

REVIEW ARTICLE



Phytochemistry, Pharmacological Activities, and Applications of *Annona squamosa* L.

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Abstract: *Annona squamosa* L., a member of the Annonaceae family, is a tropical plant esteemed for its edible fruit and extensive use in traditional medicine. The plant is a rich source of diverse bioactive phytochemicals distributed throughout its leaves, seeds, bark, and fruit. The main chemical constituents include annonaceous acetogenins, alkaloids, flavonoids, and terpenoids, which are responsible for its wide spectrum of pharmacological activities. Scientific investigations have substantiated many of its traditional applications, demonstrating significant antioxidant, antimicrobial, anti-inflammatory, and cytotoxic properties. Acetogenins, in particular, have garnered attention for their potent anticancer and neuroprotective potential by inhibiting mitochondrial complex I. Extracts from various plant parts have also shown promising results in managing metabolic disorders, such as diabetes, by modulating glucose metabolism. While the fruit pulp is utilized in the food industry for its nutritional value, by-products like seeds and peel are being explored as functional ingredients. However, the presence of potentially toxic compounds, especially in the seeds, necessitates careful toxicological evaluation to establish safe dosage limits. Current research focuses on advanced extraction techniques, genomic studies, and the development of nanoformulations to enhance the therapeutic efficacy of its derivatives. This review presents the current literature available on *A. squamosa*, showing its potential as a source for novel pharmaceuticals and functional food products.

Keywords: *Annona squamosa*; Annonaceous Acetogenins; Phytochemistry; Pharmacological Activity; Ethnomedicine

1. Introduction

Annona squamosa L., commonly known as sugar apple or custard apple, is a small, deciduous tree belonging to the Annonaceae family. Although native to the tropical Americas and the West Indies, its cultivation has spread extensively across tropical and subtropical regions worldwide, including India, Southeast Asia, and parts of Africa [1]. The plant is highly valued for its fruit, which has a sweet, aromatic, and creamy-white pulp. Beyond its culinary use, *A. squamosa* holds a significant place in various traditional medicine systems, such as Ayurveda, where different parts of the plant are utilized for treating a range of ailments [2].

The nutritional profile of the fruit is noteworthy, containing substantial amounts of carbohydrates, dietary fiber, vitamin C, and essential minerals like potassium and magnesium [3]. This composition contributes to its role as a healthy dietary component. However, the scientific interest in *A. squamosa* extends far beyond its nutritional value. The leaves, seeds, bark, and roots are rich reservoirs of bioactive phytochemicals, which are the basis for its long-standing use in ethnomedicine [4]. Traditional practices have employed various preparations of the plant to manage conditions such as diabetes, microbial infections, inflammation, and parasitic infestations [5].



Figure 1. Leaves and Fruit of *A. squamosa*

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Modern phytochemical and pharmacological research have begun to systematically validate these traditional claims. The plant is characterized by the presence of a unique class of compounds known as annonaceous acetogenins, which exhibit potent cytotoxic, insecticidal, and neuropharmacological activities [6]. In addition to acetogenins, *A. squamosa* contains a wide array of other bioactive molecules, including alkaloids, flavonoids, terpenoids, and phenolic compounds, each contributing to its diverse therapeutic properties [7]. The extraction and isolation of these compounds have become a focal point of research, aiming to develop novel therapeutic agents and functional ingredients for the pharmaceutical, nutraceutical, and food industries. This work aims to provide a detailed account of the botanical characteristics, phytochemical constitution, pharmacological activities, and potential industrial applications of *Annona squamosa*.

2. Profile and Distribution

2.1. Description

Annona squamosa is taxonomically classified within the family Annonaceae, a large family of flowering plants in the order Magnoliales.

2.1.1. Habit and Morphology

It is a small, well-branched tree or shrub that typically grows to a height of 3 to 8 meters. The plant forms a broad, open crown with numerous branches. The leaves are simple, thin, and arranged alternately on the stem. They are typically oblong-lanceolate in shape, measuring 5–17 cm in length and 2–5.5 cm in width, with a dull green upper surface and a paler, slightly pubescent underside [8].

2.1.2. Flowers

The flowers are bisexual and emerge solitarily or in small clusters from the leaf axils. They are greenish-yellow, fragrant, and approximately 1.5–3 cm long. Each flower consists of three fleshy outer petals and three rudimentary inner petals, enclosing numerous stamens and carpels [9].

2.1.3. Fruit

The fruit is a syncarp, formed by the fusion of multiple carpels, resulting in a compound structure. It is typically round or heart-shaped, measuring 5–10 cm in diameter. The outer surface is characterized by knobby, segmented sections, which become more pronounced as the fruit ripens. The skin is pale green to yellowish-green. Internally, the fruit contains a creamy, fragrant, and sweet-tasting pulp interspersed with numerous hard, blackish-brown seeds [10].

2.2. Geographic Distribution and Habitat

Annona squamosa is believed to have originated in the tropical regions of the Americas. Over centuries, it has been distributed and naturalized in various tropical and subtropical climates globally [1]. It thrives in warm, dry climates and is well-adapted to a range of soil types, although it performs best in well-drained, sandy loam soils. The plant is sensitive to frost and cannot tolerate prolonged cold temperatures, which restricts its cultivation to warmer zones. In India, it is widely cultivated in states such as Andhra Pradesh, Maharashtra, Tamil Nadu, and Assam, where it has also become naturalized in some areas [11].

3. Phytochemical Constitution

The diverse pharmacological effects of *Annona squamosa* are attributable to its complex phytochemical profile. Various classes of secondary metabolites have been isolated and identified from different parts of the plant, including the leaves, seeds, bark, and fruit.

3.1. Annonaceous Acetogenins

Perhaps the most significant group of compounds in *A. squamosa* are the annonaceous acetogenins. These are long-chain fatty acid derivatives that are almost exclusively found in the Annonaceae family. They exhibit potent biological activities, primarily through the inhibition of Complex I (NADH: ubiquinone oxidoreductase) of the mitochondrial electron transport chain, which disrupts cellular ATP production [12]. The main acetogenins identified in *A. squamosa* include squamocin, bullatacin, and annonacin. These compounds are predominantly concentrated in the seeds and have demonstrated powerful cytotoxic effects against various cancer cell lines, as well as notable insecticidal and antimicrobial properties [13, 14].

3.2. Alkaloids

Alkaloids represent another major class of bioactive compounds present in *A. squamosa*. These nitrogen-containing organic compounds are found throughout the plant, particularly in the bark and leaves. Isoquinoline alkaloids are the most common type found in this species. Compounds such as anonaine, liriodenine, and asimicine have been isolated and are known to contribute to the plant's antimicrobial, cytotoxic, and anti-inflammatory activities [15].

3.3. Flavonoids and Phenolic Compounds

The leaves, peel, and pulp of *A. squamosa* are rich in flavonoids and other phenolic compounds. These substances are powerful antioxidants that scavenge free radicals and reduce oxidative stress. The main flavonoids identified include quercetin, kaempferol, and rutin, while phenolic acids such as gallic acid and caffeic acid are also present [16]. These compounds are largely responsible for the antioxidant, anti-inflammatory, and antidiabetic effects observed in extracts from the plant [17].

Table 1. Phytochemical Constituents in Different Parts of *Annona squamosa*

Plant Part	Major Phytochemical Classes	Representative Compounds
Seeds	Annonaceous Acetogenins	Squamocin, Annonacin, Bullatacin
	Alkaloids	Liriodenine, Anonaine
	Fixed Oils & Fatty Acids	Oleic acid, Linoleic acid, Palmitic acid
	Cyclopeptides	Squamins A and B
Leaves	Flavonoids	Quercetin, Kaempferol, Rutin
	Alkaloids	Higenamine, Corydaline
	Terpenoids	α -Pinene, β -Caryophyllene, Germacrene D
	Phenolic Compounds	Caffeic acid, Ferulic acid
Pulp (Fruit)	Carbohydrates & Sugars	Glucose, Fructose, Sucrose
	Vitamins	Vitamin C (Ascorbic acid), Vitamin B6
	Minerals	Potassium, Magnesium, Iron
	Amino Acids	Arginine, Leucine, Lysine
Peel	Phenolic Compounds	Catechin, Epicatechin, Vanillic acid
	Tannins	Condensed and hydrolysable tannins
	Flavonoids	Proanthocyanidins
Bark	Alkaloids	Anonaine, Asimilobine
	Tannins	Gallotannins
	Steroids & Triterpenes	β -Sitosterol, Stigmasterol

3.4. Terpenoids and Essential Oils

The leaves and fruit of *A. squamosa* contain volatile terpenoids that contribute to its characteristic aroma. These essential oils are composed of various mono- and sesquiterpenes, such as α -pinene, β -caryophyllene, and germacrene-D [18]. These compounds have been associated with antimicrobial, analgesic, and anti-inflammatory activities.

3.5. Other Phytoconstituents

Other important phytochemicals include tannins and saponins, which are present in the leaves and bark and contribute to the plant's astringent and antimicrobial properties [19]. The seeds are also a source of fixed oil (28-31%), rich in fatty acids like oleic, linoleic, and palmitic acids, which has potential applications in the cosmetic and nutraceutical industries [20].

4. Extraction of Bioactive Compounds

The isolation of phytochemicals from *Annona squamosa* is a critical step for both pharmacological investigation and industrial application. The efficiency and selectivity of the extraction process are determined by the choice of methodology and solvent, which in turn depend on the physicochemical properties of the target compounds and the plant matrix.

4.1. Conventional Extraction Methods

Conventional solvent extraction techniques remain widely used due to their simplicity and scalability. Maceration involves soaking the powdered plant material in a selected solvent at room temperature for an extended period, making it suitable for thermolabile compounds [21]. For a more exhaustive extraction, Soxhlet apparatus is often employed. This continuous extraction method uses a recycling solvent system, which enhances extraction efficiency, particularly for lipophilic compounds like acetogenins and seed oils [22]. The choice of solvent is paramount; polar solvents such as ethanol and methanol are effective for isolating flavonoids and alkaloids, whereas non-polar solvents like hexane and chloroform are preferred for extracting lipids, essential oils, and acetogenins [23].

4.2. Advanced Extraction Technologies

In recent years, there has been a shift towards green and more efficient extraction technologies that reduce solvent consumption, extraction time, and energy input. Ultrasound-Assisted Extraction (UAE) utilizes acoustic cavitation to disrupt plant cell walls,

facilitating enhanced solvent penetration and mass transfer. UAE has proven effective for extracting phenolic compounds and antioxidants from *A. squamosa* leaves and peel with higher yields in a shorter duration compared to conventional methods [24].

Supercritical Fluid Extraction (SFE), particularly using carbon dioxide (SC-CO₂), represents another advanced technique. Operating under supercritical conditions, CO₂ exhibits properties of both a gas and a liquid, allowing for efficient extraction of non-polar to moderately polar compounds. SFE is highly valued for its ability to extract compounds like seed oils and acetogenins without leaving toxic solvent residues, preserving the integrity of heat-sensitive molecules. This method is considered environmentally sustainable and allows for selective fractionation of extracts by modulating pressure and temperature [25].

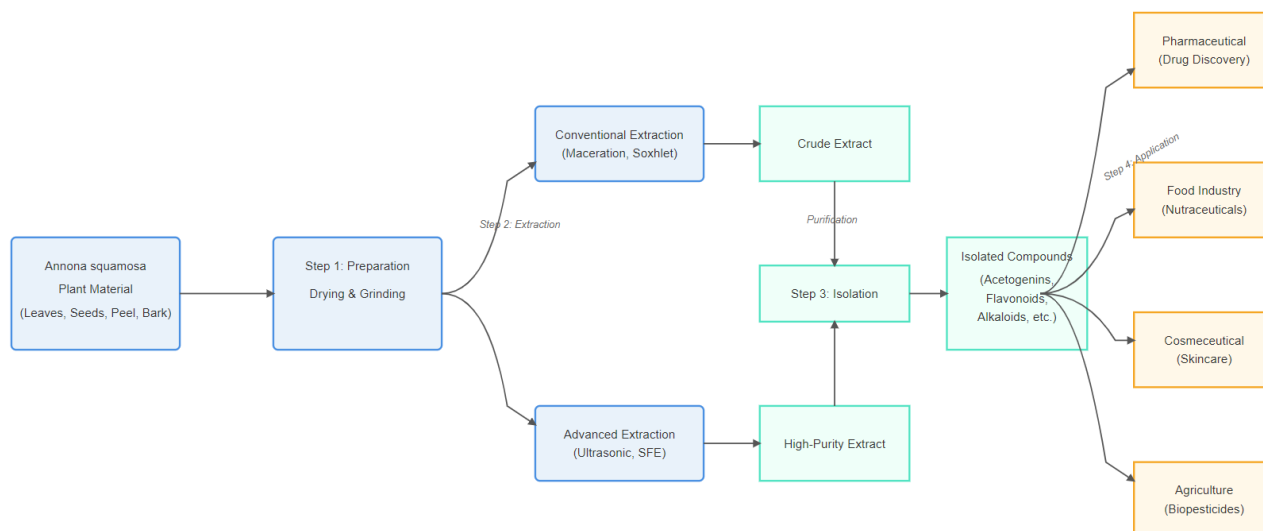


Figure 2. Processing of *Annona squamosa*

Table 2. Comparison of Extraction Methods for Bioactive Compounds from *Annona squamosa*

Extraction Method	Principle	Advantages	Disadvantages	Target Compounds
Solvent Maceration	Soaking powdered material in a solvent at room temperature.	Simple, low cost, suitable for thermolabile compounds.	Time-consuming, lower extraction efficiency, large solvent volume.	Flavonoids, Alkaloids, Phenols.
Soxhlet Extraction	Continuous extraction with a cycling hot solvent.	High extraction efficiency, requires less solvent than maceration.	Requires heating (unsuitable for thermolabile compounds), time-consuming.	Lipids, Acetogenins, Terpenoids.
Ultrasonic-Assisted	Uses acoustic cavitation to disrupt cell walls and enhance solvent penetration.	Fast, reduced solvent consumption, higher yield, energy efficient.	Potential for free radical formation, localized heating.	Phenolic compounds, Flavonoids.
Supercritical Fluid (SFE)	Uses a supercritical fluid (e.g., CO ₂) as the extraction solvent.	High selectivity, no solvent residue, environmentally friendly.	High initial equipment cost, complex operation.	Essential oils, Fatty acids, Acetogenins.

5. Pharmacological Activities

Scientific investigations into *Annona squamosa* have revealed a broad spectrum of pharmacological activities, lending credence to its extensive use in traditional medicine. These activities are attributed to the synergistic or individual actions of its diverse phytochemical constituents.

5.1. Anticancer and Cytotoxic Activity

One of the most extensively studied properties of *A. squamosa* is its anticancer potential, which is primarily linked to annonaceous acetogenins. These compounds exert potent cytotoxicity by inhibiting Complex I of the mitochondrial electron transport chain, leading to ATP depletion and subsequent apoptosis in cancer cells [12]. Research has shown that extracts from the seeds and leaves,

rich in acetogenins like squamocin and bullatacin, exhibit significant activity against a variety of cancer cell lines, including those of the breast, colon, lung, and prostate [26, 27]. Their unique mechanism of action makes them promising candidates for the development of novel chemotherapeutic agents, particularly for multidrug-resistant cancers.

5.2. Antidiabetic Activity

In traditional medicine, leaf and bark extracts of *A. squamosa* are commonly used to manage diabetes. Modern studies have substantiated these claims, demonstrating that the extracts possess significant hypoglycemic and antihyperglycemic effects. The underlying mechanisms are multifactorial and include the inhibition of carbohydrate-metabolizing enzymes like α -amylase and α -glucosidase, which reduces postprandial glucose absorption [28]. Furthermore, flavonoids and phenolic compounds in the extracts have been shown to improve insulin sensitivity and protect pancreatic β -cells from oxidative damage, thereby enhancing glycemic control [29].

5.3. Antimicrobial and Antiparasitic Activity

Extracts from various parts of *A. squamosa*, including the seeds, leaves, and bark, exhibit broad-spectrum antimicrobial activity against a range of pathogenic bacteria and fungi. This activity is attributed to the presence of alkaloids, terpenoids, and phenolic compounds that can disrupt microbial cell membranes, inhibit essential enzymes, or interfere with microbial DNA [30]. The seed extracts are particularly potent and have also demonstrated significant anthelmintic and antiparasitic effects, validating their traditional use for treating intestinal worms and head lice [31]. The insecticidal properties of acetogenins also position the plant as a potential source for natural biopesticides.

5.4. Antioxidant and Anti-inflammatory Properties

The high concentration of flavonoids and phenolic compounds in the leaves and fruit peel endows *A. squamosa* with strong antioxidant properties. These compounds effectively neutralize reactive oxygen species (ROS), thereby mitigating oxidative stress, which is implicated in the pathogenesis of numerous chronic diseases, including cardiovascular disorders and neurodegeneration [32]. Concurrently, extracts from the plant have demonstrated significant anti-inflammatory activity. They have been shown to inhibit the production of pro-inflammatory mediators such as prostaglandins and cytokines, which is beneficial in managing inflammatory conditions [33].

5.5. Hepatoprotective and Neuroprotective Effects

The antioxidant and anti-inflammatory properties of *A. squamosa* also contribute to its protective effects on vital organs. Studies have shown that leaf extracts can protect the liver from toxin-induced damage (hepatotoxicity) by reducing oxidative stress and inflammation [34]. More recently, interest has grown in the neuroprotective potential of its constituents. Acetogenins, despite their cytotoxicity, have been reported to exhibit neuroprotective effects at sub-lethal concentrations by modulating cellular stress responses. This shows the potential therapeutic role in neurodegenerative diseases, although this area requires further in-depth investigation to balance efficacy and toxicity [35].

Table 3. Pharmacological Activities of *Annona squamosa* Extracts

Pharmacological Activity	Plant Part Used	Type of Extract	Findings
Anticancer / Cytotoxic	Seeds, Leaves	Ethanollic, Methanollic	Induction of apoptosis in various cancer cell lines (e.g., breast, colon) due to acetogenins.
Antidiabetic	Leaves, Bark	Aqueous, Ethanollic	Reduction in blood glucose levels, improved insulin sensitivity in diabetic animal models.
Antioxidant	Leaves, Peel, Pulp	Methanollic, Aqueous	High free radical scavenging activity, inhibition of lipid peroxidation.
Antimicrobial	Seeds, Leaves	Ethanollic, Chloroform	Broad-spectrum activity against pathogenic bacteria (e.g., <i>S. aureus</i> , <i>E. coli</i>) and fungi.
Anti-inflammatory	Seeds, Leaves	Methanollic	Inhibition of pro-inflammatory mediators (e.g., NO, prostaglandins) in vitro and in vivo.
Hepatoprotective	Leaves, Bark	Aqueous	Protection against toxin-induced liver damage in animal models by reducing enzyme markers.
Neuroprotective	Seeds	Dichloromethane	Protection against neurotoxin-induced cell death, potential for neurodegenerative diseases.

6. Ethnomedicinal Uses

The application of *Annona squamosa* in traditional medicine is extensive and varies across different cultures. In Ayurveda, the plant is known as *Sitaphala* and is recognized for its cooling properties (*sheeta virya*), making it beneficial for pacifying *Pitta* dosha, which is associated with heat and inflammation [36]. The ripe fruit is considered a tonic that enriches the blood and builds strength. Different parts of the plant are employed to treat specific conditions. The leaves, for instance, are crushed into a poultice and applied topically to wounds, ulcers, and boils to promote healing. A decoction of the leaves is also consumed to alleviate dysentery and other gastrointestinal infections [37]. The bark and unripe fruit, being highly astringent, are traditionally used to manage diarrhea. The roots are known for their purgative action and are used in remedies for dysentery and spinal disorders [38]. The seeds, while recognized for their toxicity, are used with caution. Powdered seeds are applied externally to eradicate head lice and are also considered to have abortifacient properties in some folk traditions [39].

Table 4. Ethnomedicinal Uses of *Annona squamosa* Across Different Cultures

Ailment / Condition	Plant Part Used	Method of Preparation and Administration	Traditional System / Region
Diarrhea and Dysentery	Unripe Fruit, Bark	Decoction of dried parts is consumed orally.	Ayurveda, Indian Folk Medicine
Head Lice and Insects	Seeds	Powdered seeds are made into a paste and applied topically to the scalp.	Various Tropical Regions
Wounds, Ulcers, Boils	Leaves	Crushed fresh leaves are applied as a poultice directly on the affected area.	Latin America, Southeast Asia
Fever and Colds	Leaves	Decoction of leaves is taken orally.	Caribbean Folk Medicine
Rheumatism	Leaves	Leaves are heated and applied topically to painful joints.	Indian Folk Medicine
Indigestion / Stomachic	Ripe Fruit	Consumed directly to act as a cooling agent and digestive aid.	Ayurveda
Abortifacient	Seeds, Roots	Used as a paste or decoction (use is cautionary and often secretive).	Widespread Folk Practice

7. Toxicity

Despite its therapeutic potential, the use of *Annona squamosa* extracts warrants a thorough toxicological assessment, primarily due to the potent bioactivity of its constituents, particularly the annonaceous acetogenins concentrated in the seeds. The seeds are not consumed as food and are known to be toxic if ingested in crushed form.

7.1. Seed Toxicity

The acetogenins and alkaloids in the seeds are cytotoxic and neurotoxic. *In vitro* studies have confirmed the hemolytic activity of methanolic seed extracts on human erythrocytes [40]. Furthermore, direct contact of crushed seed powder or its extracts with the eyes can cause severe irritation, leading to keratoconjunctivitis and corneal damage, a well-documented hazard [41].

7.2. Acute and Chronic Toxicity

Acute toxicity studies in animal models generally indicate a moderate to low level of toxicity for leaf and seed extracts when administered orally. The lethal dose (LD₅₀) is typically high, suggesting a reasonable margin of safety for acute exposure [42]. However, the primary concern lies with chronic or long-term exposure. Some studies have reported genotoxic effects, with seed extracts inducing DNA damage and chromosomal aberrations in rats at certain dose levels [43]. Given the neurotoxic potential of acetogenins observed in related *Annona* species, there is a plausible risk associated with the chronic ingestion of seed-derived preparations, necessitating further long-term safety evaluations.

8. Applications in Pharmaceutical and Food Industries

The rich phytochemical profile of *Annona squamosa* provides significant opportunities for its application in both the pharmaceutical and food sectors.

8.1. Pharmaceutical Applications

The potent cytotoxic activity of acetogenins positions them as lead compounds for anticancer drug development. The seed oil has also demonstrated therapeutic potential, with studies reporting its efficacy in preclinical models of psoriasis, where it reduced

inflammation and other symptoms with a good dermal safety profile [44]. Additionally, the antioxidant and anti-inflammatory properties of leaf extracts make them suitable for incorporation into dermatological formulations, such as anti-aging creams.

8.2. Food Industry

In the food industry, the pulp is widely used to produce juices, ice creams, jellies, and other value-added products [45]. Beyond the pulp, the by-products of fruit processing, such as the peel and seeds, are gaining attention as sources of functional ingredients. These waste streams are rich in phenolic compounds and antioxidants, which can be extracted and used as natural food preservatives to enhance the shelf life and safety of food products [46]. The antimicrobial activity of leaf extracts against foodborne pathogens further supports their potential as natural additives.

9. Conclusion

Annona squamosa L. is a plant of considerable scientific and economic interest, bridging the gap between traditional medicine and modern pharmacology. Its rich array of bioactive compounds, especially the unique annonaceous acetogenins, provides a strong basis for its diverse therapeutic activities, including anticancer, antidiabetic, and antimicrobial effects. While the fruit is a valuable nutritional resource, the plant's by-products can also be used as a source of functional ingredients for industrial applications. The potential toxicity of certain constituents, particularly in the seeds, necessitates rigorous safety profiling and the establishment of standardized extracts to ensure safe consumption and application. Clinical validation of its medicinal properties and the development of sustainable, value-added products should also be prioritized.

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