Annona squamosa: A plant of promising health benefits: A Systematic Review

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Abstract
Even though many cultures have long employed plants in traditional medicine, further study is still required to determine the efficacy, safety, and quality of these treatments. Everywhere in the world, people acknowledge and incorporate the special beauty of nature into their daily activities. The little medicinal shrub Annona squamosa, also referred to as "sweet sugar," is grown for its fruit. Conventional medicine has long made use of Annona squamosa. Tropical and subtropical climates are common places to cultivate A. squamosa. According to previous research, A. squamosa has biological properties like antioxidant, antifungal, and anticancer properties in all sections of the plant, including the bark, leaves, and roots. However, the leaves are powerful in these areas. Indians have traditionally employed the young leaves of A. squamosa as an anti-diabetic, and South Chinese use the seeds to lessen the body's reaction to cancer. Hepatoprotective, neuroprotective, cytoprotective, antifungal, anti-inflammatory, anti-cancer, anti-ulcer, antidiabetic, antidiarrheal, antiplatelet, and antioxidant properties are among the pharmacological activities of A. squamosa leaves. According to the review, A. squamosa's wide range of active phytoconstituents gives it several intriguing pharmacological actions. In order to help researchers explore the plant's pharmacological activity, isolate bioactive fractions, and apply these discoveries to the treatment of various ailments, this review offers crucial information for future studies.

Keywords: Annona squamosa, Antifungal, Antidiabetic, Antidiarrheal, Anti-inflammatory, Anticancer.
How to cite this article: Singh P, Rawat AKS. Annona squamosa: A Plant of Promising Health Benefits: A Systematic Review. Int J Drug Deliv Technol. 2026;16(7): 314-327. DOI: 10.25258/ijddt.16.7.32

The Latin word "anon," which means "yearly produce," is the source of the genus name "Annona," which alludes to the production of fruits by the many species in this genus, includes about 2300 species that are known to exist[1]. The term "squamosa" describes the fruit's knobby look. Annona is a tree or shrub that can withstand dryness and is found all over the tropical regions and thrives in hot, comparatively dry temperatures, such as those found in many tropical nations' low-lying interior plains[2]. The type of Squamosa that is grown primarily for its edible fruits, also referred to as sweet sop, is heart-shaped and weighs approximately 150g, with a rough skin. The pulp has a good flavour, is creamy, and is extremely sweet when ripe. As a small tree or large shrub, the custard apple can grow to three to five meters, but under the right circumstances, it can grow to six or eight meters. The plant's leaves are used as a vermicide, while other plant components have therapeutic significance. Root bark scrapings are used to treat toothaches, and roots are a strong purgative. Fruit that has not ripened. The fruit contains a significant quantity of seeds and is astringent and ripe, making it good for malignant tumours. The seed produces roughly 30% oil. The solvent extraction procedure is one way to extract the oil. Acetogenins, which are poisonous to insects, are present in Anona seed oil. Plant-based pesticides, such as Annona Squamosa, can be very effective in managing pests in sustainable agriculture. They are comparatively safer for humans, non-target creatures, and natural adversaries because of their regenerative nature and non-persistent nature. This review aims to inform readers about recent advancements in the field of Annona research[3,4].

Anona squamosa's botanical description

The custard apple, or Annona squamosa, is a tiny tree or shrub with many branches and thin, grey bark. The crown is a flattened ball or sphere in shape. Its green leaves are 3-5 cm wide and 10-15 cm long, with a pointy or pointed tip and a round or widely wedge-shaped base. The arrangement of the leaves is asymmetrical. Variations in rainfall, temperature, and light cause dormancy. Not every tree reacts at the same time, though. It is a monoecious plant with bisexual flowers. Each bloom measures around 2.5 cm in length and has oblong, green, purplish outer petals. The flowers are grouped in clusters of two to four. Inner petals are either absent or reduced to tiny scales. Given the low rates of wind and self-pollination, nitidulid beetles are the most significant pollinators. Following pollination, berries developed noticeable scales and tubercles[5].

The leaves are oblong-lanceolate, 3-5 cm broad, 10-15 cm long, and alternately placed on short petioles. The immature leaves have tiny hairs, and the epidermal cells contain both solitary and clustered crystals[6].

The trees are partially deciduous and flower from spring to early summer, or year-round in regions with constant humidity. They are inflorescences that are supra-axillary. The flowering characteristics include bracteate, pedicellate, actinomorphic, spirocyclic, bisexual, and pistils that mature before pollen is released from the anthers. The blossom features six petals and three reduced sepals, measuring 2 to 4 cm in length. The inner whorl's petals either vanish or degenerate into tiny scales. The six petals are grouped into two whorls of three each. With several stamens at the periphery, the conical receptacle is where the numerous pistiles grow in the core of the flower. Nitidulid beetles are responsible for pollinating flowers[2].

Thin grey bark on irregular branches contains the antimalarial alkaloids duguevalline, roemerolidine, and N-nitrosoxylopine[7].

Three to four-year-old trees begin to bear fruit. July through August is when fruits are grown in India. As the name suggests, sugar apples are just as sweet as sugar. The flesh that is closest to the also has a taste similar to sugar crumbs. Its shape is typically conical, but occasionally it can be nearly circular. When it's ready to eat, it's obvious. Thick with knobby pieces, the rind will soften and split apart as it ripens, providing a delightful scent. The typical ripening temperature range was 15–30 °C. Tap roots with branches[8].

The seeds have a dark brown or black hue. An average apple has 30 to 40 seeds. Annona squamosa is a species that is diploid and has 2n=14[9].

Classification

Annona squamosa L.

Kingdom	Plantae
Subkingdom	Tracheobionta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Magnoliidae
Order	Magnoliales
Family	Annonaceae
Genus	Annona L.
Species	Annona squamosa

Annona reticulata and Annona cherimola, Annona muricata, and Annona squamosa are synonyms. Common Names: Sweetsop, Buah Nona, Seri Kaya, Anona, Nona, Sugar Apple, Custard Apple. Used parts of the Bullock's Heart plant include leaves, fruits, seeds, and stembark[10].

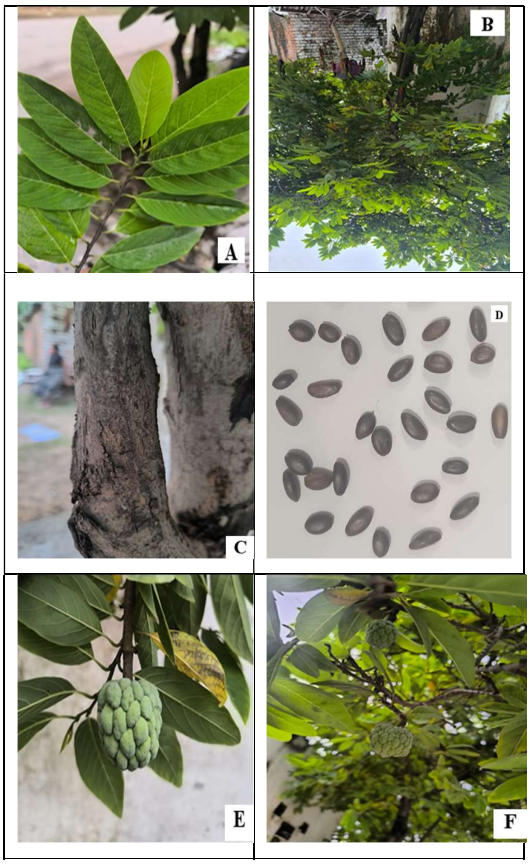


Figure 1. Annona squamosa: - (A); Leaves, (B); Tree, (C); Bark, (D); Seed (E, F) Fruit

History and Geographical Distribution

Hindu legend states that Lord Rama killed Ravana because the latter had abducted Lord Rama's wife, Mata Sita, and kept her at Ashoka Vatika in Lanka, which is now Sri Lanka. There were numerous fruit and plant varieties in Ashoka Vatika, and Mata Sita used to eat them. One of the prominent fruits was sitaphal. Because Sita Mata ate this fruit, it became famous and was given the name "sitaphal." According to some literature, Sita Mata was crying when she was taken by Ramavana, and her tears fell to the ground, creating sitaphal trees when they did. This fruit, called sitaphal, is a result of Mata Sita's tears[11].

However, A. squamosa is often found in tropical and subtropical Asian nations, such as Malaysia, Laos, Thailand, and Vietnam, and is also referred to as a sugar apple or custard apple. It is thought to be indigenous to tropical America. In the Aravalli Hills of Rajasthan, which are located throughout India, they multiply quickly[12].

Chemical Components

1. Fruits contain vitamin C, iron, calcium, thiamine, potassium, carotene, riboflavin, niacin, ascorbic acid, magnesium, dietary fibers, and sugar (up to 28%).
2. Dopamine alkaloid, isoquinoline alkaloids, acetogenine (annoreticulin and

isoannoreticuin), salsolinol, carbolic acid, carvone, eugenol, farnesol, geraniol, limonene, linalool, menthone, atropine, rhamnoside, rhamnoside, and rhamnoside-3-glycoside are among the compounds found in leaves. There were 59 chemical components found in leaf oil.

3. Liriodenine, Oxoanalobine, Borneol, Camphene, Camphor, Car-3-ene, β-Caryphyllene, Eugenol, Farnesol, Geraniol, 16-Hetriacontanone, Hexacontanol, Higemamine, Isocorydine, and Limonine are found in the roots and stems.
4. Roemerolidine, Duguevalline, Bullatacin, N-Nitrosoxylopine, Mosinone-A, Mosinone-B, Mosine-C, and Squamone are found in bark.
5. Triterpenoids (stigmasterol and sitosterol), acetogenin, solamin, annotomeyin-1, annotomeyin-2, squamocin, cholesterol, and glucopyranoside in the seeds[13-17].

THE VALUE OF NUTRITION

A number of minerals are present in sufficient amounts in the leaves of A. squamosa. Minerals are essential for the protection of the human body because they can support a variety of physiological processes, including blood pressure control, immune system functioning, blood coagulation, nerve function, muscle contraction and relaxation, energy metabolism, maintenance of healthy bones and teeth, and control of numerous enzymes. One of the vitamins found in A. squamosa extract is vitamin C. Vitamin C is used by the body for several purposes, such as immune response, bone production, wound healing, connective tissue strength, and maintaining healthy skin. Other vitamins that act as cofactors in enzymes involved in oxidation-reduction and glucose metabolism are B1, B2, and B3.

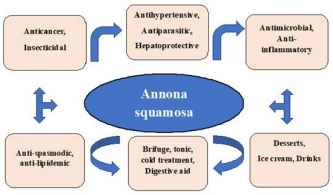
Compared with its seeds and fruit, the A. squamosa plant's an Egyptian study found that the highest protein concentration is found in leaves. A. squamosa leaf extract, which contains more protein than other A. squamosa varieties, can be used by both people and animals to boost the nutritional content of food. The methanol and water-based leaf extracts of A. squamosa contain notable levels of protein and amino acids. These findings were supported by the Milon test, which verified the presence of proteins and amino acids in the methanolic A. squamosa leaf extract, and the Biuret test, which verified their presence in the aqueous A. squamosa leaf extract[18].

Nutritive value of one hundred grammes of custard apple (Source: USDA National Nutrient Database)[19].

S. No.	Principle	Nutrient value	% of RDA (Recommended Dietary Allowance)
1	Carbohydrates	25.20 gram	19
2	Energy	101 Kcal	5.0
3	Dietary fiber	02.04 gram	6.0
4	Cholesterol	0 mg	0
5	Total fat	60 grams	3.0
6	Protein	01.70 grams	3.0
	Vitamins		
1	Vit. C	19.02 mg	32
2	Vit. A	33 IU	1.0
3	Niacin	0.500 mg	03.5
4	Pantothenic acid	0.135 mg	02.5
5	Pyridoxine	0.221 mg	17
6	Riboflavin	0.100 mg	8.0
7	Thiamine	0.80 mg	7.0
	Electrolytes		
1	Na (Sodium)	3.0 mg	Less than 1%
2	K (Potassium)	382 mg	8.0
	Minerals		
1	Ca (Calcium)	30 mg	3.0
2	Fe (Iron)	0.71 mg	9.0
3	Mg (Magnesium)	18 mg	04.5
4	Mn (Manganese)	0.093 mg	4.0
5	P (Phosphorus)	21 mg	3.0
	Phyto-nutrients		
1	Proanthocyanidin monomers	6.2 mg	-
2	Proanthocyanidin dimers	14.2 mg	--
3	Epicatechin	5.6 mg	

Traditional uses

According to the WHO, herbal remedies are used in most countries worldwide. Herbal medicine is used alongside traditional medicine in Asia, Latin America, and Africa. A. squamosa is one such plant that has many traditional uses. The A. squamosa tree is widely found in Australia, South America, the Caribbean, and Indo-Malaya. Communities commonly employ all parts to cure a range of acute and chronic illnesses, such as cancer, skin disorders, and bug stings. Annona squamosa is mostly used in the making of ice cream, beverages, and desserts. Certain parts of Annona squamosa have been associated with a variety of ethnomedical applications, such as cardiac sedative, cool medicinal medicine, apothegmatic, tonic, and abortifacient. Many investigations have discovered that Annona squamosa has antimaximum cancer, antihypertensive ,antioxidant, anti-diabetic, , hepatoprotective, antiparasitic, anti-malarial, insecticidal, antibacterial, and molluscicide activities[20-22].



The leaf of A. squamosa is used to treat diarrhoea and urinary tract infections in America, India, and Thailand[23]. The leaves of A. squamosa possess antimicrobial and wound-healing activities. A. squamosa leaves are widely used in Indonesia to cure diarrhoea, and there is growing evidence

that they may also be utilised to treat more serious conditions, including cancer. Even in India, the leaf is crushed and used as a traditional remedy for wounds. According to traditional American medicine, rheumatic pain can also be effectively treated in a bath with a decoction of A. squamosa leaves or a mixture of these leaves and other herbs[24-27].

Medicinal value

Since ancient times, alternative medicine has made use of natural compounds derived from therapeutic plants. It is believed that using medicinal plants as an alternative form of treatment is beneficial to human health[28,29]. Numerous studies have been conducted on the advantages of A. squamosa leaves, and the findings show that these leaves provide a range of health advantages associated with phytochemical diversity. The phenol-based chemicals included in A. squamosa leaves include proanthocyanidins and eighteen other phenolic compounds. Hepatoprotective, lipid-lowering, antidiabetic, anti-obesity, antioxidant, and anticancer activities are among the biological qualities of A. squamosa leaf extract[30,31]. The leaves of A. squamosa are also reported to contain several chemical compounds that are good for the body, including hydroxyl isomers of alkaloids and ketones. Insect bites, abscesses, cancer, vermicide activity, and skin problems can all be treated using A. squamosa leaves. Crumbled A. squamosa leaves into smaller components have been used to treat skin sores and wounds[32]. A. squamosa leaves, when dried and powdered, are used as a laxative and as an alternate medication for slimy diarrhoea[33]. Extract of leaf methanol from the leaves of A. squamosa has the potential to be an alternative antioxidant material, meaning that it can be employed as a natural element to create different kinds of medications that can postpone or even stop cell damage[34]. Methanol extract from A. squamosa leaves shows potential for application in cosmetic goods that lighten skin and as a dermatological anti-hyperpigmentation agent. This is supported by test results showing that methanol extract from A. squamosa leaves can prevent MSH-induced melanogenesis in B16F10 cells and activate p38 phosphorylation, which can lower tyrosinase, TRP1, TRP2, and MITF[35,36].

Phytochemistry: -

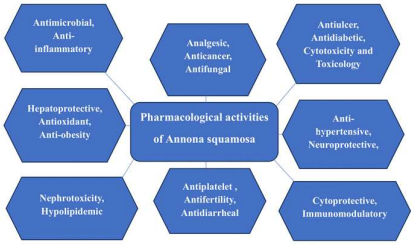
The pulp of the Annona Squamosa L. fruit is fragrant and delectable. The pulp's main sugar, sucrose, makes up 2.53% of its roughly 28% sugar content. Dextrose and laevulose make up 5.05% and 0.04%, respectively. Amino acids, ascorbic acid, calcium, carotene, iron, magnesium, potassium, niacin, riboflavin, thiamine, and vitamin C are also present in significant amounts. Annona Squamosa L. has a low glycaemic index and a moderate glycaemic load while having a substantial amount of sugar in its pulp. Certain chemical components, such as organic acids like hexanoic, purine, and octanoic acid, and aliphatic ketones like palmitone, have been isolated[37].

A total of 59 chemical components were found during gas chromatography-mass spectrometry (GC-MS) study of Annona Squamosa L. leaves and oil. β caryophyllene, a naturally occurring bicyclic sesquiterpene, accounts for 31.4% of the chemical components found in Annona Squamosa L. leaves and oil. Other constituents include δ-cadinene, which is 6.7%, α-muurolene, which is 5.5%, α-cadinol, which is 4.3%, and isoquinoline alkaloids. Using Annona Squamosa L. leaves, two acetogenins were extracted and identified: anoreticuin and isoannoreticuin. These acetogenins have cytotoxic specificity towards specific human tumours[38].

Annona Squamosa's chemical components are identified using nuclear magnetic resonance (NMR) spectroscopy. Bark and roots of L. The bark contains oxyaporphine compounds such liriodenine and oxoanalobine. The root extract of Annona Squamosa L. contains a variety of chemical components, including limonine, camphor, car-3-ene, carvone, borneol, β-caryphyllene, eugenol, farnesol, geraniol, 16-hexatriacontane, hexacontanol, higenamine, isocorydine, and camphene. After analysing Annona Squamosa L. seeds, thirty acetogenins were identified, including squamocins B through N, coumarinoligans, annotemyin-1, annotemyin-2, glucopyranoside, squamocin, and cholesteryl, which seemed to exhibit cytotoxic and antibacterial properties[39,40].

Pharmacological activities

Due to their comparatively low cost of production and the generally milder side effects of utilising therapies containing compounds from medicinal plants as opposed to synthetic drugs, medicinal plants are important in the creation of novel medications. Below is a description of A. squamosa's pharmacological activity:



Antimicrobial activity

Neethu et al. (2016) used clinical isolates of P. aeruginosa and E. coli to test the antibacterial activity of ethanol extract from A. squamosa leaves and DMSO. They found that the administration of A.

squamosa leaf ethanol extract had a mechanism of inhibiting the growth of these two microbes. At a concentration of 25, an ethanol extract of A. squamosa leaf in this investigation did not exhibit a zone of inhibition. At a concentration of 100 l, isolates of P. aeruginosa had no inhibition zone, whereas isolates of E. coli had one measuring 15 mm and isolates of P. coli had one measuring 17 mm with an inhibition zone of mm. Due to its secondary metabolites, which include flavonoids, phenols, terpenoids, and alkaloids, A. squamosa is employed as an antibacterial agent. Gram-positive and gram-negative strains of Escherichia coli and Bacillus coagulans are both susceptible to the methanolic extract of Annona squamosa stem bark's antibacterial activity in vitro[41,42]. Positive results were obtained from the plant's antibacterial properties against Vibrio alginolyticus, Staphylococcus aureus, Staphylococcus epidermidis, and Bacillus subtilis[43,44].

Anti-inflammatory and analgesic activity

50 mg per kg b.wt. of the squamosa Annona species barks extract in unsaponified petroleum ether and 12.5 & 25 mg per kg b.wt. of carotellene oxides collected via barks. showed potent central analgesic and anti-inflammatory properties. An additional investigation demonstrated the analgesic and anti-inflammatory properties of 18-acetoxy-ent-Kaur-16-ene, which was extracted from a petroleum ether preparation of custard apple bark[45-47].

The extract significantly reduced colonic malondialdehyde (MDA) and increased glutathione (GSH), glutathione peroxidase (GPx), and catalase (CAT) activities. Regarding the anti-inflammatory qualities of Annona squamosa seeds, it has been demonstrated that their cyclic peptides inhibit activated macrophages from generating proinflammatory cytokines such as TNFˆand IL-6[48]. When it comes to avoiding urolithiasis, the ethanol-based extract of Annona squamosa is almost the same as the treatment. A. squamosa leaf extract's pharmacologically effective analgesic and anti-inflammatory ingredients help reduce the discomfort brought on by inflammation of the urinary tract. It has been demonstrated that improving kidney function, healing damaged cells, and modifying serum and urine parameters can all help to reduce urinary tract smooth muscle spasms. As a measure of inflammatory activity, leukocyte migration decreased in connection with the assessment of Atemoya's ethanol extraction takes off. A subcutaneous discussion package test is used to determine whether movement has stopped after a peritoneal cavity check. Because of the cyclooxygenase action, the inflammatory activity inhibits the generation of mediators. TNF-, plasma exudation, IL-1, IL-8, IL-6, and carrageenan can all cause inflammation by triggering the migration of defence cells[49,50].

Antifungal activity

The growth of Fusarium oxysporum and Colletotrichum capsici has been demonstrated to be inhibited by A. squamosa leaf extract[51-53].

Anticancer activity

All components of A. squamosa are traditionally used by ethnic communities to treat a variety of illnesses, including skin conditions, cancerous tumours, bug bites, and other ailments[53]. However, the seeds of this plant contain a toxic component that can be used to eradicate lice and head lice[54]. The leaves of A. squamosa have hepatoprotective and immunomodulatory properties[55].

A. squamosa has been studied in the past for its anti-cancer properties, specifically its acetogenin and other non-alkaloidal moieties[56]. Two benzylisoquinoline alkaloids were found in an investigation into the alkaloids section of A. squamosa. Separate Alkaloids since benzylisoquinoline alkaloids are linked to the activity of cancer cells, I show exceptional action against human breast cancer cells (MCF-7) and cancer cells of the colon (HTC116)[57].

Antiulcer activity

In A. squamosa, the leaves contain potent antiulcerants. In a recent study, indomethacin was utilised to cause ulcers in male albino-Wistar rats that were used as experimental participants. When compared to the control group, the results showed that aqueous extract dosages of 175 mg/kg and 350 mg/kg significantly reduced ulcer index, stomach volume, and free acidity. Acute oral toxicity tests for the plant's aqueous extract demonstrated its safety and absence of adverse effects; hence, A. squamosa leaves can be used to treat peptic ulcers[58].

A. squamosa has active phytoconstituents that may be used to treat ulcerative colitis, especially methylarmepavine and isocorydine. These substances block important enzymes and pumps involved in acid secretion and lower pepsin and stomach acid levels. According to studies, they can reduce the development of stomach ulcers by blocking the ATPase, potassium, and hydrogen pumps, which lowers the release of hydrochloric acid.

Additionally, they alter pepsin activity, protecting tissue and maintaining the stomach mucosal barrier. Isocorydine and methylarmepavine are intriguing treatment options for ulceritis because of their diverse mechanisms of action. To fully comprehend their mechanisms and maximise their application in the treatment of gastrointestinal illnesses, more research is required[59].

Antidiabetic activity

These compounds may be the cause of the antidiabetic and antioxidant qualities of A. squamosa leaf extract. Because streptozotocin specifically damages islet cells, blood glucose levels rise as a result of its induction. Since gliclazide is known to cause hypoglycemia, it is frequently

employed as the standard medication in STZ-induced models of mild diabetes to compare the antidiabetic effects of other substances. When A. squamosa leaf extract was given to diabetic rats that had been given STZ, their blood glucose levels significantly dropped[60-62].

Antiplatelet activity

Ent-kaurane diterpenoids, which are isolated from A. squamosa's stem, are being investigated for their antiplatelet properties. The entkaurane diterpenoids "ent-Kaur-16-en-19-oic acid" and "16alpha-hydro19-al-entkauran-17-oic acids" show how it is possible to misuse Annona species to produce extremely valuable restorative products[63,64].

Antifertility activity

Testicular indices were significantly lower on average in animal individuals that were given A. squamosa leaf extract. This occurred as a result of testicular mass loss, which is an indication of antifertility action. The leaf extract from A. squamosa affects the hormonal systems that control spermatogenesis, lowering the caudal epididymal sperm count[65]. When the ethanol extract was given, many spermatozoa abnormalities were visible, including bent tails, spermatozoa without tails, spermatozoa without heads, and spermatozoa with two heads[66].

Antidiarrheal activity

Alkaloids, tannins, steroids, flavonoids, and saponins are all found in A. squamosa leaves. Tannin is an astringent that can be used to treat diarrhoea and dysentery[67]. To be more specific, the chemical leaves are alkaloids, 2, 3, 4-tetrahydroisoquinoline, and 6-dimethoxy-1-(α-hydroxy-4-methoxybenzyl)-2-methyl-1[68]. An investigation demonstrated the antidiarrheal properties of an ethanolic extract of A. squamosa leaves[69,70].

Anti-hypertensive activity

There have been strong results in controlling hypertension with the methanolic extract of A. squamosa seeds. Research conducted on a rat model showed that the extract might reverse aortic vasoconstriction, a major contributing factor to hypertension. After being separated from the seeds, the phytoconstituent cyclosquamosin was discovered to block voltage-dependent calcium channels, which lessened the contraction of the vascular smooth muscle and increased vasodilation. According to these results, cyclosquamosin may be a new antihypertensive medication, and A. squamosa seeds may provide less harmful alternatives to traditional medications. Its safety, clinical effectiveness, and pharmacokinetics require more investigation [71].

Hepatoprotective activity

Lipid peroxidation inhibitors found in A. squamosa leaves shield the liver, and their incredibly strong antioxidant activity combats free radicals. Researchers discovered that administering 1000 mg/kg body weight of A. squamosa leaf extract could considerably lower blood levels of glutamate pyruvate transaminase and glutamate oxaloacetate while also increasing protein levels, thereby protecting liver cells[72-74].

Nephrotoxicity activity

After 24 hours, rats' kidney tissue that had been intoxicated by paracetamol was examined histopathologically at the expense of the animals. Upon examination, the tubular epithelium showed severe necrosis and degradation. These alterations are most frequently linked to histological alterations and imply cell degeneration on the side of severe tubular necrosis. Pretreated (200 and 400 mg/kg) ethanolic extract of A. squamosa leaves showed negligible oedema or direct necrosis and significantly ($P < 0.001$) decreased BUN, creatinine, and urate corrosive levels in a urate-dependent manner. At the dosage that seems to have the ability to regenerate kidney cells[75].

Hypolipidemic activity

TGs and total cholesterol levels were found to be greater in diabetic mice than in control mice. A. squamosa leaf extracts, both aqueous and ethanolic, were used in therapy to raise HDL cholesterol while decreasing mean levels of LDL cholesterol, triglycerides, and cholesterol. The activation of the lipoprotein lipase enzyme and the induction of β-cells, which release a reasonable quantity of insulin to remove triglycerides from the plasma, may be the cause of this[76-78].

Cytoprotective activity

A. squamosa exhibits cytoprotective action, as demonstrated by the rise in mucin levels in the pyloric ligation paradigm and the alcohol-induced protection of the aspirin mouse[79].

Immunomodulatory activity

A potent immunostimulant with a nonspecific immunological mechanism may be possible with A. squamosa leaf water extract. Clarias batrachus fish displayed the immunomodulatory movement of leaf extract observed in A. squamosa in haematological parameters. The concentrations of extract (10ml) 50% and (15ml) 100% increased critically. The number of TEC, haemoglobin levels, TLC counts, and differentiating leukocytes all increased, according to an analysis of the haematological parameters in fish blood at that time[80]. After being treated with an ethanol extract of A. squamosa leaves and fruit, haematological data, including haemoglobin and blood cell counts, showed significant modifications. This study's significant rise in WBC assay in treated mice could be the result of immune system stimulation[81-83].

Neuroprotective activity

The leaves of A. squamosa provide a number of benefits. The sugar apple leaf extract, which contains anonaine, can be used to treat epilepsy, mood disorders, and memory problems, according to Reddy et al.'s (2020) study on neurone protection. Phenolic chemicals are present in A. squamosa

leaves, according to a phytochemical examination of the leaf extract utilising petroleum and ethanol[84-86].

Antioxidant activity

The molecules known as antioxidants help prevent or shield living things from harm that results from the unchecked creation of reactive oxygen species[87]. Oxidative stress can lead to several diseases, including diabetes, cancer, and inflammatory disorders. Because they scavenge free radicals, antioxidants can help combat oxidative stress in this situation[88]. It has been shown that various phenolic chemicals and flavonoids, which are natural antioxidants, can shield cells from free radical damage[89]. The ethanol extract of A. squamosa leaves contains flavonoids in the form of rutin and hyperoside, according to the findings of multiple investigations on the antioxidant component content of the leaves. Compounds with biological properties linked to antioxidant processes include rutin and hyperosid[90].

The chloroform solution of A. squamosa leaf extract had a high IC50 of 308.3 mg/mL for free radical scavenging activity. Using a methanol solution, however, their leaf extract demonstrated an IC50 of 342.5 mg/mL for free radical scavenging activity. In contrast, their extract's aqueous solution demonstrated comparatively low free radical scavenging activity (IC50 439.6 mg/mL). At IC50 of 35.26 mg/mL, the extract containing ascorbic acid exhibited the highest level of free radical scavenging activity[91].

Anti-obesity activity

Bioactive components include quercetin, thiamine, epigallocatechin 3-gallate (EGCG), sitosterol, and stigmasterol give A. squamosa the ability to prevent obesity. Adipogenesis is inhibited and lipid metabolism is modulated by quercetin. Thiamine affects lipid and energy metabolism. EGCG promotes fat metabolism and prevents the development of adipocytes. In addition to having anti-inflammatory properties, sitosterol and stigmasterol regulate the absorption of cholesterol. These results lend credence to A. squamosa's status as a natural anti-obesity agent, hence justifying additional investigation to maximise its application in the treatment of obesity and metabolic disorders[92].

Cytotoxicity and Toxicology

After looking through several journals and articles, it was discovered that different authors had provided varying LD50 values and toxicity studies of the chosen plant. For example, the methanolic extract's LD50 value was found to be 5000 mg/kg of body weight[93], while the plant's safety profile was established and stated that it should not exceed 2000 mg/kg of body weight, which is the same as LD50[94,95]. The chosen plant, A. squamosa's seed and leaf extracts had respective values of 510 mg/kg and 500 mg/kg body weight[96]. According to one study, the ethanolic fraction's LD50 value was over 1500 mg/kg body weight, while other investigations found that the plant extract's LD50 was greater than 200 mg/kg body weight[97-99].

Antithyroid activity

The plant's ability to regulate thyroid function was shown when Annona squamosa seed extract (200 mg/kg) was administered to mice with hyperthyroidism (produced using T4) for 10 days. The results indicated encouraging results in restoring the thyroid abnormalities associated with hyperthyroidism. Additionally, mice's thyroids were inhibited by an A. squamosa leaf extract; however, at greater concentrations, indicators of hepatotoxicity were seen[100].

Larvicidal activity

The transmission of dangerous diseases by mosquitoes poses a serious hazard to human health. A number of factors, including the emergence of resistance and cross-resistance, the growing expense, and potential toxicity risks associated with the use of synthetic insecticides, contributed to the recent interest in the development of plant-based treatments. Against An. stephensi and other mosquitoes, Annona squamosa has been shown to have larvicidal and growth-regulating properties. It was determined that Annona squamosa has a high larvicide efficacy against mosquito species; nevertheless, it is necessary to identify the active ingredient that has a poisonous substance against the larval species[101,102].

Insecticidal activity

The common housefly, Musca domestica (Diptera: Muscidae), is a mechanical vector of numerous bacterial and pathogenic germs that affect both humans and animals. These microbes have developed resistance. Annonaceous acetogenins, which were isolated from tree leaves, bark, and seeds, have anti-feedant qualities against insects. When A. squamosa leaf ethanolic extracts were tested for their ability to kill Musca domestica, it was discovered that the extracts' LC50 values ranged between around 282.5 and 550 mg/l. According to the results, the leaf extracts of the aforementioned plant could be used as potential candidates for the creation of bioinsecticides in order to as a more cost-effective and safer substitute for synthetic insecticides, to manage the Musca domestica population. The polyphagous lepidopteran Spodoptera litura (Noctuidae) was used to test crude ethanolic seed extracts of A. squamosa for its ability to prevent larval growth. The extracts demonstrated a substantially higher (20-fold) insecticidal activity[103,104].

Wound healing activity

When applied topically, an ethanolic extract of A. squamosa leaves was found to promote collagen synthesis and cell proliferation, which could aid in wound healing. Another study assessed the wound-healing potential of an alcoholic extract of A. squamosa leaves applied topically to diabetic rats caused by streptozotocin. By boosting collagen,

protein, DNA, and cellular proliferation at the wound site, the extract was shown to aid in wound healing[105,106].

Because of its strong anti-cancer properties, Annona plants are currently attracting a lot of attention. Numerous chemicals discovered in Annona species have exceptional anti-cancer capabilities that have attracted the curiosity of researchers[107-109].

Additionally, research on the use of nanoparticle drug delivery systems combined with various A. squamosa extracts for various therapeutic objectives has significantly increased[110-112]. Additionally, there is growing attention in certain Annona species' prospective antidiabetic effects. Because of all of these factors, A. squamosa is a prime candidate for further research [113-115].

Conclusion

A. squamosa is a useful medicinal plant with a long history of use in traditional medicine for the management and treatment of various illnesses due to its broad range of medicinal applications and pharmacological activity. The goal of this page was to present the plant's activities and availability in its entirety, including its toxicity, phytochemistry, pharmacological activity, traditional uses, and botanical features. Several publications that demonstrated the application of various plant parts in the management and treatment of various diseases were viewed and organised in this article. This article will assist researchers in identifying the various phytochemicals found in various plant parts. Based on these findings, any additional research can be conducted. For example, this plant has not been studied specifically for the treatment of obesity, but there is compelling evidence that it can do so due to the essential phytoconstituents it contains. Antitumor, anticancer, antidiabetic, antimalarial, antithyroidal, antifungal, antibacterial, antigenotoxic, antioxidant, antihypertensive, antiulcer, and many other properties have already been demonstrated for the chosen plants, which have very promising pharmacological approaches for the treatment of various diseases. These properties have been thoroughly explained in this article. In light of the literature study, A. squamosa may be researched in the future, and clinical testing of the plant is crucial to guaranteeing its safety for pharmacological and therapeutic applications.

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