

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.

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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 exist¹. 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 plains². 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 *Annona* 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}.

Annona 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 tubercles⁵.

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 crystals⁶.

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 flowers².

Thin grey bark on irregular branches contains the antimalarial alkaloids duguevalline, roemerolidine, and N-nitrosoxylopin⁷.

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 branches⁸. 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, Annona, Nona, Sugar Apple, Custard Apple. Used parts of the Bullock's Heart plant include leaves, fruits, seeds, and stem bark¹⁰.

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

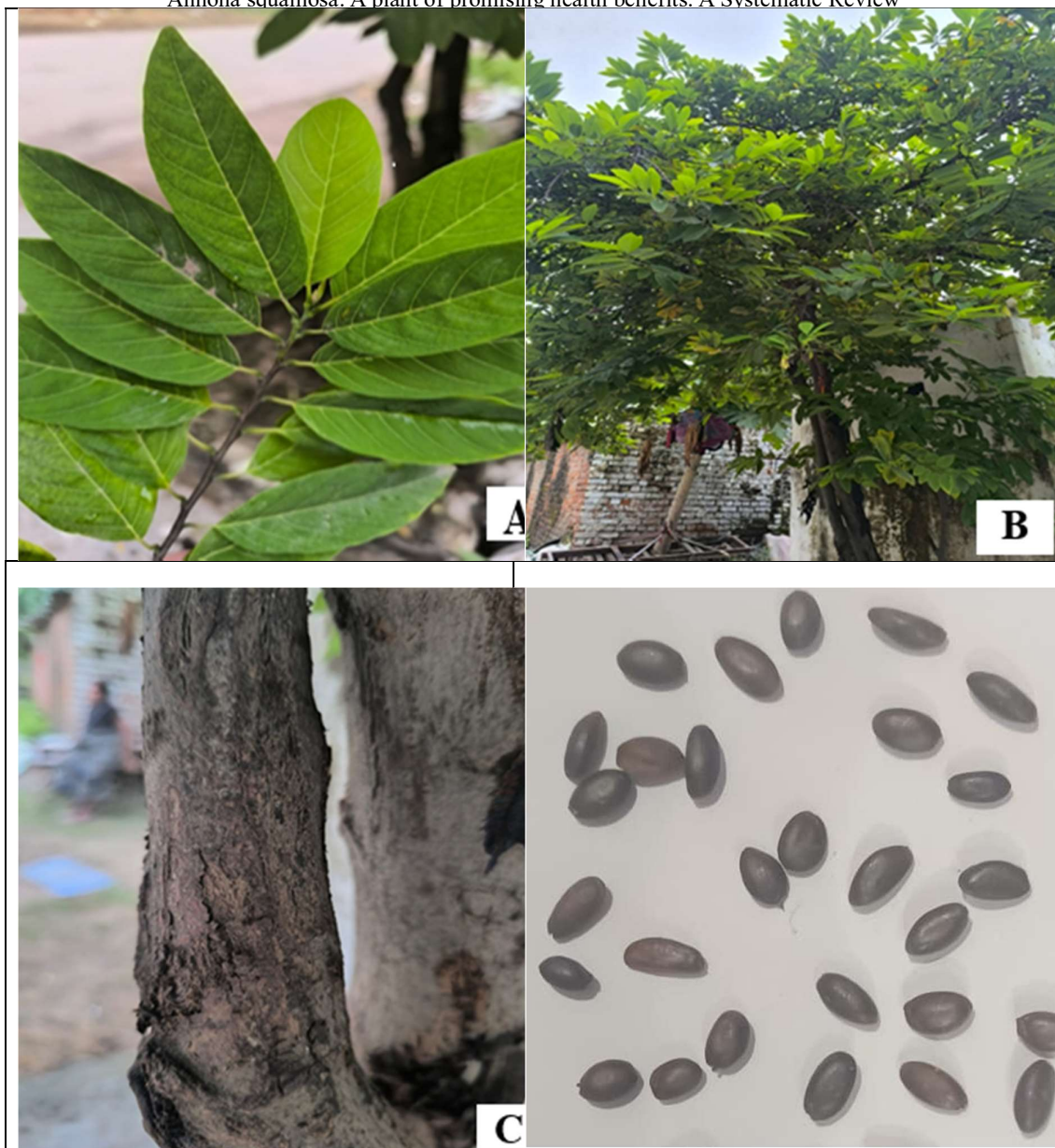
History and Geographical Distribution

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 tears¹¹.

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 quickly¹².

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, acetogenin (annonetulin and isoannonetulin), 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, Oxonalobine, Borneol, Camphene, Camphor, Car-3-ene, β -Caryophyllene, Eugenol, Farnesol, Geraniol, 16-Hetriacontanone, Hexacontanol, Higemamine, Isocorydine, and Limonene 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 seeds¹³⁻¹⁷.

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.

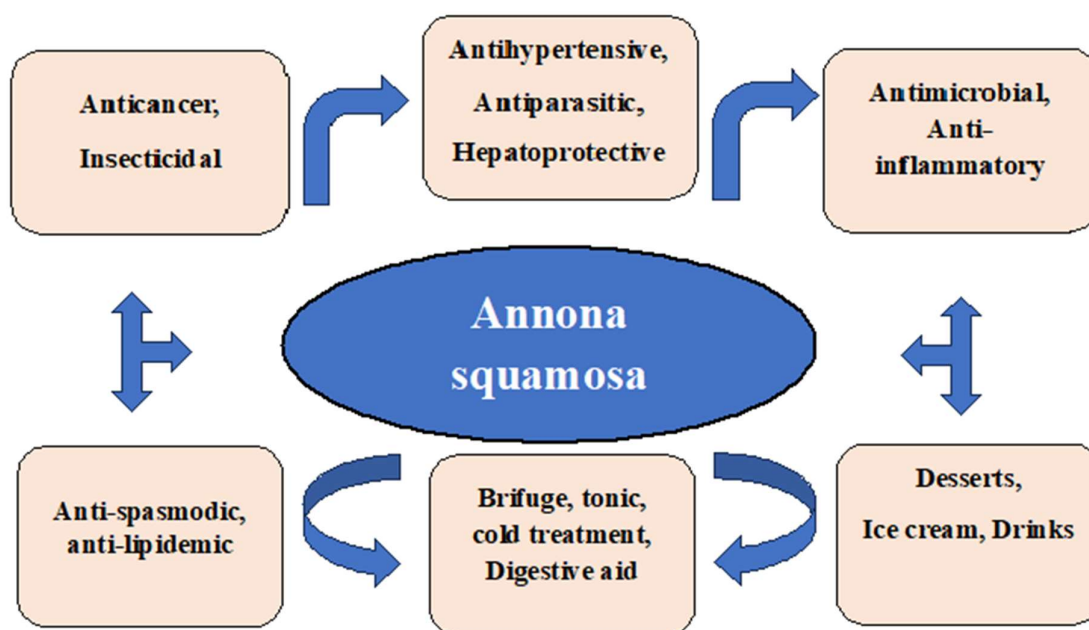
Compared with its seeds and fruit, the *A. squamosa* plant's an Egyptian study found that the highest protein concentration is found in leaves. *A. squamosa* leaf extract, which contains more protein than other *A. squamosa* varieties, can be used by both people and animals to boost the nutritional content 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 extract¹⁸. 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 antitumor cancer, antihypertensive, antioxidant, anti-diabetic, hepatoprotective, antiparasitic, anti-malarial, insecticidal, antibacterial, and molluscicide activities²⁰⁻²².



The leaf of *A. squamosa* is used to treat diarrhoea and urinary tract infections in America, India, and Thailand²³. 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 herbs²⁴⁻²⁷.

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 wounds³². *A. squamosa* leaves, when dried and powdered, are used as a laxative and as an alternate medication for slimy diarrhoea³³. 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 damage³⁴. 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 isolated³⁷.

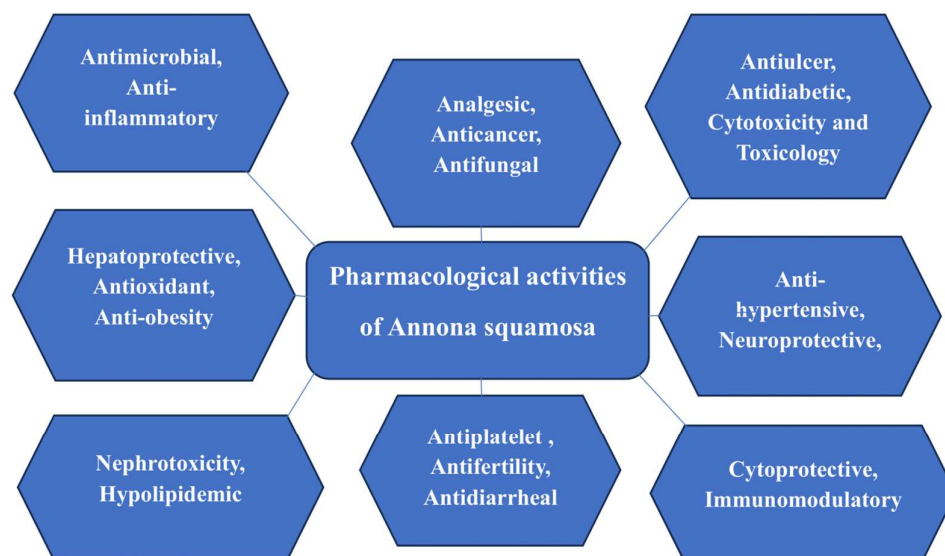
A total of 59 chemical components were found during gas chromatography-mass spectrometry (GC-MS) study of *Annona Squamosa* L. leaves and oil. β caryophyllene, a naturally occurring bicyclic sesquiterpene, accounts for

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 isoanoreticuin. These acetogenins have cytotoxic specificity towards specific human tumours³⁸.

Annona Squamosa's chemical components are identified using nuclear magnetic resonance (NMR) spectroscopy. Bark and roots of L. The bark contains oxyaporphine compounds such as liriodenine and oxoanalogine. The root extract of *Annona Squamosa* L. contains a variety of chemical components, including limonene, camphor, car-3-ene, carvone, borneol, β -caryophyllene, 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, annotemycin-1, annotemycin-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 bark⁴⁵⁻⁴⁷.

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 TNF α and IL-6⁴⁸.

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 extract⁵¹⁻⁵³.

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 ailments⁵³. However, the seeds of this plant contain a toxic component that can be used to eradicate lice and head lice⁵⁴. The leaves of *A. squamosa* have hepatoprotective and immunomodulatory properties⁵⁵.

A. squamosa has been studied in the past for its anti-cancer properties, specifically its acetogenin and other non-alkaloidal moieties⁵⁶. 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 ulcers⁵⁸.

A. squamosa has active phytoconstituents that may be used to treat ulcerative colitis, especially methylarnepavine 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 methylarnepavine 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 required⁵⁹.

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 dropped⁶⁰⁻⁶².

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 "16 α -hydro-19-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 count⁶⁵. When the ethanol extract was given, many spermatozoa abnormalities were visible, including bent tails, spermatozoa without tails, spermatozoa without heads, and spermatozoa with two heads⁶⁶.

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 dysentery⁶⁷. To be more specific, the chemical leaves are alkaloids, 2, 3, 4-

tetrahydroisoquinoline, and 6-dimethoxy-1-(α -hydroxy-4-methoxybenzyl)-2-methyl-1⁶⁸. 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 investigation⁷¹.

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 cells⁷²⁻⁷⁴.

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 cells⁷⁵.

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 this⁷⁶⁻⁷⁸.

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 mouse⁷⁹.

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 time⁸⁰. 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 stimulation⁸¹⁻⁸³.

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 ethanol⁸⁴⁻⁸⁶.

Antioxidant activity

The molecules known as antioxidants help prevent or shield living things from harm that results from the unchecked creation of reactive oxygen species⁸⁷. 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 situation⁸⁸. It has been shown that various phenolic chemicals and flavonoids, which are natural antioxidants, can shield cells from free radical damage⁸⁹. 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 hyperosid⁹⁰.

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 activity⁹¹.

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 disorders⁹².

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 weight⁹³, 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 weight⁹⁶. 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 weight⁹⁷⁻⁹⁹.

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 seen¹⁰⁰.

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 researchers¹⁰⁷⁻¹⁰⁹.

Additionally, research on the use of nanoparticle drug delivery systems combined with various *A. squamosa* extracts for various therapeutic objectives has significantly increased¹¹⁰⁻¹¹². 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 research¹¹³⁻¹¹⁵.

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.

References: -

1. Leatemia, J. Audrey, and Murray B. Isman. "Insecticidal activity of crude seed extracts of *Annona* spp., *Lansium domesticum* and *Sandoricum koetjape* against lepidopteran larvae." *Phytoparasitica* 32 (2004): 30-37.
2. Vyas, Kapil, Hansraj Manda, Rahul Kumar Sharma, and Gaurav Singhal. "An update review on *Annona Squamosa*." *IJPT* 3, no. 2 (2012): 107-118.
3. Chuang, Pei-Hsuan, Pei-Wen Hsieh, Yu-Liang Yang, Kuo-Feng Hua, Fang-Rong Chang, Jentaie Shiea, Shih-Hsiung Wu, and Yang-Chang Wu. "Cyclopeptides with anti-inflammatory activity from seeds of *Annona montana*." *Journal of Natural Products* 71, no. 8 (2008): 1365-1370.
4. Shashirekha, Mysore N., Revathy Baskaran, Lingamallu Jaganmohan Rao, Munusamy R. Vijayalakshmi, and Somasundaram Rajarathnam. "Influence of processing conditions on flavour compounds of custard apple (*Annona squamosa* L.)." *LWT-Food Science and Technology* 41, no. 2 (2008): 236-243.
5. Kharchoufa, Loubna, Ilyass Alami Merrouni, Amal Yamani, and Mostafa Elachouri. "Profile on medicinal plants used by the people of North Eastern Morocco: Toxicity concerns." *Toxicon* 154 (2018): 90-113.
6. Kumar, C. Dinesh, K. Rajendran, Richard Lobo, and Annie Shirwaikar. "An identity based pharmacognostical profile of folium *Annona squamosa*." *Natural Product Sciences* 11, no. 4 (2005): 213-219.
7. Johns, Tylor, Arnold Windust, Thomas Jurgens, and Saleh Muhammad Mansor. "Antimalarial alkaloids isolated from *Annona squamosa*." *Phytopharmacology* 1, no. 3 (2011): 49-53.
8. Podsiedlik, Maria, Magdalena Markowicz-Piasecka, and Joanna Sikora. "Erythrocytes as model cells for biocompatibility assessment, cytotoxicity screening of xenobiotics and drug delivery." *Chemico-Biological Interactions* 332 (2020): 109305.
9. Litz, Richard E., ed. *Biotechnology of fruit and nut crops*. CAB International, 2005.
10. Safira, Arifia, Prasita Widayani, Dhiya An-Najaaty, Cinta Atsa Mahesa Rani, Mela Septiani, Yan Arengga Syah Putra, Tridiganita Intan Solikhah, Aswin Rafif Khairullah, and Hartanto Mulyo Raharjo. "A review of an important plant: *Annona squamosa* leaf." *Pharmacognosy Journal* 14, no. 2 (2022).
11. Kaur, Jaswinder, Amit Mittal, Saurabh Singh, and Dileep Singh Baghel. "A Comprehensive Review on custard apple (*Annona squamosa*)." (2018).
12. Ahirwar, Suneel, Saumya Jain, and Parveen Nisha. "*Annona squamosa* L.: A brief review on biological activities and their phytochemicals." *Asian Journal of Pharmacy and Pharmacology* 9, no. 1 (2023): 13-19.
13. Yang, Tsang-Hsiung, and Chi-Ming Chen. "Studies on the Constituents of *Annona squamosa* L." *Journal of the Chinese Chemical Society* 17, no. 4 (1970): 243-250.
14. Morita, Hiroshi, Yumiko Sato, Kit-Lam Chan, Chee-Yan Choo, Hideji Itokawa, Koichi Takeya, and Jun'ichi Kobayashi. "Samoquasine A, a Benzoquinazoline Alkaloid from the Seeds of *Annona squamosa*." *Journal of Natural Products* 63, no. 12 (2000): 1707-1708.
15. Yang, Yu-Liang, Fang-Rong Chang, and Yang-Chang Wu. "Annosqualine: A novel alkaloid from the stems of *Annona squamosa*." *Helvetica chimica acta* 87, no. 6 (2004): 1392-1399.
16. Zahid, Mohammad, Mohd Mujahid, Prashant Kumar Singh, Sana Farooqui, Kuldeep Singh, Shahla Parveen, and Muhammad Arif. "*Annona squamosa* linn.(Custard apple)An aromatic medicinal plant fruit with immense nutraceutical and therapeutic potentials." *Int. J. Pharm. Sci. Res* 9, no. 5 (2018): 1745-1759.
17. Lim, T. K. "*Annona squamosa*." In *Edible Medicinal and Non-Medicinal Plants: Volume 1, Fruits*, pp. 207-220. Dordrecht: Springer Netherlands, 2011.
18. Barros, Francisca Janielle, Raíra Justino Oliveira Costa, Francisco Rafael Alves

- Santana Cesário, Lindaiane Bezerra Rodrigues, José Galberto Martins da Costa, Henrique Douglas Melo Coutinho, Hericka Bruna Figueiredo Galvao, and Irwin Rose Alencar de Menezes. "Activity of essential oils of Piper aduncum and Cinnamomum zeylanicum by evaluating osmotic and morphologic fragility of erythrocytes." *European Journal of Integrative Medicine* 8, no. 4 (2016): 505-512.
19. Brandão, Anary PM Egydio, and Déborah Yara AC Santos. "Nutritional value of the pulp of different sugar apple cultivars (Annona squamosa L.)." In *Nutritional composition of fruit cultivars*, pp. 195-214. Academic Press, 2016.
20. Chen, Yong, Yayun Chen, Yeye Shi, Chengyao Ma, Xunan Wang, Yue Li, Yunjie Miao, Jianwei Chen, and Xiang Li. "Antitumor activity of Annona squamosa seed oil." *Journal of Ethnopharmacology* 193 (2016): 362-367.
21. Yang, Run-mei, Wen-min Li, Wei-jun Hu, Wen-hua Huang, Chun-yan Zhu, Jing-guang Yu, Xin Zhao, Da-yong Cai, and Nan-nan Gao. "Anticancer effect of total annonaceous acetogenins on hepatocarcinoma." *Chinese journal of integrative medicine* 21 (2015): 682-688.
22. Oo, Win Min, and Myat Mon Khine. "Pharmacological activities of Annona squamosa: Updated." *Chemistry* 3, no. 6 (2017): 86-93.
23. Yusha'u, M., D. W. Taura, B. Bello, and N. Abdullahi. "Screening of Annona squamosa extracts for antibacterial activity against some respiratory tract isolates." (2011): 237-241.
24. Shenoy, Chitra, M. B. Patil, and Ravi Kumar. "Antibacterial and wound healing activity of the leaves of Annona squamosa Linn. (Annonaceae)." *Research Journal of Pharmacognosy and Phytochemistry* 1, no. 1 (2009): 44-50.
25. Andalia, Nurlena, Rina Yulian, and Muhammad Ridhwan. "Persepsi masyarakat gampong Lampaya Lhoknga terhadap tanaman sirsak sebagai pencegah kanker." *Serambi Saintia: Jurnal Sains dan Aplikasi* 6, no. 1 (2018).
26. Pandey, Neha, and Dushyant Barve. "Phytochemical and pharmacological review on Annona squamosa Linn." *International Journal of Research in Pharmaceutical and Biomedical Sciences* 2, no. 4 (2011): 1404-1412.
27. Bhattacharya, Anshuman, and Raja Chakraverty. "The pharmacological properties of Annona squamosa Linn: A Review." *Int. J. Pharm. Eng* 4, no. 2 (2016): 692-699.
28. Zahid, Mohammad, Mohd Mujahid, Prashant Kumar Singh, Sana Farooqui, Kuldeep Singh, Shahla Parveen, and Muhammad Arif. "Annona squamosa linn.(Custard apple)An aromatic medicinal plant fruit with immense nutraceutical and therapeutic potentials." *Int. J. Pharm. Sci. Res* 9, no. 5 (2018): 1745-1759.
29. Podsiedlik, Maria, Magdalena Markowicz-Piasecka, and Joanna Sikora. "Erythrocytes as model cells for biocompatibility assessment, cytotoxicity screening of xenobiotics and drug delivery." *Chemico-Biological Interactions* 332 (2020): 109305.
30. Kumar, Manoj, Sushil Changan, Maharishi Tomar, Uma Prajapati, Vivek Saurabh, Muzaffar Hasan, Minnu Sasi et al. "Custard apple (Annona squamosa L.) leaves: Nutritional composition, phytochemical profile, and health-promoting biological activities." *Biomolecules* 11, no. 5 (2021): 614.
31. de Freitas, Mariana V., M. Netto Rita de Cássia, Juliana C. da Costa Huss, Tatiana Maria T. de Souza, Junia O. Costa, Cynthia B. Firmino, and Nilson Penha-Silva. "Influence of aqueous crude extracts of medicinal plants on the osmotic stability of human erythrocytes." *Toxicology in vitro* 22, no. 1 (2008): 219-224.
32. Singh, Yogendra, Prerak Bhatnagar, and Nidhika Thakur. "A review on insight of immense nutraceutical and medicinal potential of custard apple (Annona squamosa Linn.)." *Int. J. Chem. Stud* 7, no. 2 (2019): 1237-1245.
33. Nagori, R., P. Sharma, and S. D. Purohit. "Molecular characterization of diversity in Annona squamosa L.: a high value tropical medicinal plant." (2018): 20203410351.
34. Marahatta, Anant Babu, Aashish Aryal, Ram Chandra Basnyat, and C. Anant Babu Marahatta. "The phytochemical and nutritional analysis and biological activity of Annona squamosa Linn." *Int. J. Herb. Med* 7, no. 4 (2019): 19-28.
35. Ko, Gyeong-A., Hye Rim Kang, Jeong Yong Moon, Meran Keshawa Ediriweera, Sangmi Eum, Tran The Bach, and Somi Kim Cho. "Annona squamosa L. leaves inhibit alpha-melanocyte-stimulating hormone (α -MSH) stimulated melanogenesis via p38 signaling pathway in B16F10 melanoma cells." *Journal of Cosmetic Dermatology* 19, no. 7 (2020): 1785-1792.

36. Duarte, Antonia Eliene, Emily Pansera Waczuk, Katiane Roversi, Maria Arlene Pessoa Da Silva, Luiz Marivando Barros, Francisco Assis Bezerra Da Cunha, Irwin Rose Alencar De Menezes et al. "Polyphenolic composition and evaluation of antioxidant activity, osmotic fragility and cytotoxic effects of Raphiodon echinus (Nees & Mart.) Schauer." *Molecules* 21, no. 1 (2015): 2.
37. Singh, Yogendra, Prerak Bhatnagar, and Nidhika Thakur. "A review on insight of immense nutraceutical and medicinal potential of custard apple (*Annona squamosa* Linn.)." *Int. J. Chem. Stud* 7, no. 2 (2019): 1237-1245.
38. Pandey, Neha, and Dushyant Barve. "Phytochemical and pharmacological review on *Annona squamosa* Linn." *International Journal of research in pharmaceutical and biomedical sciences* 2, no. 4 (2011): 1404-1412.
39. Pérez-Amador, M. C., A. González-Esquinca, M. C. Morales, and F. Toriz. "Oxoaporphine alkaloids in *Guatteria diospyroides* baill. and *Annona squamosa* L." *Phyton* 53 (2004): 53-55.
40. Yu, J. G., X. Z. Luo, Lan Sun, D. Y. Li, W. H. Huang, and C. Y. Liu. "Chemical constituents from the seeds of *Annona squamosa*." *Yao Xue Xue Bao= Acta Pharmaceutica Sinica* 40, no. 2 (2005): 153-158.
41. Neethu Simon, K., R. Santhoshkumar, and S. Kumar Neethu. "Phytochemical analysis and antimicrobial activities of *Annona squamosa* (L) leaf extracts." *Journal of Pharmacognosy and Phytochemistry* 5, no. 4 (2016): 128-131.
42. Kachhawa, J. B. S., N. Sharma, S. Tyagi, and K. K. Sharma. "Screening of stem bark methanol extract of *Annona squamosa* for antibacterial activity." *Int J Curr Pharm Res* 4, no. 1 (2012): 48-50.
43. Padhi, L. P., S. K. Panda, S. N. Satapathy, and S. K. Dutta. "In vitro evaluation of antibacterial potential of *Annona squamosa* L. and *Annona reticulata* L. from Similipal Biosphere Reserve, Orissa, India." (2011): 133-142.
44. Aher, P. S., Y. S. Shinde, and P. P. Chavan. "In vitro evaluation of antibacterial potential of *Annona squamosa* L. against pathogenic bacteria." *International Journal of Pharmaceutical Sciences and Research* 3, no. 5 (2012): 1457-60.
45. Patel, Jayshree D., and Vipin Kumar. "*Annona squamosa* L.: phytochemical analysis and antimicrobial screening." *J Pharm Res* 1, no. 1 (2008): 34-38.
46. Chavan, M. J., P. S. Wakte, and D. B. Shinde. "Analgesic and anti-inflammatory activity of Caryophyllene oxide from *Annona squamosa* L. bark." *Phytomedicine* 17, no. 2 (2010): 149-151.
47. Chavan, M. J., P. S. Wakte, and D. B. Shinde. "Analgesic and anti-inflammatory activities of 18-acetoxy-ent-kaur-16-ene from *Annona squamosa* L. bark." *Inflammopharmacology* 19 (2011): 111-115.
48. Badola, Hemant K., and Stephen Aitken. "The Himalayas of India: A treasury of medicinal plants under siege." *Biodiversity* 4, no. 3 (2003): 3-13.
49. Aher, P. S., Y. S. Shinde, and P. P. Chavan. "In vitro evaluation of antibacterial potential of *Annona squamosa* L. against pathogenic bacteria." *International Journal of Pharmaceutical Sciences and Research* 3, no. 5 (2012): 1457-60.
50. Korah, Mejo C., Junaid Rahman, R. Rajeswari, Haja Sherief, V. Lalitha, S. Sengottavelu, and T. Sivakumar. "Evaluation of diuretic efficacy and antiurolithiatic potential of ethanolic leaf extract of *Annona squamosa* Linn. in experimental animal models." *Indian Journal of Pharmacology* 52, no. 3 (2020): 196-202.
51. do Nascimento Silva, Hallison, Suzana Vieira Rabêlo, Tâmara Coimbra Diniz, Fernanda Granja da Silva Oliveira, Roxana Braga de Andrade Teles, Juliane Cabral Silva, Mariana Gama e Silva, Henrique Douglas Melo Coutinho, Irwin Rose Alencar de Menezes, and Jackson Roberto Guedes da Silva Almeida. "Antinociceptive and anti-inflammatory activities of ethanolic extract from atemoya (*Annona cherimola* Mill x *Annona squamosa* L.)." *African Journal of Pharmacy and Pharmacology* 11, no. 18 (2017): 224-232.
52. Pawar, Digambar Subhashrao, and Sahera Nasreen. "HR-LCMS of phytoconstituents and antifungal activity of medicinal plants." *J. Med. Plants* 6, no. 1 (2018): 173-176.
53. Ansori, Arif Nur Muhammad, Amaq Fadholly, Annise Proboningrat, Yulanda Antonius, Suhailah Hayaza, Raden Joko Kuncoroningrat Susilo, Bilqis Inayatillah et al. "Novel antiviral investigation of *Annona squamosa* Leaf extract against the Dengue Virus Type-2: In vitro study." *Pharmacognosy Journal* 13, no. 2 (2021).

54. Novianti, Dewi. "Toksisitas Ekstrak Daun Srikaya (*Annona squamosa* Linn.) Terhadap Jamur *Fusarium* sp." *Sainmatika: Jurnal Ilmiah Matematika dan Ilmu Pengetahuan Alam* 16, no. 2 (2019): 130-136.
55. Saha, Rajsekhar. "Pharmacognosy and pharmacology of *Annona squamosa*." *Int. J. Pharm. Life Sci* 2 (2011): 1183-1189.
56. Soni, Vishal Kumar, Manisha Pathak, Dinesh Kumar Yadav, Rakesh Maurya, Mahendra Sahai, Swatantra Kumar Jain, and Shailja Misra-Bhattacharya. "Immunomodulatory constituents from *Annona squamosa* twigs provoke differential immune response in BALB/c mice." *Current Science* (2013): 1224-1230.
57. Reddy, Chada Raji, Motatipally Damoder Reddy, and Uredi Dilipkumar. "Total synthesis of a pyrrole lactone alkaloid, longanlactone." *European Journal of Organic Chemistry* 2014, no. 28 (2014): 6310-6313.
58. Yadav DK, Singh N, Dev K. Anti-ulcer constituents of *Annona squamosa* twigs. *Fitoterapia*. 2011;82(4):666-675.
59. Yadav, Dinesh K., Neetu Singh, Kapil Dev, Rolee Sharma, Mahendra Sahai, Gautam Palit, and Rakesh Maurya. "Anti-ulcer constituents of *Annona squamosa* twigs." *Fitoterapia* 82, no. 4 (2011): 666-675.
60. Oo, Win Min, and Myat Mon Khine. "Pharmacological activities of *Annona squamosa*: Updated." *Chemistry* 3, no. 6 (2017): 86-93.
61. Basha, SK Hayath, and S. Subramanian. "Biochemical evaluation of antidiabetic and antioxidant potentials of *Annona squamosa* leaves extracts studied in STZ induced diabetic rats." *International Journal of Pharmaceutical Sciences and Research* 2, no. 3 (2011): 643.
62. Kaleem, M., M. Asif, Q. U. Ahmed, and B. Bano. "Antidiabetic and antioxidant activity of *Annona squamosa* extract in streptozotocin-induced diabetic rats." *Singapore medical journal* 47, no. 8 (2006): 670.
63. Shirwaikar, Annie, K. Rajendran, C. Dinesh Kumar, and Ramgopal Bodla. "Antidiabetic activity of aqueous leaf extract of *Annona squamosa* in streptozotocin–nicotinamide type 2 diabetic rats." *Journal of ethnopharmacology* 91, no. 1 (2004): 171-175.
64. Yang, Yu-Liang, Fang-Rong Chang, Chin-Chung Wu, Wei-Ya Wang, and Yang-Chang Wu. "New E Nt-Kaurane Diterpenoids with Anti-Platelet Aggregation Activity from *Annona Quamosa*." *Journal of natural products* 65, no. 10 (2002): 1462-1467.
65. Singh, Yogendra, Prerak Bhatnagar, and Nidhika Thakur. "A review on insight of immense nutraceutical and medicinal potential of custard apple (*Annona squamosa* Linn.)." *Int. J. Chem. Stud* 7, no. 2 (2019): 1237-1245.
66. Kushwaha, Veena B., and Preeti Singh. "Effect of Ethanolic Extract of Different Parts of Plant (*Annona squamosa*) on the fertility of male rats." *Biomed J Sci Tech Res* 1, no. 5 (2017): 1319-1324.
67. Hidayati, Nur Laili Dwi, Tita Nopianti, Nur Rahayuningsih, Yuliana Dewi, and Yani Suryani. "Antifertility activities of ethanol extract of sugar apple leaves (*Annona squamosa* L.) in the reproductive system: spermatogenesis and sperm quality study." *Pharmaciana* 8, no. 2 (2018): 339-348.
68. Agrawal, Anurag A., Georg Petschenka, Robin A. Bingham, Marjorie G. Weber, and Sergio Rasmann. "Toxic cardenolides: chemical ecology and coevolution of specialized plant–herbivore interactions." *New Phytologist* 194, no. 1 (2012): 28-45.
69. Al-Ghazzawi, Adel M. "Anti-cancer activity of new benzyl isoquinoline alkaloid from Saudi plant *Annona squamosa*." *BMC Chemistry* 13 (2019): 1-6.
70. Safira, Arifia, Prasita Widayani, Dhiya An-Najaaty, Cinta Atsa Mahesa Rani, Mela Septiani, Yan Arengga Syah Putra, Tridiganita Intan Solikhah, Aswin Rafif Khairullah, and Hartanto Mulyo Raharjo. "A review of an important plant: *Annona squamosa* leaf." *Pharmacognosy Journal* 14, no. 2 (2022).
71. Afroz, Nahida, Md Ahsanul Hoq, Sharmin Jahan, Md Mainul Islam, Firoz Ahmed, A. F. M. Shahid-Ud-Daula, and M. D. Hasanuzzaman. "Methanol soluble fraction of fruits of *Annona muricata* possesses significant antidiarrheal activities." *Heliyon* 6, no. 1 (2020).
72. Ma, Chengyao, Yayun Chen, Jianwei Chen, Xiang Li, and Yong Chen. "A review on *Annona squamosa* L.: phytochemicals and biological activities." *The American Journal of Chinese Medicine* 45, no. 05 (2017): 933-964.
73. Raj, D. Sobiya, J. Jannet Vennila, C. Aiyavu, and K. Panneerselvam. "The hepatoprotective effect of alcoholic extract of *Annona squamosa* leaves on experimentally induced liver injury in

- Swiss albino mice." *International Journal of Integrative Biology* 5, no. 3 (2009): 182-186.
74. Mehta, Shuchi Dave, and Sarvesh Paliwal. "Hepatoprotective activity of hydroalcoholic extract of *Annona squamosa* seeds." *Int J Pharm Phyto Res* 9 (2017): 997-1000.
75. Rajeshkumar, S., B. Tamilarasan, and V. Sivakumar. "Phytochemical screening and hepatoprotective efficacy of leaves extracts of *Annona squamosa* against paracetamol induced liver Toxicity in rats." *Int. J. Pharmacogn* 22 (2015): 178-185.
76. Neelima, S., P. Dwarakanadha Reddy, and Chandra Sekhar Kothapalli Bannoth. "Nephroprotective activity of *Annona Squamosa* leaves against paracetamol-induced nephrotoxicity in rats: in vitro and in vivo experiments." *Future Journal of Pharmaceutical Sciences* 6 (2020): 1-8.
77. Sharma, Sanjay Kumar, Moti Lal Gupta, and Baidyanath Kumar. "Hypocholesterolemic efficacy of *Annona squamosa* (L.) extract in diabetic models." *J. Biotechnol. Biochem* 5 (2019): 41-45.
78. El-Baz, Dina M., and A. K. Hssan. "Effects of Egyptian *Annona squamosa* leaves extracts against alloxan-induced hyperglycemia in rats." *World J. Pharm. Pharm. Sci* 8 (2019): 145-163.
79. Rahman, Hafeedza Abdul, Najla Gooda Sahib, Nazamid Saari, Faridah Abas, Amin Ismail, Muhammad Waseem Mumtaz, and Azizah Abdul Hamid. "Anti-obesity effect of ethanolic extract from *Cosmos caudatus* Kunth leaf in lean rats fed a high-fat diet." *BMC complementary and alternative medicine* 17 (2017): 1-17.
80. Saha, Rajsekhar. "Pharmacognosy and pharmacology of *Annona squamosa*." *Int. J. Pharm. Life Sci* 2 (2011): 1183-1189.
81. Paul, Runa, Asha Khanna, Daya Shankar Gautam, Rita Bhandari, Divya Patel, and Pranjul Nigam. "Effect of aqueous leaf extract of *Annona squamosa* on *Clarias batrachus* fish infected with *Aeromonas hydrophila* concerning haematological parameters." *World J. Pharm. Res* 7 (2017): 992-1005.
82. Singh, Preeti, and Veena Batra Kushwaha. "Effect of ethanolic extract of the leaves of plant *Annona squamosa* on hematological and biochemical parameters in normal rats." *Int J Environ Agric Biotechnol* 2, no. 1 (2017): 273-276.
83. Soni, Vishal Kumar, Dinesh Kumar Yadav, Nasreen Bano, Preety Dixit, Manisha Pathak, Rakesh Maurya, Mahendra Sahai, Swatantra Kumar Jain, and Shailja Misra-Bhattacharya. "N-methyl-6, 7-dimethoxyisoquinolone in *Annona squamosa* twigs is the major immune modifier to elicit polarized Th1 immune response in BALB/c mice." *Fitoterapia* 83, no. 1 (2012): 110-116.
84. Sultana, Nighat. "Lipoxygenase inhibition by novel fatty acid ester from *Annona squamosa* seeds." *Journal of Enzyme Inhibition and Medicinal Chemistry* 23, no. 6 (2008): 877-881.
85. Somasekhar Reddy, Kanala, Bhupalam Pradeepkumar, Akkiraju Sudheer, and Mallela Vijayajyothi. "Effect of aluminium chloride induced Alzheimer's disease in rats." *Egyptian Pharmaceutical Journal* 19, no. 4 (2020): 330-337.
86. Porwal, Mayur, and Arvind Kumar. "Neuroprotective effect of *Annona squamosa* & (-) Anonaine in decreased GABA receptor of epileptic rats." *Journal of Applied Pharmaceutical Science* 5, no. 1 (2015): 018-023.
87. Varadharajan, Vanitha, Umadevi Kumba Janarthanan, and Vijayalakshmi Krishnamurthy. "Physicochemical, phytochemical screening and profiling of secondary metabolites of *Annona squamosa* leaf extract." *World Journal of Pharmaceutical Research* 1, no. 4 (2012): 1143-1164.
88. Srividya, B. Y., K. Ravishankar, and P. P. Bhandhavi. "Evaluation of in vitro antioxidant activity of *Calotropis procera* fruit extract." (2013): 573-578.
89. Kiranmayi, G. V. N., and S. Thirumala Devi. "Evaluation of anti-fatigue and antioxidant activities of ethanolic leaf extracts of *Annona squamosa* and *Annona reticulata*." *Biochem Biotechnol Res* 8, no. 3 (2020): 34-42.
90. Arshan, M. M. K., F. Magi, and R. Mishra. "Phytochemical screening and antioxidant activity of different solvent extracts from *Annona squamosa* Linn. leaves." *Asian J Adv Res* 4, no. 1 (2020): 35-40.
91. Kalidindi N, Thimmaiah NV, Jagadeesh NV, Nandeep R, Swetha S, Kalidindi B. Antifungal and antioxidant activities of organic and aqueous extracts of *Annona squamosa* Linn. leaves. *J Food Drug Anal.* 2015;23(4):795-802.
92. Pratap Singh, Ravi, and Ashok Kumar Pattnaik. "Anti-obesity potential of bioactive guided fractions of *Annona squamosa* linn. leaves extract: a combination of in-vitro, in-vivo and in-silico studies along with profiling of lead

- compounds by HPTLC MS-MS n method." *3 Biotech* 13, no. 6 (2023): 171.
93. Onwusonye, J. C., A. Uwakwe, A. Patrick, and K. P. Iwuanyanwu. "Acute and sub-acute toxicity studies of methanol leaf extracts of *Annona squamosa* linn. in mice." *Sky J Biochem Res* 3, no. 7 (2014): 053-059.
94. Madhu, C. H., P. Jonathan Brainard, G. Prithvi Raj, J. Swapn, and A. Samba Siva Rao. "Anti ulcer activity of aqueous extract of *Annona squamosa* leaves on rats." *International Journal of Pharmaceutical Sciences and Research* 3, no. 11 (2012): 4429.
95. Sharma, A., and V. N. P. Goray. "Pharmacognostical studies on the leaf of *Annona squamosa* Linn." *Pharmacogn. J* 1 (2009): 88-93.
96. El-Banna, E., A. Ramadan, and H. Sayed. "Some pharmacological and toxicological activities of *Annona squamosa* linn. Ethanolic extract." *WORLD J Pharm Pharm Sci S SJIF Impact Factor* 6, no. 5 (2016): 188-202.
97. Kumar, S. A., V. Venkatarathanamma, N. Saibabu, and S. K. Ram. "Antipyretic activity of *Annona* plants leaves on brewer's yeast induced febrile rats." *Asian Journal of Pharmaceutical and clinical research* 8, no. 3 (2015): 210-212.
98. Singh, Dewasya Pratap, Brijeshkunvar Mishra, and Richa Mishra. "Anti-nociceptive and anti-inflammatory activity of *Annona squamosa* L. leaf extract in mice and rats." *Research Journal of Pharmacognosy and Phytochemistry* 4, no. 3 (2012): 182-185.
99. Masimba, Pax J., Ester Innocent, and Baraka Samwel. "Oral acute toxicity study of *annona squamosa* l. Leaves extract and fractions in albino mice." *Journal of Advanced Scientific Research* 7, no. 1 (2016): 38-42.
100. Shaikh, Noor Mohammad, Shaikh Muzammil, and Shaikh Mohammad Sofi Ali. "A Review on *Annona squamosa* L." *International Journal of Research in Pharmacy and Allied Science* 4, no. 4 (2025): 56-65.
101. Kaushik, R., and P. Saini. "Screening of some semi-arid region plants for larvicidal activity against *Aedes aegypti* mosquitoes." *Journal of Vector Borne Diseases* 46, no. 3 (2009): 244.
102. Magadula, Joseph J., Ester Innocent, and Joseph N. Otieno. "Mosquito larvicidal and cytotoxic activities of 3 *Annona* species and isolation of active principles." *J Med Plants Res* 3, no. 9 (2009): 674-680.
103. Begum, Nigat, Bechan Sharma, and Ravi S. Pandey. "Evaluation of insecticidal efficacy of *Calotropis procera* and *Annona squamosa* ethanol extracts against *Musca domestica*." *Journal of Biofertilizers & Biopesticides* 1, no. 1 (2010): 2-6.
104. Leatemala, J. Audrey, and Murray B. Isman. "Insecticidal activity of crude seed extracts of *Annona* spp., *Lansium domesticum* and *Sandoricum koetjape* against lepidopteran larvae." *Phytoparasitica* 32 (2004): 30-37.
105. Ponrasu, Thangavel, and Lonchin Suguna. "Efficacy of *Annona squamosa* L in the synthesis of glycosaminoglycans and collagen during wound repair in streptozotocin induced diabetic rats." *BioMed research international* 2014, no. 1 (2014): 124352.
106. Ponrasu, Thangavel, and Lonchin Suguna. "Efficacy of *Annona squamosa* on wound healing in streptozotocin-induced diabetic rats." *International wound journal* 9, no. 6 (2012): 613-623.
107. Al-Nemari, Rawan, Abir Ben Bacha, Abdulrahman Al-Senaigy, Mikhliid H. Almutairi, Maha Arafah, Hadel Al-Saran, Nael Abutaha, and Abdelhabib Semlali. "Cytotoxic effects of *Annona squamosa* leaves against breast cancer cells via apoptotic signaling proteins." *Journal of King Saud University-Science* 34, no. 4 (2022): 102013.
108. Awada, Nour, Abeer J. Ayoub, Ali Jaber, Farah Ibrahim, Nadine El Ghotmi, and Edmond Cheble. "Evaluation of the Anticancer, Anti-Inflammatory, and Antioxidant properties of various extracts of *Annona Squamosa* L." (2023).
109. Swantara, Made Dira, Wiwik Susanah Rita, Made Asmarani Dira, and Kadek Karang Agustina. "Cervical anticancer activities of *Annona squamosa* Linn. leaf isolate." *Veterinary World* 15, no. 1 (2022): 124.
110. Mohamad, Ebtesam A., Karim Kamal Abdellatif, Doaa Ibrahim Maihop, Doha Magdy Abdelmonaem, Fatema Bahaaaldine, and Aisha Edress Abdelkhalik. "Antitumor efficacy of *Annona squamosa* loaded niosomes." *BioNanoScience* 13, no. 4 (2023): 2225-2231.
111. Mokhtar, Fatma A., Nabil M. Selim, Seham S. Elhawary, Soha R. Abd El Hadi, Mona H. Hetta, Marzough A. Albalawi, Ali A. Shati et al. "Green biosynthesis of silver nanoparticles using *annona glabra* and *annona squamosa* extracts with antimicrobial, anticancer, apoptosis potentials, assisted by in silico modeling, and metabolic

- profiling." *Pharmaceuticals* 15, no. 11 (2022): 1354.
112. Malik, Maria, Muhammad Aamir Iqbal, Mariam Malik, Muhammad Akram Raza, Wajeehah Shahid, Jeong Ryeol Choi, and Phuong V. Pham. "Biosynthesis and characterizations of silver nanoparticles from *Annona squamosa* leaf and fruit extracts for size-dependent biomedical applications." *Nanomaterials* 12, no. 4 (2022): 616.
113. Ansari, Prawej, J. M. A. Hannan, Veronique Seidel, and Yasser HA Abdel-Wahab. "Polyphenol-rich leaf of *annona squamosa* stimulates insulin release from BRIN-BD11 cells and isolated mouse islets, reduces (CH₂O) n digestion and absorption, and improves glucose tolerance and GLP-1 (7-36) levels in high-fat-fed rats." *Metabolites* 12, no. 10 (2022): 995.
114. Alkhalidy, Hana, Anas Al-Nabulsi, Reham Mhawish, and Dongmin Liu. "Low-dose of phenolic rich extract from *Annona squamosa* Linn leaves ameliorates insulin sensitivity and reduces body weight gain in HF diet-induced obesity." *Frontiers in Nutrition* 10 (2023): 1146021.
115. Ponce-Sánchez, Claudia, Víctor Hugo Oidor-Chan, Erika Lorena Álvarez-Ramírez, Rocio Gómez-Cansino, Addy Leticia Zarza-García, José Luis Gómez-Olivares, Fernando Díaz de León-Sánchez, and José Alberto Mendoza-Espinoza. "Chemical profile and study of the antidiabetic effect of *Annona squamosa* L. peel." *Waste and Biomass Valorization* 15, no. 2 (2024): 1053-1063.