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A REVIEW ON PHARMACOLOGICAL ACTIVITIES OF *ANNONA SQUAMOSA L.*

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Abstract: The custard apple, or *Annona squamosa L*, is a hybrid of the sugar apple (*Annona squamosa*) and the cherimoya (*Annona cherimola*) species of the Annonaceae family. In tropical and subtropical regions including north and south America, Asia, Africa, and Australia, it is extensively grown. There are around 119 species of trees and shrubs in the genus Annona, which is one of the 120 genera in the Annonaceae family. Over 105 species have been documented in tropical America, home to most species. Annona fruits are currently gaining attention from those who are interested in eating foods that promote health because of its phytochemical composition, whose actions have not before been investigated. This plant possesses the seed, peel, and pulp of two cultivars of *Annona squamosa (Annona b. and Annona h.)* that have potential anticancer, antioxidant, and antibacterial properties in vitro. The primary sources of bioactive chemicals in plants are their fruits and waste products. The plant sample displays a wide range of bioactive components, including glycosides, proteins, carbohydrates, saponins, alkaloids, flavonoids, and phenolics. These constituents have been shown to possess notable antioxidant, antibacterial, antiviral, anticancer, antidiabetic, anti-inflammatory, anti-ulcer, and skin-protective qualities. The leaves have a high protein content and contain essential oils that are rich in terpenes and sesquiterpenes, which have been demonstrated to have medicinal properties.

Key words-Traditional medicines, Phytoconstituents, Annona squamosa,Annonaceae, Bioactive Compounds, pharmacological effects, Review.

I. Introduction

Bearing edible fruits known as sugar apples or sweetsops, *Annona squamosa* is a tiny, well-branched tree or shrub in the Annonaceae family. Its ability to withstand the tropical lowland climate makes it more generally farmed than its relatives Annona reticulata and *Annona cherimola*, whose fruits frequently have the same name. *Annona squamosa*, resembling soursop (*Annona muricata*), is a tiny, much-branched, semi-deciduous shrub or small tree that grows to a height of 3 to 8 meters (10 to 26 feet) [(1).] Native to the tropical regions of the Americas and the West Indies, it was introduced to Asia by Spanish traders on Manila galleons that anchored in the Philippines [2].

Global cultivation is the ubiquitous sultry fruit known as *Annona squamosa L*. It belongs to the family Annonaceae.1. Recent studies have demonstrated the phytochemical richness and potential of many plant wastes, including pomace, seeds, husk, coat, bran peel, and leaves of both fruits and vegetables [2, 3]. Plant extracts from the *A. squamosa* plant, including those from the bark, leaves, roots, stem, peel, fruit, and seeds, have been used traditionally in medicine in several countries to treat a wide range of illnesses. In the body of

existing research, there is a dearth of thorough compilations of important data regarding the phytochemical, nutraceutical, and formulation qualities of A. squamosa [4].

As of right now, only a small number of these species are economically valuable. These species include *A. squamosa L.* (sugar apple), *A. cherimola* Mill. (cherimoya), *A. muricata L*. (guanabana or soursop), *A. reticulata L*. (custard apple), *A. glabra L*. (pond-apple), and *A. macrosporophyll* Donn. Sm. (ilima). The growing number of outbreaks of food-borne illnesses brought on by pathogenic microorganisms has also raised fresh worries over food safety [2]. As a result, for a variety of microbe-control problems, natural antimicrobials are getting a lot of attention. Some of the advantages include lowering the need for antibiotics, preventing microbial contamination in food, enhancing shelf-life extension technologies to get rid of unwanted pathogens and/or postpone microbial spoilage, preventing the growth of antibiotic-resistant pathogenic microorganisms, and boosting human immune systems [4].

Previous studies on the phytochemistry of the plant have demonstrated that it contains a wide range of chemicals, such as acetogenins, which have been shown to have anti-feed ant, anti-malarial, cytotoxic, and immunosuppressive properties. Diterpenes that were extracted from *Annona squamosa* have anti-platelet aggregation and anti-HIV properties [5].

The same source identified the partly purified flavonoids as the active ingredient in the anti-microbial and other pesticidal properties. The presence of other hydroxyl ketones and certain lignans was also discovered in this plant. Several alkaloids from this plant have been identified; these include aporphine and benzo quinazoline. The information presented above indicates that the plant is well-known for its range of therapeutic benefits [6].

Fruits are regarded in Ayurveda as a good tonic, enriching blood, utilized as expectorant, strengthening muscles, cooling, reducing burning sensation and biliousness inclination, sedative to heart, and relieving vomiting. This portion of the fruit was chosen for the study because of its special ability to treat a variety of illnesses. Cellulitis, impetigo, and folliculitis are among the most frequent skin and soft tissue infections caused by the Gram-positive extracellular bacteria Staphylococcus aureus.

Taxonomical Classification [11]-

Table.01-Taxonomical classification

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

Synonyms [8]-

sugar apple or sweetsop, *Annona reticulata and Annona cherimola*, *Annona muricata*, *Annona squamosa*

Common Name:

Sugar Apple**,** Custard Apple, Sweetsop, Buah Nona, Seri Kaya, Anona, Nona, Bullock's Heart

Plant part used-

Leaves, fruits, seed, stembark

Leaves

Flower

Fruit & seed

Fig.01- *Annona squamosa*

II. Botanical description [8][9]-

Table No. 02-Botanical description of *Annona squamosa*

Annona squamosa is small and semi-deciduous, height of 3–7 meters.	
Leaves	Single leaves are 6–17 × 3-6 cm, lanceolate or oblong lanceolate, pale green on both surfaces & are glabrate. Petioles 0.6-1.3 cm long, green, and sparsely hairy apex short or long pointed; base short pointed or rounded.
Flowers	Greenish-yellow, fragrant, on slender, hairy stalks; produced singly or in short lateral clusters of two to four flowers.
	Sepals-pointed, hairy, green, about 16 mm long
	Petals-Oblong, thick, and rounded at the tips, fleshy, 1.6-2.5 cm long, 0.6 cm wide, yellow-green
	Stamens-Very numerous, crowded, white, less than 16 mm long
	Ovary-light green, styles white, crowded on the raised axis
Fruit	Round, heart-shaped, ovate, or conical, the fruit has many round protuberances and is greenish-yellow when ripe, with a white, powdery bloom. Fruit pulp- white, edible, and sweetly aromatic
Seed	Each carpel contains an oblong, shiny, smooth seed that is 1.3–1.6 cm long and numerous, blackish, or dark brown.

III. Traditional uses-

This plant has traditionally been used for its insecticidal and anticancer properties, as well as its anti-diabetic, anti-oxidant, anti-lipidemic, and anti-inflammatory properties. It is also used for cardiac defense, digestion, and has an antispasmodic property that may be attributed to the presence of cyclic peptides. It is stated that the seeds contain anti-parasitic properties (against lice). In India, beaten leaves are applied to wounds and sores, and a leaf decoction is consumed when a patient has diarrhea [22].

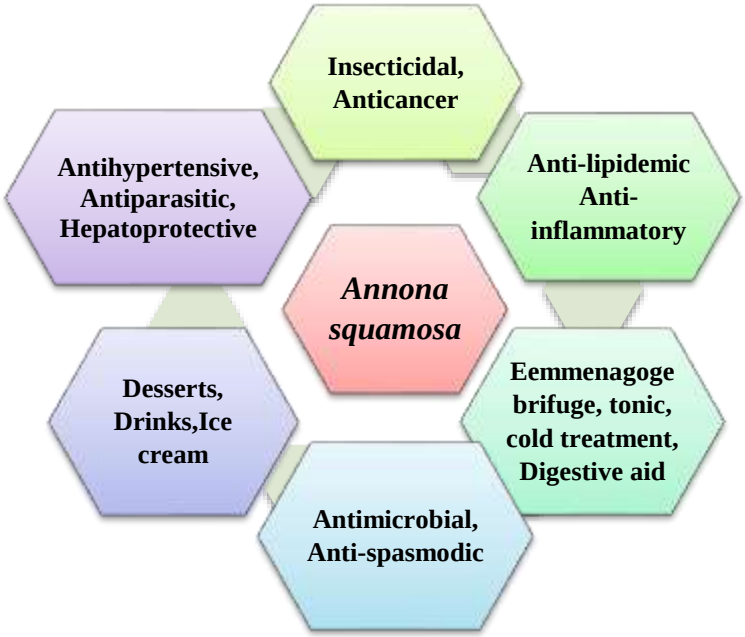

Fig.02- *Annona squamosa* traditional uses

To treat diabetes, peasants in the Aligarh district in Northern India used to consume a combination of four to five freshly grown, younger *Annona squamosa* leaves along with black pepper (Piper nigrum). To prevent diarrhea, the bark decoction is administered as a tonic [23]. To ease rheumatic pain, the leaf decoction is often used in baths. Annona squamosa are mostly utilized in the preparation of desserts, drinks, and ice cream. Specific sections of Annona squamosa have been linked to a wide range of ethno-medical uses, including as an apothegmatizing, tonic, cool medicinal medicine, abortient, and cardiac sedative. The antimaximum cancer, antioxidant, anti-diabetic, antihypertensive, hepatoprotective, antiparasitic, anti-malarial, insecticidal, antimicrobial, and molluscicide properties of Annona squamosa have been found through numerous investigations. [22][23]

IV. Phytoconstituents & bioactive compounds of *Annona squamosa*-

A. squamosa, a wide range of phytochemicals, including proteins, saponins, phenolics, carbohydrates, alkaloids, flavonoids, and glycosides, have been found in leaf extracts through phytochemical studies. It has been demonstrated that leaves contain the highest protein concentration when compared to seeds and fruit. Both the methanolic and aqueous extracts contained large amounts of proteins and amino acids. Further research is necessary to examine the protein and amino acid profiles of these foods because there are not enough studies measuring the amounts of protein and amino acids in leaf extract. [19]

Both the methanolic and aqueous extracts had high quantities of amino acids. 43 of the components of essential oil from leaves have been found in shade-dried leaves from the lower Himalayas, according to numerous studies that have examined the components of leaf essential oil. Leaf extracts include around 59 distinct chemical components, most of which are terpenes and sesquiterpenes, with δ-cadinene (6.7%) and β-caryophyllene (31.1%) being the most prevalent. Fresh A. squamosa leaves were used to extract 0.12% essential oil, of which 18 components made up 86%. Leaf products contain bioactive phytochemicals that may help prevent diabetes, the common cold, cancer, viruses, bacteria, obesity, and diarrhea [20].

The active components annotemoyin-2, annotemoyin-1, squamocin, and cholesteryl glucopyranoside are produced by A. squamosa Linn. These chemicals' cytotoxic and antibacterial qualities are especially notable. The remaining 0.15% in the roots is composed of the essential oils gurjunene, caryophyllene, pinene, and humulene. One of the active components of the A. squamosa Linn plant's chloroform extract is annotemoyin. Flavonoids isolated from the aqueous extract of A. squamosa Linn. exhibit antimicrobial action. For instance, in vitro tests on the chemical bullatacin revealed antitumoral and pesticidal effects. It has been demonstrated that an ethanolic extract of the stem and leaves can stop the spread of cancer [21, 22].

V. Marketed Formulations-

Fig. 03- *Annona squamosa L* Marketed formulations

VI. Pharmacological activity-

1. Anti-tumour [16]-

When administered orally to mice bearing H22 xenografts, the seed oil demonstrates anti-tumor action with a peak inhibitory rate of 53.54%. Its primary chemical component, unsaturated fatty acids, was shown to have an anti-tumor impact by downregulating the Interleukin-6/Jak/Stat3 signaling pathway. Annona squamosa is the source of acknowledged anticancer drugs, such as anonaceous acetogens [23]. Using human cancer cell lines and mouse H22 cells, 12,15-cissquamostatin-A and bullatacin were extracted from seed oil and demonstrated strong anti-cancer properties [24]. The H460 cell line was found to be specifically active against squamoxinone-D [25]. An oral dose of 300 mg/kg of *Annona squamosa* leaf aqueous extract was administered to mice to counteract acetic acid-induced colitis for a duration of one month.

2. Anti-inflammatory Activity [26]-

The extract markedly elevated colonic glutathione (GSH), glutathione peroxidase (GPx), and catalase (CAT) activity and markedly decreased colonic malondialdehyde (MDA). In relation to the seeds' anti-inflammatory properties, *Annona squamosa* seeds' cyclosquamosin D and cherimolacyclopeptide B have been shown to prevent activated macrophages from producing proinflammatory cytokines including IL-6 and TNF-α [26].

3. Antibacterial activity [4][27]-

The antibacterial activity of three distinct solvent extracts from Annona squamosa L. seeds was investigated. Using two Gram-positive (Bacillus subtilis and Staphylococcus aureus) and three Gram-negative (Escherichia coli, Pseudomonas aeruginosa, and Klebsiella pneumoniae) bacteria, the Agar cup method was chosen to investigate antibacterial activity. According to the screening results, the methanol extract for Annona squamosa seed exhibited the highest level of inhibition, followed by the extracts made of petroleum ether and chloroform. The test species that exhibit the highest sensitivity include Bacillus subtilis, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, and Staphylococcus aureus [27]

4. Anti-ulcer activity [13]-

Twelve recognized chemicals from *A. squamosa* twigs are found in the study, including one believed to be synthesized ethane. When the H+ K+-ATPase activity of these compounds was measured, they showed positive anti-secretory activity comparable to that of the medicine omeprazole. A. squamosa (AS) has been found to have a significant inhibitory effect on a variety of ulcer models, including those caused by alcohol, cold constraint, pyloric ligation, aspirin, and histamine-induced duodenal ulcers. These represent more research findings. In addition to showing anti-secretory activity, AS and its active ingredients reduced the development of ulcers [29]

5. Hypoglycaemic and anti-diabetic activity [30]-

Many medicinal plants or their extracts have been used orally to treat diabetes since ancient times. When given orally at varying doses to streptozotocin (STZ)-induced diabetic rats, alloxan-induced diabetic rabbits, and normal rats, the ethanolic extract of Annona squamosa leaves demonstrated that a dose of 350 mg/kg body weight reduced both the fasting blood glucose (FBG) level by 6.0% and the normal rats' peak blood glucose during the glucose tolerance test (GTT) by 17.1%.In rabbits with alloxan-induced diabetes, the same dosage of the ethanolic extract decreased the FBG level by 26.8% and increased the glucose tolerance by 38.5 and 40.6% during the GTT. During GTT11, rats with STZ diabetes showed a decrease of 13.0% in FBG and an improvement of 37.2 and 60.6% in glucose tolerance. Similarly, the antidiabetic activity of an aqueous extract of Annona squamosal roots at doses of 250 mg/kg and 500 mg/kg body weight was evaluated in Streptozotocin (STZ)-induced hyperglycemic rats. This extract causes the blood glucose in STZ-induced diabetic rats to decrease from 285.52 to 208.81 mg/d [30][31]

6. Hepatoprotective activity [20]-

To investigate its potential for treating hepatotoxicity in humans, the hepatoprotective effects of *Annona squamosa's* water and alcohol extract were assessed in rats that had been subjected to hepatotoxic stress. According to the experimental investigation, Annona squamosa extracts were able to reduce the effects of isoniazid and rifampicin on the liver, but they were unable to fully reverse the hepatic harm that had been caused by these medications. The antioxidative properties of the flavonoids found in Annona squamosa leaf extracts may be the source of their protective properties. Rats were used to assess the protective effect of Annona squamosa methanolic extract on isoniazid-rifampicin-induced hepatotoxicity, and it was discovered that the rats also displayed a protective effect against the liver injury [32].

7. Vasorelaxant activity [20]-

Agents that are helpful in treating cerebral vasospasm, hypertension, and improving peripheral circulation are known as vasodilators. It was discovered that the cyclic octapeptide cyclosquamosin B, which was extracted from Annona squamosa seeds, may have a vasorelaxant effect on the rat aorta. One possible major explanation for the vasorelaxant effect of cyclosquamosin is that it inhibits the extracellular space's calcium influx through voltage-dependent calcium channels [32].

8. Antimicrobial activity [22]-

The antibacterial activity of three distinct solvent extracts from *Annona squamosa L.* seeds was investigated. Using two Gram-positive (Bacillus subtilis and Staphylococcus aureus) and three Gram-negative (Escherichia coli, Pseudomonas aeruginosa, and Klebsiella pneumoniae) bacteria, the Agar cup method was chosen to investigate antibacterial activity. According to the screening results, the methanol extract for *Annona squamosa* seed exhibited the highest level of inhibition, followed by the extracts made of petroleum ether and chloroform. The microorganisms that are most sensitive to testing are Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, and Staphylococcus aureus. [26]

9. Anti-oxidant and anti-lipidemic activity [33]-

Antioxidants are the substances that shield living things from oxidative stress brought on by excessive generation of reactive oxygen species, which can also cause protein degradation, lipid peroxidation, DNA strand breaks, and other harm. Numerous plants, such as *Annona squamosa*, have been shown in ethnomedical literature to be effective against diabetes, a condition in which free radicals and ROS are crucial. An assessment was conducted on the impact of *Annona squamosa* leaf water extract on the lipid profile and antioxidant enzymes in animal models of type 2 non-insulin dependent diabetic mellitus (NIDDM).The increased activities of the scavenging enzymes catalase (CAT), superoxide dismutase (SOD), reduced glutathione (GSH), glutathione reductase (GR), and glutathione-stransferase (GST) and the significantly lower levels of malondialdehyde that were expressed in the various tissues were the parameters used to measure the above activities. When compared to the untreated diabetic rats (control group), the treated group's triglyceride and total cholesterol levels were significantly lower in the *Annona squamosa* aqueous extract, while the HDL cholesterol level gradually increased. It was discovered that these modifications helped to enhance lipid metabolism in diabetics and avoid problems from developing from their diabetes [33].

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