Exploring *Annona squamosa* (Custard Apple): Nutritional Insights and Therapeutic Potential in Disease Management

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ABSTRACT

Introduction: *Annona squamosa L.*, commonly known by names such as custard apple, cherimoya, sitaphal, sharifa, and sugar apple, is a tropical fleshy fruit belonging to the *Annonaceae* family. Native to regions including Brazil, India, Peru, the West Indies, South & Central America, this plant species has gained attention for its diverse properties.

Method: The leaves of *Annona squamosa* have been extensively studied, revealing a range of beneficial attributes. These include antioxidant, antidiabetic, antimicrobial, antiobesity, and anti-cancer properties. The leaves' nutritional profile contributes to combating free radicals, regulating blood pressure, improving digestion, boosting immunity, and reducing inflammation.

Result: Chemical analysis of the cherimoya plant uncovered a variety of phytochemicals, including organic acids like hexanoic acid and octanoic acid, as well as purines. Notable compounds such as β-caryophyllene, δ-cadinene, α-muurolene, α-cadinol, and isoquinoline alkaloids were found in leaf oil. Acetogenins extracted from the leaves, like annoreticuin and isoannoreticuin, demonstrated selective cytotoxicity against certain tumor cells. Different parts of the plant yielded compounds such as borneol, camphene, carvone, and more.

Conclusion: In light of its significant nutritional value and potential as a nutraceutical resource, *Annona squamosa* has been utilized as a flavoring agent and food additive in homes and eateries. This versatile tree, known for its edible fruits, serves multifaceted purposes. While promising results have emerged from in-vitro and in-vivo studies, further research, including clinical trials, is essential to fully comprehend the effects of leaf extracts and other plant components on human health.

Keywords: *chiramoya, multifaceted, acetogenins, GC-MS , food additives.*

1. INTRODUCTION

Annona squamosa L., commonly referred to as "custard apple," is a tropical plant belonging to the Annonaceae family. It is indigenous to regions such as West Indies, South America, Central America, Peru, Brazil, Mexico, Bahamas, Bermuda, and Egypt, while also being cultivated in other parts of the world. In India, the Indian Council of Agricultural Research (ICAR) reports significant cultivation of *Annona squamosa* across various states including Maharashtra, Gujarat, Madhya Pradesh, Chhattisgarh, Assam, Uttar Pradesh, Bihar, Rajasthan, Andhra Pradesh, and Tamil Nadu.[1,2,3]

Recognized for its edible fruits, *Annona squamosa* is an evergreen tree that can grow up to heights of 3 to 8 meters. The leaves are oblong or lanceolate, approximately 6–17 cm long and 3–5 cm wide, arranged alternately on short petioles. The bark is thin and gray, while the flowers are green and drooping, appearing more abundantly on leafy shoots than on older wood. The fruits vary in shape from round to heart-shaped, ovate, or conical, measuring 5–10 cm in diameter with numerous round protrusions. Seeds are smooth, shiny, oblong, and blackish or dark brown, typically around 1.3–1.6 cm in length. *Annona* has been employed for its natural and herbal medicinal properties, including its utilization as a flavoring agent in ice cream due to its pulpy texture. The edible portion of the custard apple fruit contains ample amounts of vitamin C (35–42 mg per 100 g), dietary fibers, vitamin B1, and potassium. Leaves of the plant have insecticidal properties, with a mixture of seed powder and leaf juice used for scalp lice removal. Seeds are known for their abortifacient activity, while the root functions as a purgative and is used to treat blood dysentery. The fruit has sedative effects on the heart and possesses anti-bilious, anti-emetic, and expectorant properties. Ripe fruit combined with betel leaves is applied to tumors to promote suppuration. The leaves, bark, and unripe fruit are strongly astringent and are employed in the treatment of diarrhea and dysentery. Notably, the leaves contain a cardiotonic alkaloid called quinoline. Certain compounds found in *Annona squamosa*, such as squamone and bullatacinone, exhibit selective cytotoxicity against human breast carcinoma.[1,4,5,6]

Cherimoya harbors flavonoids, such as catechin, epicatechin, and epigallocatechin, which demonstrate efficacy as cancer chemo-preventive polyphenols. These compounds have exhibited the ability to impede cancer cell growth in in vitro studies [7]. *Annona* encompasses a range of anti-inflammatory compounds, including kaurenoic acid [8], renowned for its potent anti-inflammatory effects. Research has indicated its capacity to reduce specific inflammatory proteins in animal experiments [9]..

A fraction derived from the roots contains alkaloids, displaying antihypertensive, antispasmodic, antihistaminic, and bronchodilatory properties. *Annona* leaves house a cardiotonic alkaloid named quinoline. Furthermore, cytotoxic compounds such as squamone and bullatacinone exhibit a preference for targeting human breast carcinoma cells. Sitaphal, or custard apple, contains amino acids L-lysine and L-proline, contributing to collagen production within the human body. The abundant antioxidants present in custard apple confer protection to cell membranes against damage from free radicals, bolstering the body's ability to combat signs of aging. The fruit of *A. squamosa* serves as a sedative in various scenarios, including heart conditions, and offers potential for alleviating vomiting and addressing

certain tumor types [10]. Additionally, it holds notable concentrations of diverse minerals, such as phosphorus, potassium, iron, calcium, magnesium, sodium, copper, selenium, and zinc, along with essential vitamins like A, C, E, B1, B2, B3, and B9. These nutrients are vital for maintaining optimal human health and are involved in various physiological functions of the human body [11,12]. The below given figure 1. shows the leaves, fruits and seeds of *Annona squamosa* [13].

Figure 1. Fruits, Leaves and Seeds of *Annona squamosa*

2. PHYTOCHEMICAL PROFILE

Custard apple, also known as cherimoya, possesses a delightful sweetness and is rich in aromatic flavors. Despite its high sugar content, cherimoya boasts a low glycemic index. An analysis of extracts from Annona squamosa revealed the presence of a variety of phytochemicals, including proteins, carbohydrates, saponins, alkaloids, flavonoids, phenolics, and glycosides [14].

This fruit is a significant source of essential nutrients such as Vitamin C, iron, calcium, thiamine, amino acids, potassium, carotene, riboflavin, niacin, ascorbic acid, magnesium, and dietary fibers. Remarkably, despite its sugar content, custard apple maintains a low glycemic index and a moderate glycemic load. Specific chemical compounds found in custard apple

extracts include aliphatic ketones like palmitone, organic acids like hexanoic and octanoic acid, and purines [15].

A comprehensive GC-MS analysis of the leaf oil revealed the presence of 59 compounds, with key components being β-caryophyllene, δ-cadinene, α-muurolene, α-cadinol, and isoquinoline alkaloids. Notably, acetogenins annoreticuin and isoannoreticuin were selectively cytotoxic to specific human tumors. The plant's leaves and stems also contain alkaloids such as dopamine, salsolinol, coclaurine, anonaine, aporphine, coryeline, isocorydine, norcorydine, and glaucine [14].

Isolated alkaloids from the plant include samoquasine, aporphine, benzylisoquinoline, protoberberine, and tetrahydroisoquinoline. Other constituents found in the plant include oxophoebine, reticuline, atidine, histidine, hetidine, hetisine, heterophyllisine, heterophylline, heterlophylline, isoatisine, dihydroatisine, hetisinone, and benzoyl heteratisine. In the root and stem bark, oxoaporphine compounds like liriodenine and oxoanalobine were identified using NMR spectra. Stem root extracts of the plant contain various chemical constituents such as borneol, camphene, camphor, car-3-ene, carvone, β-caryophyllene, eugenol, farnesol, geraniol, 16-hetriacontanone, hexacontanol, higemamine, isocorydine, and limonine [16]

Further exploration of the plant revealed that stem bark yields acetogenin solamin and triterpenoids stigmasterol and sitosterol, along with compounds like squamocins B to N, coumarinoligans, annotemoyin-1, annotemoyin-2, squamocin, and cholesteryl glucopyranoside, which demonstrate noteworthy antimicrobial and cytotoxic activities [17,18].

3. PHARMACOLOGICAL ACTIVITY

A. Antidiabetic Activity

Various studies have demonstrated that the antidiabetic properties of *Annona muricata / Annona squamosa* aqueous extract can be attributed to its hypolipidemic impact, which includes antioxidant and protective actions on pancreatic β-cells, leading to enhanced glucose metabolism. The effectiveness of Annona as a remedy for diabetes is well-recognized among tribal communities and villages in Uttar Pradesh's Aligarh district. Local inhabitants blend 4 to 5 freshly emerged leaves with five grains of black pepper in the early morning, resulting in approximately 80% positive outcomes with consistent use [19]. Research involving the use of *Annona squamosa* aqueous extract on type 2 diabetic rats induced with streptozotocin and nicotinamide exhibited a noticeable reduction in plasma glucose levels, indicating potential anti-hypoglycemic properties. The study revealed that the extract's anti-hyperglycemic effect remained consistent regardless of the dosage, as no significant disparity in outcomes was observed between 250 and 500 mg/kg extract doses [20]. Consequently, the historical usage of this medicinal plant and its various extract forms for diabetes management is rooted in its capacity to alleviate hyperglycemia without adverse effects [11].

B. Anticancer/Antitumor Activity

Cherimoya possesses flavonoids like catechin, epicatechin, and epigallocatechin, known for their cancer chemo-preventive properties. The plant *Annona squamosa Linn,* commonly referred to as Custard apple, has been traditionally recognized for its rich reservoir of

bioactive compounds found throughout its various parts. Notably, prior research has demonstrated the remarkable anti-tumor properties of *Annona squamosa* seed extract against human hepatoma cells, both in laboratory settings (in vitro) and in living organisms (in vivo). These findings highlight a promising avenue for the development of a novel treatment for liver cancer using the extract. Furthermore, the aqueous extracts derived from *Annona squamosa* seeds have displayed noteworthy effectiveness in combatting tumors, as evidenced by their significant antitumor activity against AD-5 tumors in live subjects. This suggests the potential utility of these extracts in the realm of cancer treatment.[21]

Researchers successfully created seed oil nanoparticles (ASSO-NPs) using TPGS as a stabilizer to enhance the solubility and application of *Annona squamosa* seed oil (ASSO), which has potent antitumor properties. These nanoparticles were spherical, under 200 nm in size, and stable at room temperature. They were suitable for oral and intravenous use. In vitro and in vivo tests demonstrated that ASSO-NPs were more effective against tumors compared to free ASSO. In mice with 4T1 tumors, ASSO-NPs at 15 mg/kg had a higher tumor inhibition rate (TIR) as compared to ASSO solution . The nanoparticles also exhibited improved tumor-targeting potential. [22]

C. Hepatoprotective Activity

The methanol extract derived from *Annona squamosa* leaves has exhibited hepatoprotective properties. It effectively mitigates hepatotoxicity induced by isoniazid-rifampicin in rats, leading to a restoration of elevated liver enzymes such as ALT, AST, GGT, and ALP, as well as serum bilirubin and TBARs levels. Additionally, there is an improvement observed in total protein and reduced glutathione levels . Similarly, the hydroalcoholic seed extract of Annona squamosa has shown hepatoprotective effects against CCl-4 induced hepatotoxicity when administered at doses of 100mg/kg, 200mg/kg, and 400mg/kg (extract per body weight) over a one-week period [23,24,25].

D. Wound Healing Activity

The use of ethanolic extract from *Annona squamosa* leaves on wounds has been found to promote wound healing by boosting collagen and glycosaminoglycan synthesis, along with enhancing cellular proliferation at the site of injury, as indicated by sources [95, 96]. These findings validate the historical practice of applying *Annona squamosa* leaves topically to treat wounds and ulcers [26,27]

E. Anti-ulcer Activity

The active components found in *Annona squamosa* twigs offer protection against peptic ulcers. Substances like (+)-O-methylarmepavine, N-methylcorydaldine, and isocorydine exhibit anti-secretory properties, effectively reducing gastric acidity, pepsin and gastrin levels, while also inhibiting the H+-K+ ATPase pump. These effects are comparable to the actions of Omeprazole [28], validating the traditional application of these twigs for peptic ulcers. Similarly, *Annona squamosa* leaf extract demonstrated protective effects against ulcers induced by aspirin and pyloric ligation in mice [29].

F. Vasorelaxant Activity

Vasorelaxant activity has been attributed to Cyclosquamosin B, an extract from *Annona squamosa* seeds. The suggested mechanism involves inhibiting calcium release from the extracellular region by targeting voltage-gated calcium channels [30]. Nevertheless, ongoing research is exploring the potential therapeutic applications of cyclosquamosin B.

G. Anti-inflammatory activities

An aqueous extract derived from *Annona squamosa* leaves exhibited the ability to counteract acetic acid-induced colitis in mice when administered orally at a dosage of 300mg/kg over the course of one month. This extract displayed a notable reduction in colonic malondialdehyde (MDA) levels, alongside a significant increase in colonic glutathione (GSH), glutathione peroxidase (GPx), and catalase (CAT) activities [31]. Furthermore, novel cyclic peptides, fanlizhicyclopeptide A and fanlizhicyclopeptide B, obtained from the pericarp of Annona squamosa, demonstrated the capacity to reduce TNF-α and IL-6 generation in activated macrophages [32]. Moreover, the ethanolic extract of *Annona squamosa* was observed to lower CD40 expression and downregulate the NF-kB signaling pathway [33].

H. Other reported activities

As mentioned previously, the seeds of *A. squamosa* display various pharmacological activities. For instance, cyclosquamosin B from custard apple seeds exhibits vasorelaxant properties on rat aortas. This is achieved by reducing Ca2+ release from the extracellular medium through voltage-gated Ca2+ channels at a concentration of 10−5M. Custard apple seed powder was found to have anti-implantation activity in rabbits. However, these findings are not promising for pharmacological use. *A. squamosa* seeds, when combined with coconut oil (ratio 1:2), demonstrate potent anti-headlice activity, effectively eliminating 98% of head lice. Petroleum ether seed extract mixed with coconut oil eradicates lice (90%) in vitro within 26 minutes. The seed extract of *A. squamosa* displays antihelminthic properties against earthworms (Pheritima posthuma) and Haemonchus contortus, a nematode worm affecting goats and sheep. Moreover, the ethanolic seed extract inhibits larval growth (20-fold) in Spodoptera litura, in comparison to *A. muricata*. The various findings highlight the diverse pharmacological potentials of A. squamosa seed extracts [30,34,35,36].

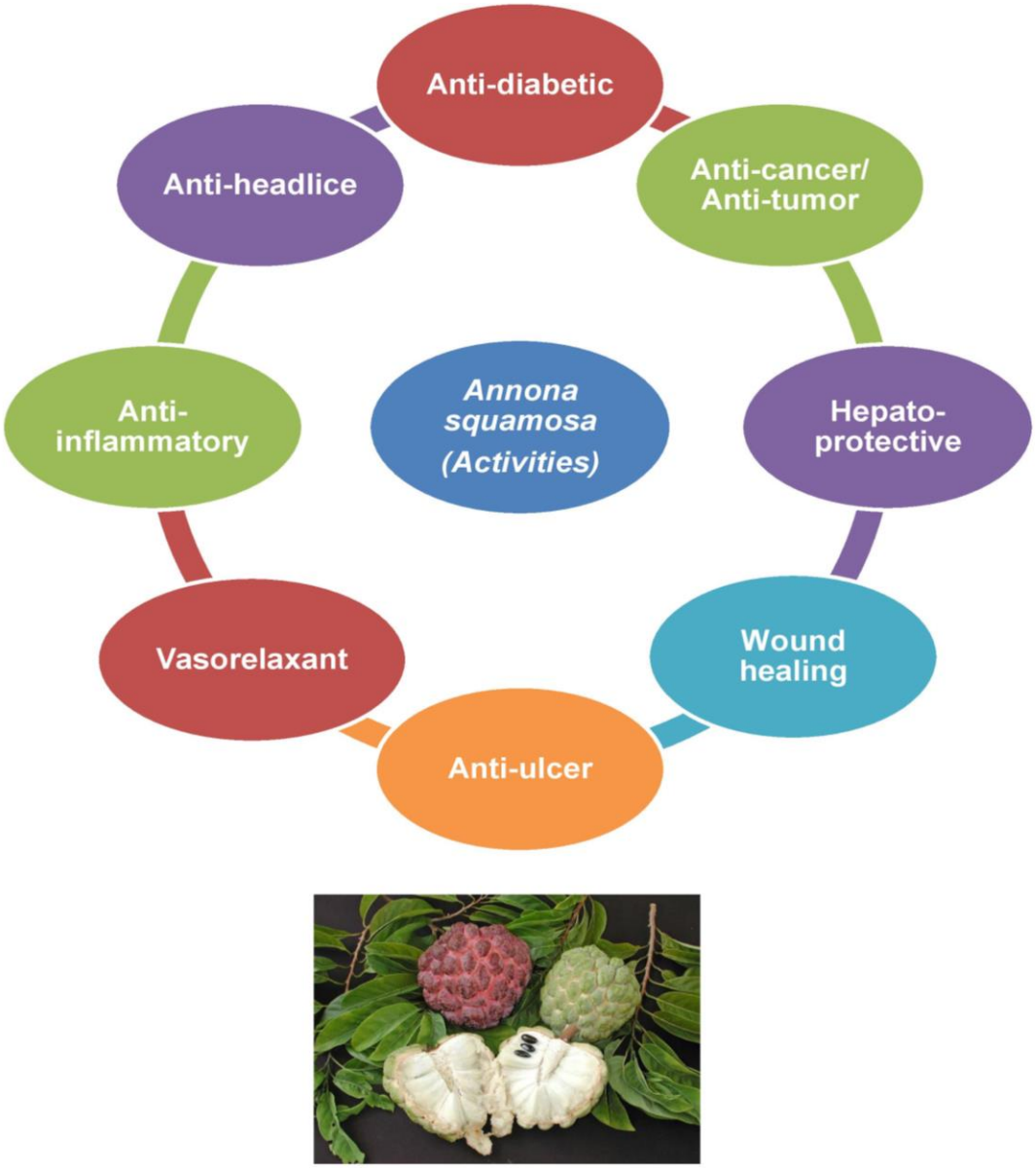

Figure 2. Various reported activities of *Annona squamosa*

4. CONCLUSION

In summary, *Annona squamosa*, commonly referred to as custard apple, exhibits a diverse array of documented pharmacological activities (Figure 2). Thorough investigations into its seeds have unveiled a range of potentials. Notably, cyclosquamosin B, an extract from custard apple seeds, demonstrates vasorelaxant properties by influencing calcium release through voltage-gated channels. While custard apple seed powder has shown anti-implantation effects in rabbit studies, its viability for pharmacological purposes remains uncertain due to limited encouraging results. However, the extracts from *A. squamosa* seeds exhibit impressive efficacy against head lice, with a combination of seed extract and coconut

oil displaying noteworthy success in eradicating these parasites. Additionally, the seed extracts of *A. squamosa* hold promise as anthelminthic agents, capable of targeting both earthworms and nematode worms that impact livestock. The observed inhibition of larval growth in certain insects also points to potential insecticidal properties inherent in these extracts. In essence, the documented activities associated with Annona squamosa seeds indicate a broad spectrum of potential applications, ranging from vasorelaxation potential to effective pest control solutions. Further dedicated research and exploration of these activities have the potential to unveil fresh therapeutic avenues and agricultural applications. This continued effort contributes significantly to expanding our comprehension of the versatile attributes possessed by this plant.

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