	200 mg/kg	COX inhibition	Reduced edema comparable to NSAIDs	Anti-inflammatory herbal therapy	Cardioprotective	Leaves	Flavonoid-rich extract	Hyperlipidemic rats	250 mg/kg	Lipid regulation	Lower cholesterol & triglycerides	Cardiovascular health support
Anti-inflammatory	Leaves	Phenolic fraction	Cytokine assay	—	TNF-α suppression	Lower inflammatory markers	Chronic inflammation management	Insecticidal	Seeds	Crude seed powder	Agricultural pest model	—	Mitochondrial toxicity	High insect mortality	Botanical pesticide
								Wound healing	Leaves	Topical paste	Dermal wound model	—	Anti-inflammatory + antioxidant	Accelerated tissue repair	Herbal dermatology
Anticancer	Seeds	Squamocin	Breast cancer cell line	IC50 2–5 µM	Apoptosis induction	Selective tumor cytotoxicity	Chemotherapeutic lead compound								
Anticancer	Leaves	Acetogenin mix	Colon cancer cells	—	ATP synthesis inhibition	Tumor growth suppression	Targeted cancer therapy								

6. Toxicological Considerations and Safety Profile

Although *Annona squamosa* demonstrates substantial therapeutic promise, its safety profile warrants careful evaluation due to the presence of potent bioactive metabolites, particularly annonaceous acetogenins. These compounds are biologically active mitochondrial inhibitors, and while their cytotoxicity is beneficial in anticancer research, uncontrolled exposure may pose toxicological risks. The dual nature of

these phytochemicals highlights the importance of dose regulation and proper extraction practices (Ito et al., 2024; Qi et al., 2025). Seeds contain the highest concentration of acetogenins and are considered the most toxic part of the plant. Experimental toxicology studies suggest that excessive exposure to seed-derived acetogenins may induce neurotoxic effects through inhibition of neuronal energy metabolism. Chronic exposure to annonaceous compounds in other Annonaceae species has been associated with atypical neurodegenerative syndromes in epidemiological reports. Traditional medical systems demonstrate an early understanding of this risk by restricting seed use to topical insecticidal or anti-parasitic applications and explicitly discouraging ingestion (Al Kazman et al., 2023; Ma et al., 2024; Ma et al., 2019). In contrast, leaf extracts appear to exhibit a wider safety margin when prepared using controlled methods. Subacute animal toxicity studies involving aqueous and hydroalcoholic leaf extracts generally report no significant alterations in liver enzymes, renal function markers, or hematological parameters at therapeutic doses. Histopathological examination of major organs typically shows preserved tissue architecture, suggesting that properly standardized leaf preparations may be safe for short-term medicinal use (Al Kazman et al., 2022; Leite et al., 2020).

However, the absence of long-term toxicity data remains a major limitation. Chronic exposure studies are scarce, and there is insufficient information regarding cumulative toxicity, reproductive safety, or potential teratogenic effects. Herbal medicines are often consumed over extended periods, making long-term evaluation essential. Additionally, phytochemical variability due to geography, harvest season, and extraction method may influence acetogenin concentration, thereby altering safety profiles between preparations. Standardization of herbal extracts is therefore critical. Controlled extraction procedures can significantly reduce toxic constituents while preserving therapeutic compounds. Modern quality control approaches recommend chromatographic fingerprinting and marker compound quantification to ensure reproducible safety and efficacy. Without such measures, variability in crude extracts may lead to unpredictable toxicological outcomes (Qi et al., 2025; Quílez et al., 2018).

Regulatory authorities increasingly require rigorous safety documentation for herbal products. International frameworks emphasize genotoxicity testing, reproductive toxicity assessment, and long-term carcinogenicity studies. Pharmacovigilance systems are also necessary to monitor adverse events in real-world use. Until comprehensive clinical safety data are available, therapeutic application of *Annona squamosa* should prioritize standardized leaf extracts and avoid ingestion of seed-derived products. The current evidence suggests that the plant can be used safely within defined boundaries, but scientific caution remains essential. Bridging the gap between traditional knowledge and modern toxicology will require systematic safety evaluation and clinical validation.

Table 7. Toxicological Profile and Safety Assessment of *Annona squamosa*

Plant Part	**Major Toxic Constituents**	**Reported Toxic Effect**	**Evidence Source**	**Safety Recommendation**
Seeds	Acetogenins	Neurotoxicity at high exposure	Experimental toxicology studies	External use only
Leaves	Low acetogenin levels	No significant organ toxicity at therapeutic dose	Subacute animal studies	Safe when standardized
Bark	Alkaloids, phenolics	Limited data	Ethnobotanical records	Use cautiously
Roots	Mixed phytochemicals	Insufficient data	Traditional use reports	Requires study
Fruit pulp	Minimal toxic compounds	Considered safe food	Nutritional consumption	Safe as dietary fruit

This toxicological overview underscores the importance of standardized preparation, controlled dosing, and further clinical research. Proper scientific evaluation will determine how *Annona squamosa* can transition safely from traditional remedy to regulated phytopharmaceutical product.

7. Pharmaceutical and Nutraceutical Applications

The phytochemical richness of *Annona squamosa* positions it as a promising candidate for pharmaceutical development. Extracts can be formulated into antioxidant supplements, antidiabetic nutraceuticals, and topical anti-inflammatory preparations. Modern drug delivery systems, including nanoformulations, could enhance bioavailability and targeted delivery of active constituents (Aati et al., 2025; "Correction to "GC-MS Profiling and In Vitro and Silico Evaluation of Biological Propensities of Saudi Cultivar of Sugar Apple (Annona squamosa L.): A Preliminary Multidimensional

Approach for the Development of Nutraceuticals"," 2025; Kazman et al., 2020; Rangel et al., 2025). The fruit pulp has potential as a functional food due to its nutritional and antioxidant properties. Cosmetic applications include anti-aging formulations leveraging its free radical scavenging capacity. Integration into standardized phytopharmaceutical products requires quality control measures such as chromatographic fingerprinting and marker compound quantification (Chatatikun & Chiabchalard, 2017; Ko et al., 2020; Ruddaraju et al., 2019).

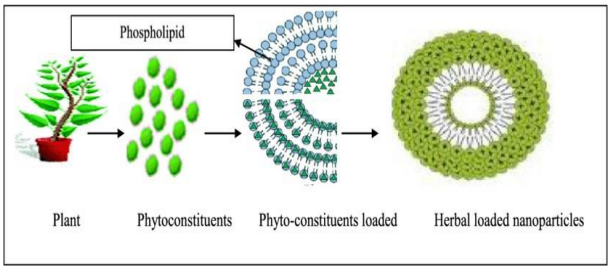

Figure 5. Potential pharmaceutical and nutraceutical applications of *Annona squamosa* extracts in modern drug delivery and functional health products.

8. Research Gaps and Future Perspectives

Although pharmacological evidence is extensive, translation into clinical medicine remains limited. Key research gaps include:

• Absence of well-designed human clinical trials
• Variability in phytochemical composition due to geography
• Lack of standardized extraction protocols
• Insufficient toxicological profiling
• Limited bioavailability studies
• Need for nano-delivery systems to enhance therapeutic efficacy

Future research should focus on isolating specific bioactive molecules, elucidating molecular targets, and conducting rigorous clinical evaluation. Interdisciplinary collaboration between pharmacognosy, medicinal chemistry, and clinical pharmacology will be essential for successful translation (Abd-Elghany et al., 2022; Al Kazman et al., 2022; Anand et al., 2022; Chatatikun & Chiabchalard, 2017; Ko et al., 2020; Malik et al., 2022; Ruddaraju et al., 2019).

9. Conclusion

Annona squamosa stands out as a pharmacologically rich medicinal species whose long-standing ethnobotanical relevance has been increasingly supported by modern scientific investigation. The accumulated evidence reviewed in this article demonstrates that the plant contains a chemically diverse array of bioactive metabolites capable of modulating multiple biological pathways. Its antioxidant, antimicrobial, antidiabetic, anti-inflammatory, anticancer, neuroprotective, hepatoprotective, and cardiometabolic effects collectively position it as a promising multi-target therapeutic resource. The convergence of traditional knowledge with experimental validation highlights the enduring value of ethnopharmacology as a foundation for contemporary drug discovery.

The phytochemical complexity of *Annona squamosa* is both a strength and a challenge. While synergistic interactions among its constituents likely contribute to therapeutic efficacy, variability in composition introduces issues of reproducibility and safety. In particular, acetogenins represent a double-edged sword: they are potent cytotoxic agents with anticancer potential, yet they raise legitimate toxicological concerns when poorly controlled. This underscores the urgent need for standardized extraction protocols, marker-based quality control, and regulatory oversight to ensure safe therapeutic use. Another major limitation in the current evidence base is the scarcity of human clinical data. Most pharmacological findings derive from in vitro assays or animal models, which, although informative, cannot fully predict clinical efficacy or long-term safety. Translational research must therefore move toward well-designed clinical trials, pharmacokinetic studies, and pharmacovigilance frameworks. Such efforts will be essential to establish therapeutic dosing, identify contraindications, and evaluate interactions with conventional medicines.

From a pharmaceutical perspective, *Annona squamosa* offers significant opportunities for formulation science and product development. Advances in nanotechnology, controlled-release systems, and phytopharmaceutical standardization could enhance bioavailability, reduce toxicity, and enable targeted delivery of active compounds. At the same time, its nutritional and antioxidant properties support its potential role in nutraceuticals and functional foods aimed at chronic disease prevention. In summary, *Annona squamosa* represents a bridge between traditional medicine and modern therapeutics. Its broad pharmacological spectrum and chemical richness make it a valuable candidate for future drug discovery and health product innovation. Realizing this potential will require interdisciplinary collaboration that integrates pharmacognosy, toxicology, medicinal chemistry, clinical pharmacology, and regulatory science. With rigorous scientific advancement and responsible standardization, *Annona squamosa* could evolve from a traditional remedy into a validated contributor to modern evidence-based healthcare.

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