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Review Article

Phytoconstituents and Bioactivities of *Annona Squamosa*: A Phytopharmacological Perspective

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ABSTRACT

Annona squamosa Linn., commonly known as custard apple or sugar apple, is a widely distributed tropical fruit tree belonging to the Annonaceae family. Beyond its culinary value, the plant is rich in bioactive phytoconstituents, including acetogenins, flavonoids, alkaloids, phenolics, terpenoids, and essential oils, that contribute to a broad spectrum of pharmacological activities. Traditionally used in Ayurveda, Unani, and folk medicine for treating ailments such as dysentery, ulcers, diabetes, and parasitic infestations, recent scientific investigations have validated many of its ethnobotanical applications. This review consolidates data from phytochemical analyses and preclinical pharmacological studies to present a comprehensive profile of A. squamosa. Methanolic and ethanolic extracts from various parts of the plant exhibit significant antioxidant, antidiabetic, hepatoprotective, antimicrobial, anti-inflammatory, and antitumor effects. Mechanistically, these activities are attributed to modulation of oxidative stress, inflammatory mediators, insulin signaling, and apoptotic pathways. Notably, nanoparticle formulations have enhanced the bioavailability and therapeutic efficacy of seed oil and leaf extracts in cancer and hepatotoxicity models. Additionally, A. squamosa demonstrates promising wound healing, antiulcer, and cytotoxic properties, further expanding its potential applications in phytotherapy. However, despite extensive preclinical evidence, translation into clinical use remains limited due to challenges in standardization, dosage determination, and toxicity evaluation. In conclusion, Annona squamosa represents a pharmacologically versatile and underutilized medicinal plant. With further research focusing on clinical trials, compound isolation, and safety profiling, this species could contribute significantly to the development of plant-based therapeutic agents and nutraceuticals.

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INTRODUCTION

Annona squamosa Linn., commonly referred to as the sugar apple, custard apple, or sweet sop, is a small, semi-deciduous or evergreen tropical tree belonging to the family Annonaceae, which encompasses over 2,300 species across approximately 135 genera. [1] Indigenous to the tropical Americas and the West Indies, it has been naturalized and cultivated extensively across tropical and subtropical regions, including India**,** Brazil**,** China**,** Thailand**,** and the Philippines. Morphologically, the plant typically grows to 3–8 meters, bearing greenish-yellow, heart-shaped or spherical fruits covered in knobby segments. The sweet, creamy white pulp is highly prized for its flavour and nutritional value. Beyond its culinary appeal, *A. squamosa* is renowned for its resilience in arid conditions, making it a valuable species for cultivation in diverse agro-climatic zones.

Historical and Ethnobotanical Context

Annona squamosa Linn., traditionally known as sitaphal or sharifa, is prominent in various traditional medical systems, including Ayurveda, Unani, and Chinese medicine. It has been used for its tonic, digestive, and cardioprotective properties, with different parts of the plant employed to treat conditions such as ulcers, fevers, lice infestations, and skin ailments. Its seeds, fruits, leaves, and bark have been utilized across regions like India, China, Cuba, Malaysia, and Brazil, both medicinally and nutritionally. This widespread ethnobotanical use highlights its cultural and therapeutic relevance, supporting its continued pharmacological exploration. [2]

Review objectives and scope

This review synthesizes current scientific literature on *Annona squamosa*, aiming to bridge its traditional uses with modern pharmacological research. Key objectives include documenting its ethnobotanical significance, analyzing its phytochemical profile—particularly acetogenins, alkaloids, flavonoids, and terpenoids—evaluating its antidiabetic, antioxidant, anticancer, anti-inflammatory, and antimicrobial properties, and examining its toxicological aspects, especially concerning seeds and bark. The review also addresses conservation and cultivation challenges, emphasizing the need for genetic preservation and sustainable use. This holistic approach supports its potential in drug discovery and future clinical applications.

2. Phytochemistry and Chemical Constituents

Annona squamosa Linn. possesses an extensive phytochemical profile, comprising several classes of bioactive secondary metabolites. These include acetogenins**,** alkaloids**,** flavonoids**,** terpenoids**,** phenolics**,** cyclopeptides**,** and essential oils**,** which have been isolated from various parts of the plant, namely the leaves, bark, seeds, fruits, roots, and pericarp. Their distribution and concentration underpin the plant's vast therapeutic potential.

Overview of Phytochemical Complexity

Key Phytochemical Classes

Annonaceous Acetogenins (ACGs)

Acetogenins are a class of polyketide-derived long-chain fatty acid derivatives (C_{32}–C_{34}), unique to the Annonaceae family. More than 88 ACGs have been reported from *A. squamosa*, including annonacin, squamocin, and bullatacin, known for their potent cytotoxic, antitumor, and nematicidal activities.

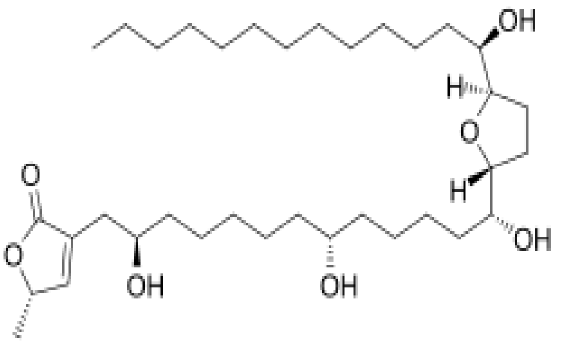

Fig 1: Annonacin

Alkaloids

Aporphine-type alkaloids such as liriodenine, anonaine, salsolinol, and roemerolidine have been isolated mainly from the leaves and stem bark. These alkaloids exhibit a variety of biological activities, including antispasmodic, bronchodilatory, antihypertensive, and anti-inflammatory effects. [3]

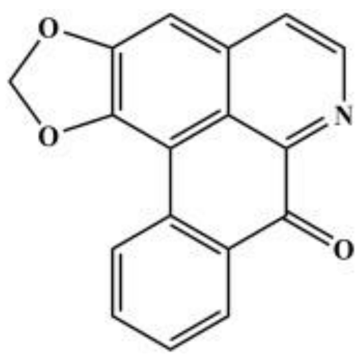

Fig 2: Liriodenine

Flavonoids and Polyphenols

Flavonoids such as quercetin, kaempferol, rutin, isoquercitrin, and quercetin-3-glucoside have been detected in high concentrations, especially in ethanolic leaf extracts. These molecules contribute to antioxidant, hepatoprotective, and antidiabetic properties.

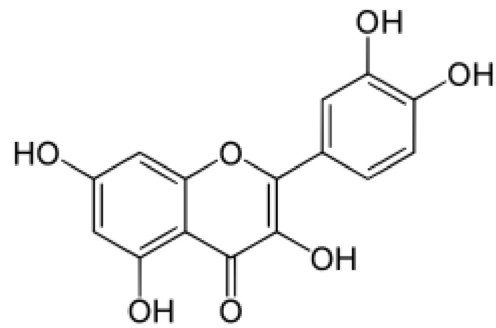

Fig 3: Quercetin

Terpenoids and Diterpenes

Approximately 33 ent-kaurane diterpenoids have been identified from the plant, including annosquamosins A to G. These compounds are primarily isolated from the fruit, bark, and stem, and exhibit activities such as anti-inflammatory, anticancer, and antiplatelet aggregation.

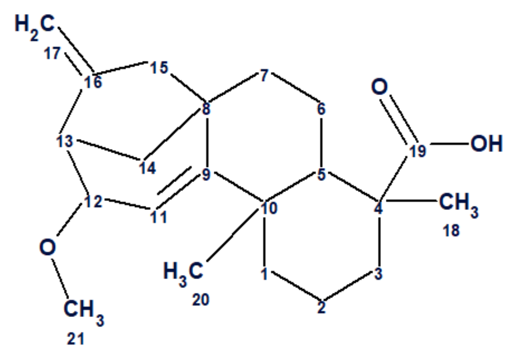

Fig 4: Ent-Kaurane Diterpenoids

Cyclopeptides

Cyclopeptides, including cyclosquamosin B and D, cherimolacyclopeptides, and others, have shown vasorelaxant, analgesic, and immunomodulatory effects, and are chiefly present in seeds and bark.

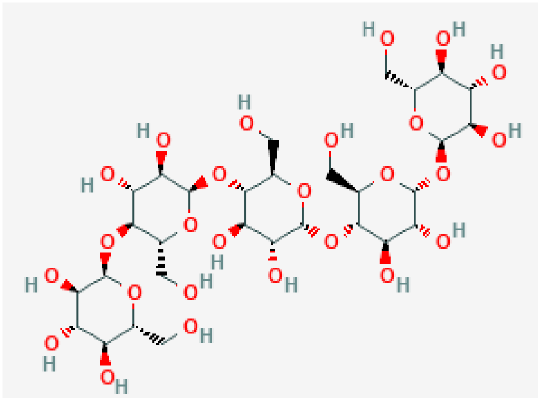

Fig 5: Cyclosquamosin B

Essential Oils

Essential oils and aromatic Compounds. Volatile compounds such as β-pinene, α-pinene, sabinene, and germacrene have been identified using GC-MS in seed and leaf extracts. These constituents contribute antimicrobial, aromatic, and pesticidal properties. [4]

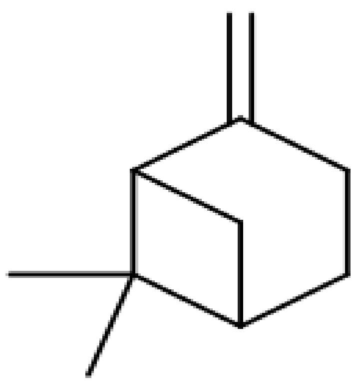

Fig 5: Cyclosquamosin B

Phytochemical Analysis Techniques

Multiple extraction solvents, ranging from hexane and chloroform to ethyl acetate and methanol, have been used to isolate different phytochemical classes. Among these, ethanol and methanol extracts yielded the richest concentrations of flavonoids, phenolics, and tannins. Identification and structural characterization of these compounds were carried out using qualitative screening tests, TLC, LC-MS, GC-MS, and NMR spectroscopy.[5]

4. Taxonomy And Botanical Description

Taxonomic Classification

Family	**Annonaceae**
Genus	***Annona***
Species	Includes more than 119 species such as *Annona squamosa*, *A. cherimola*, *A. muricata*, *A. reticulata*, *A. macroprophyllata*, *A. coriacea*, *A. senegalensis*, etc.
Subspecies/Varieties	For instance, *A. senegalensis* includes varieties such as *A. senegalensis var. arenaria*, *var. glabrescens*, and *var. cuneata*

The *Annona* genus belongs to the family Annonaceae, order Magnoliales, class Magnoliopsida. The Annonaceae is a large family of flowering plants comprising tropical and subtropical trees, shrubs, and lianas. *Annona* is among the most studied genera due to its ethnomedicinal relevance and edible fruit-bearing species. [6]

Morphological Characteristics

General Habit: Most *Annona* species are small to medium-sized trees or shrubs ranging from 3 to 11 meters tall, with spreading or moderately erect forms. Bark is typically brown and furrowed with age; young stems are tomentose, becoming glabrous with maturity.

Leaves: Leaves are alternate, simple, exstipulate, and vary in shape (oblong, elliptic, or ovate). They may be glabrous or pubescent, often displaying a shiny surface with impressed venation. Some species, such as *A. coriacea*, have glabrous ventral surfaces and undulating margins. [7]

Flowers: Flowers are solitary or in small groups, hermaphroditic, and structurally trimerous with three sepals and six petals in two whorls. They are typically aromatic and exhibit protogynous dichogamy (female stage precedes male stage), encouraging cross-pollination. Petals often shift in color from green to brown during anthesis. [8]

Fruits: The fruit is a syncarp, formed by the fusion of multiple carpels. It is typically conical, ovoid, or heart-shaped and features a creamy edible pulp surrounding numerous seeds. Fruits are highly valued for their nutritional content and are widely consumed fresh or processed.

Seeds: Seeds are hard, oblong, and blackish or brown in color. They possess a copious endosperm with a minute embryo. Some are toxic and contain bioactive compounds of pharmacological relevance. [9]

Morphological Comparison Table

Species	Leaf Type	Flower Timing	Fruit Shape	Distribution
A. squamosa	Thin, oblong	Oct–Dec	Round, scaly	India, Egypt
A. muricata	Glossy, oblong	Mar–May	Spiny, ovoid	Central America
A. reticulata	Lanceolate	Nov–Dec	Heart-shaped	Tropics worldwide
A. macroprophyllata	Broad, leathery	May–Jun	Large, round	Mesoamerica

Fig 7: Fruits of *Annona squamosa*

Fig 8: Flowers of *Annona squamosa*

Fig 9: Leaves of *Annona squamosa*

Fig 10: Seeds of *Annona squamosa*

Nutritional Composition of *Annona Squamosa* L.

Nutritional Profile

The fruit of *A. squamosa* offers considerable nutritional benefits and is commonly consumed in tropical regions. A 100 g edible portion of the fruit contains:

Energy	**104 kcal**
Protein	1.6 g
Fat	0.4 g
Carbohydrates	23.5 g
Fiber	3.1 g
Calcium	17 mg
Phosphorus	47 mg
Iron	4.37 mg
Vitamin C	37 mg

This composition is comparable to other tropical fruits like *Annona muricata* and mango, though *A. squamosa* generally has higher sugar content and a richer vitamin C profile, supporting its role as a nutritious dessert fruit. [10]

Analytical Methods

Several modern analytical techniques have been employed for the identification and quantification of phytochemicals in *A. squamosa*:

- **Gas Chromatography-Mass Spectrometry (GC-MS)**: Used to identify volatile oils and essential compounds in bark and seeds, revealing constituents such as caryophyllene oxide and kaur-16-ene.
- **High Performance Thin Layer Chromatography (HPTLC)**: Applied for fingerprinting phytoconstituents and quantifying bioactive compounds in extracts of different plant parts. [11]
- **Spectrophotometric Methods**: Utilized to determine total phenolic content, flavonoid concentration, and antioxidant capacity (e.g., DPPH and FRAP assays).
- **Chromatographic Isolation Techniques**: Employed for the isolation of acetogenins and flavonoids from seeds and leaves, followed by spectroscopic characterization (NMR, IR, MS). [12]

5. Pharmacological Evaluation

1. Anti-Cancer Activity

Cancer remains a major global health challenge, prompting the search for safer and more effective therapeutics. Phytochemicals from traditional medicinal plants, such as *Annona squamosa* (Annonaceae), have shown promising anticancer potential, largely attributed to their rich content of acetogenins.

Extraction and Isolation:

Methanolic leaf extracts of *A. squamosa* were fractionated using solvents like n-hexane, chloroform, and n-butanol. The chloroform fraction, exhibiting the highest cytotoxicity, was further purified via silica gel column chromatography, yielding four subfractions (FA–FD). The most active isolate (FA) underwent additional purification and LC-MS analysis. [13] Another study utilized ultrasonic extraction of *A. squamosa* seed oil (ASSO), followed by nanoparticle formulation with TPGS to improve solubility and bioavailability. The nanoparticles were characterized using DLS, zeta potential, and TEM techniques. Additionally, in silico docking was conducted using Biovia Discovery Studio 4.0 and CHARMM force fields to assess interactions between *A. squamosa* seed compounds and breast cancer targets.

Toxicity and Cytotoxicity:

- *Brine Shrimp Lethality Test* assessed general cytotoxicity of leaf extracts.
- *MTT Assay (HeLa Cells)* showed moderate cytotoxicity of FA fraction (IC_{50} = 70.90 ppm).
- *MTS Assay (4T1 Cells)* demonstrated superior efficacy of ASSO-loaded nanoparticles over free ASSO.
- *In Vivo Studies* revealed that ASSO-NPs achieved a tumor inhibition rate of 69.8%, significantly higher than the ASSO solution (52.7%). [14]

Molecular Docking and Apoptosis Induction:

Docking studies showed high binding affinities of seed-derived compounds to cancer-related targets, including ERα (3ERT: 164.20), PR (4OAR: 176.75), Caspase-3 (4QTX: 75.79), and NF-κB p65 (6QHL: 124.10). The FA isolate was found to induce apoptosis via mitochondrial dysfunction, with LC-MS identifying loliolide and linolenic acid as key bioactives linked to ROS-mediated apoptosis. The acetogenins' interaction with ERα, PR, NF-κB, and Caspase-3 supports their role in inhibiting proliferation, inducing apoptosis, and suppressing metastasis.

Nanoparticle Delivery

Nanoparticle formulation using TPGS improved the solubility, cellular uptake, and tumor-specific accumulation of ASSO. In vivo biodistribution studies showed enhanced tumor targeting (RTTI = 1.47x vs. free ACGs). [15]

Study	Sample	IC_{50} / TIR	Model
Swantara et al. (2022)	Leaf extract (FA)	IC_{50} = 70.90 µg/mL	HeLa cells
Ao et al. (2022)	ASSO-NPs	TIR = 69.8%	4T1 mice model
Behera et al. (2023)	Seed extract compounds	Docking score: 176.75 (PR)	In silico

Annona squamosa demonstrates notable anticancer potential, supported by both experimental and computational studies. Its bioactive constituents, including acetogenins and fatty acids, modulate key pathways involved in apoptosis and hormonal signaling. Nanoparticle-based delivery systems further enhance its therapeutic efficacy. While preclinical findings are promising, comprehensive toxicological evaluations and clinical trials are essential to advance its development as a viable anticancer agent.

2. Anti-Diabetic Activity

Annona squamosa exhibits strong antidiabetic potential, validated by a range of in vitro and in vivo studies. Its leaves contain key phytoconstituents, flavonoids (rutin, kaempferol), polyphenols, alkaloids, tannins, and glycosides, that act through multiple mechanisms. Various solvent extracts (hot water, ethanolic, hydroalcoholic, and hexane) demonstrate insulinotropic activity via membrane depolarization, calcium influx, and KATP-independent pathways. [16] Extracts also inhibit DPP-IV, enhancing GLP-1 levels and insulin secretion. Furthermore, they reduce enzymatic starch digestion, glucose absorption, and insulin glycation. Hexane extracts improve insulin sensitivity by upregulating GLUT4 and PI3K, increasing IR-β and IRS-1 phosphorylation, and inhibiting PTP1B. [17] Animal studies using high-fat-fed rats, ob/ob mice, and alloxan-induced diabetic rats showed significant improvements in fasting glucose, insulin levels, lipid profiles, glucose tolerance, and pancreatic islet morphology. [18] Hydroalcoholic extracts performed comparably to glibenclamide in glycemic control. Key active compounds like rutin, proanthocyanidins, and squafosacin G are implicated in these effects. [19] Collectively, these findings highlight *A. squamosa*'s therapeutic promise for type 2 diabetes through synergistic modulation of insulin secretion, sensitivity, and glucose metabolism. Further standardization of extracts and clinical trials are essential for pharmaceutical development.

3. Antimicrobial Activity

Annona squamosa (custard apple), a traditional medicinal plant, is gaining recognition for its antimicrobial efficacy. Various solvent extracts and biogenic nanoparticles derived from its leaves, seeds, and bark show broad-spectrum antibacterial activity, targeting both Gram-positive and Gram-negative bacteria.

Antibacterial Activity of Extracts

Ethanolic leaf extracts demonstrated concentration-dependent inhibition of *Staphylococcus aureus*, with MIC and MBC values of 30% and 32.5%, respectively. Petroleum ether and ethanolic extracts were particularly effective, inhibiting *S. aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa*, and also enhanced wound healing parameters in vivo. [20]

Nanoparticle-Mediated Antimicrobial Activity

Copper oxide nanoparticles (CuO NPs) synthesized using seed extracts exhibited potent antibacterial activity against *Xanthomonas oryzae*, showing uniform nanoscale morphology (~11 nm) and high efficacy. Silver, gold, and bimetallic nanoparticles derived from leaf extracts showed enhanced bactericidal action, especially BMNPs (2.05 ± 0.76 nm), against *S. aureus* and *E. coli*, driven by synergistic interactions of phytochemicals with metals. [21]

Mechanisms of Action

Antimicrobial effects stem from:

- **Phytochemical disruption** of bacterial membranes and nucleic acid synthesis (flavonoids, tannins)
- **Nanoparticle-induced ROS generation**, damaging microbial DNA and proteins [22]
- **Pro-healing effects**, enhancing angiogenesis and fibroblast activity alongside infection control. [23]

The dual antimicrobial and wound-healing properties of *A. squamosa*, particularly via eco-friendly nanoparticles, offer a promising phytotherapeutic alternative. Future work should focus on clinical validation, methodological standardization, and formulation development for therapeutic use.

4. Antioxidant Activity

Annona squamosa L. (custard apple) is widely recognized for its antioxidant properties, owing to its rich phytochemical profile. This review synthesizes evidence highlighting the antioxidant activity of its fruits, leaves, and seeds, which is relevant for combating oxidative stress implicated in chronic diseases like diabetes, cardiovascular disease, and cancer.

Phytochemical Composition and Antioxidant Constituents

A. squamosa is abundant in phenolics, flavonoids, alkaloids, tannins, and ascorbic acid. Seed extracts showed the highest levels of phenols (32.53 ± 2.13 µg GAE/mg) and flavonoids (893.3 ± 11.55 µg QE/g), while the pulp had significant vitamin C content (1.01 ± 0.08 mg/100 g). GC-MS profiling of leaf extracts identified bioactive molecules such as patchouli alcohol and bisphenol derivatives with antioxidant activity. [24]

In Vitro Antioxidant Activity

DPPH Radical Scavenging Assay Methanolic leaf extracts displayed an IC50 of 6.87 ppm, approaching the potency of ascorbic acid (3.03 ppm). Fruit extracts from the Brahmaputra Valley had an IC50 of 26.21 ± 1.34 µg/mL, confirming moderate antioxidant potential.

ABTS and Other Radical-Based Assays

ABTS assay showed greater scavenging by seed extract (IC50 = 0.14 ± 0.02 mg/mL) than pulp (0.38 ± 0.02 mg/mL). β-carotene bleaching and FRAP assays affirmed significant antioxidant effects, supporting the prevention of lipid peroxidation and oxidative DNA damage. [25]

Bioactivity-Guided Fractionation and Compound Isolation

Subfraction ASE-3, isolated from methanolic leaf extract, showed superior antioxidant activity. TLC-GC-MS analysis identified 19 compounds, including dodecanoic acid methyl ester and bisphenol-type phenolics, contributing to radical scavenging. [26]

Nutraceutical Potential

Custard apple fruit combines nutritional richness (proteins, fiber, vitamins, and minerals) with strong antioxidant properties, positioning it as a functional food candidate with applications in managing oxidative stress-related disorders. Multiple studies confirm the potent antioxidant capacity of A. squamosa, particularly in its methanolic seed, pulp, and leaf extracts. Its phytochemical richness, bioactivity-guided fraction efficacy, and favorable comparisons to synthetic antioxidants highlight its potential in nutraceuticals and preventive medicine. [27]

5. Anti-Inflammatory Activity

Annona squamosa exhibits significant anti-inflammatory and wound healing effects due to its rich phytochemical profile, including flavonoids, sterols, and tannins.

In Vitro Anti-Inflammatory Activity

Methanolic leaf and bark extracts, especially those from ultrasound-assisted extraction (UAE), reduced IL-6 and PGE2 levels in LPS-stimulated THP-1 macrophages. LNUMe and BNUMe extracts showed dose-dependent effects, likely via NF-κB and COX pathway inhibition.

Gastroprotective Effects

Ethanolic fruit extract (EEA) protected rats from ethanol-induced gastric lesions, preserving mucosal integrity and reducing TNF-α and IL-1α expression. Its efficacy was comparable to omeprazole, indicating antioxidant and cytokine-modulating properties. [28]

Anti-Arthritic Effects

In rheumatoid arthritis mouse models, peel extracts reduced joint inflammation and leukocyte infiltration, restoring joint architecture. Effects correlated with high phenolic content, supporting systemic anti-inflammatory action.

Wound Healing Potential

Petroleum ether and alcoholic extracts enhanced healing in rat wound models. Petroleum ether extract achieved 91.12% contraction by day 18 and improved tensile strength and granulation tissue, indicating enhanced fibroblast activity and collagen synthesis.

Mechanism and Antibacterial Synergy

The extracts' antioxidant and antimicrobial actions further support healing by reducing oxidative stress and preventing infection. Petroleum ether, chloroform water, and alcoholic extracts inhibited both Gram-positive and Gram-negative bacteria [29] *A. squamosa* demonstrates strong anti-inflammatory and wound healing potential through cytokine suppression, antioxidant action, and tissue regeneration. Extraction method and solvent type significantly impact bioactivity, warranting standardization in future studies.

6. Hepatoprotective Activity

Liver disorders caused by hepatotoxic agents such as isoniazid, rifampin, and paracetamol are a major health concern. *Annona squamosa*, rich in flavonoids, alkaloids, phenolics, and acetogenins, has shown promising hepatoprotective effects.

Protection Against Isoniazid-Rifampin Toxicity

Ethanolic leaf extracts (200 and 400 mg/kg) significantly lowered SGOT, SGPT, and ALP levels in rats with isoniazid-rifampin-induced hepatotoxicity, with efficacy comparable to silymarin. Histological studies confirmed improved liver architecture and reduced necrosis. [30]

Protection Against Paracetamol Toxicity

Ethanolic stem bark extract (150–600 mg/kg) reduced SGOT and SGPT levels in paracetamol-treated rats. The 150 mg/kg dose showed optimal liver protection, supported by improved liver morphology and presence of antioxidant-rich alkaloids, steroids, and phenolics. [31]

Zinc Oxide Nanoparticle-Enhanced Protection

Zinc oxide nanoparticles synthesized from alcoholic seed extracts preserved hepatic architecture in rats over 30–45 days. No necrosis or degeneration was observed, indicating enhanced bioavailability and sustained hepatoprotection.

Mechanisms of Action

Antioxidant activity: Neutralization of oxidative stress through phenolic compounds.

Membrane stabilization: Reduced enzyme leakage via hepatocyte membrane protection.

Cytoprotection: Histological regeneration of hepatic cells and lobular structure. [32] In vivo evidence supports *A. squamosa* as a potent hepatoprotective agent. Its antioxidant and membrane-stabilizing effects are comparable to standard therapies like silymarin.

CONCLUSION

Annona squamosa is a phytochemically diverse medicinal plant with validated bioactivities, including antioxidant, anti-inflammatory, antimicrobial, antidiabetic, hepatoprotective, and wound healing effects. Its various parts, leaves, seeds, bark, and fruits, contain active compounds like acetogenins, flavonoids, alkaloids, and phenolics that contribute to its therapeutic potential. Extracts, especially those derived using ethanol and methanol, have shown consistent efficacy in both in vitro and in vivo models, with enhanced performance when delivered via nanoparticle formulations. Despite this, clinical validation, safety profiling, and standardized extraction protocols remain underexplored. Given its ethnomedicinal heritage and growing pharmacological relevance, *A. squamosa* warrants further multidisciplinary research and conservation efforts. Its potential for natural drug development is significant and deserving of greater scientific and industrial attention.

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