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Review Article

Exploring The Pharmacognostical And Pharmacological Profile Of *Annona squamosa* Linn – A Review

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ABSTRACT

Annona squamosa Linn, commonly known as sugar apple or custard apple, is a tropical fruit-bearing tree with significant pharmacological importance due to its various medicinal properties found widely distributed in various regions of the world, making it a valuable source of natural products. This review aims to provide a comprehensive overview of the pharmacognostical and pharmacological profile of *Annona squamosa* Linn., shedding light on its traditional uses and therapeutic potential, pharmacognostical profile, botanical description, geographical distribution, phytochemical composition, medicinal value, traditional uses are discussed. Phytochemical analysis has identified various bioactive compounds such as alkaloids, flavonoids, terpenoids, and phenolic compounds, which contribute to its medicinal properties and pharmacological activities. Pharmacological investigations have revealed a broad spectrum of biological, therapeutic activities exhibited by *Annona squamosa* Linn such as antioxidant, anti-inflammatory, antimicrobial, antidiabetic, antitumor, anticancer, antimalarial analgesic, hepato protective, cardio protective, and neuroprotective effects etc., reported in preclinical studies. These pharmacological actions are attributed to its rich phytochemical composition, particularly alkaloids, acetogenins, annonaceous and flavonoids, which exert their effects through various mechanisms such as inflammation, apoptosis, free radical scavenging, enzyme inhibition, etc., The *Annona squamosa* Linn fruit and its various plant parts have been traditionally used in different cultures and folk medicine for treatment of various ailments such as diarrhea, dysentery, fever, respiratory infections, skin disorders, and cancer, among others, that has been validated through scientific studies, supporting its therapeutic potential in the management of various diseases and disorders. Furthermore, modern scientific research continues to explore its therapeutic potential and elucidate the underlying mechanisms of action to explore its

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pharmacological spectrum, optimize dosage regimens, and assess its safety profile for clinical use. Overall, this review highlights the potential of *Annona squamosa* Linn in the realm of natural medicine, holds promise as a valuable source of bioactive compounds with diverse pharmacological properties, warranting further exploration for its therapeutic applications leading to the discovery of novel therapeutic agents with enhanced efficacy and safety profiles.

INTRODUCTION

Since ancient times, throughout the history, plants have been revered for their multifaceted medicinal properties, playing a significant role in traditional medicine systems worldwide. The exploration of their Pharmacognostical characteristics holds immense importance in unraveling the therapeutic potential and enhancing utilization of plants in modern healthcare practices. Plants play vital role in maintaining human health and contribute towards improvement of human life. Indigenous sources of medicinal plants and their parts such as the leaves, fruits, the barks, roots and even the seeds have been extensively used in different traditions for preparation of various medicine for treatments. (1) Cancer, a complex and multifaceted disease, one of the most formidable health challenges of our time continues to pose significant challenges to modern medicine despite advances in diagnosis and treatment. Cancer, characterized by its complex etiology, heterogeneity, and often elusive treatment outcomes. Conventional therapies such as chemotherapy, radiation, and surgery remain the cornerstone of cancer management, yet their efficacy is often accompanied by debilitating side effects and the emergence of drug resistance. In the pursuit of safer and more efficacious treatment modalities, the exploration of herbal approaches in cancer management has garnered increasing attention. (2) For millennia, diverse cultures worldwide have relied on herbal remedies derived from plants to alleviate ailments and promote well-being. In recent decades, scientific research has

begun to unravel the pharmacological properties of these botanicals, revealing their potential as adjunctive or standalone therapies in the fight against cancer. Herbal medicines offer a rich source of bioactive compounds, including alkaloids, flavonoids, polyphenols, and terpenoids, many of which exhibit promising anticancer properties through various mechanisms such as apoptosis induction, inhibition of angiogenesis, and modulation of immune responses. (3) *Annona squamosa* Linn, commonly known as sugar apple or custard apple, is a member of the Annonaceae family, widely distributed in tropical and subtropical regions. With a rich phytochemical composition comprising alkaloids, flavonoids, terpenoids, and phenolic compounds among others, *Annona squamosa* Linn exhibits a diverse array of pharmacological activities ranging from anticancer and antimicrobial to antidiabetic and anti-inflammatory effects. The genus name, 'Annona' is from the Latin word 'anon', meaning 'yearly produce', referring to the production of fruits of the various species in this genus. *Annona squamosa* Linn has been named botanically from Jamaica (4). The leaves of the plants have been used as insecticide, anthelmintic, styptic, externally used as suppurant. Unripe and dried Fruit work as antidyenteric. Bark is used as powerful astringent, anti-dysenteric and vermifuge. Rootbark, leaves and stems gave isoquinoline alkaloids. Powdered seeds are used to kill head-lice and fleas but care should be taken that the powder does not come in contact with the eyes as this causes great pain. Two acetogenins, annorecticin and isoannorecticin, isolated from the leaves, were found to be selectively cytotoxic to certain human tumors. The leaves and stems also gave alkaloids dopamine, salsolinol and coclaurine. However, a comprehensive understanding of its Pharmacognostical attributes, including macroscopic and microscopic features,



chemical composition, and pharmacological activities, is essential to harness its full therapeutic potential. (5)

PHARMACOGNOSTICAL PROFILE

Taxonomical Classification(6,80)

Kingdom:	Plantae
Division:	Magnoliophyta
Class:	Magnoliopsida (Dicotyledons)
Subclass:	Magnoliidae
Order:	Magnoliales
Family:	Annonaceae (Custard-apple family)
Subfamily:	Maloideae
Tribe:	Abreae
Genus:	Annona L.
Species:	Annona squamosa L.

Vernacular Names (4,5)

It is known as custard apple, sugar apple, sweet après in english, & sharifa in hindi & sitaphalam in telugu in india, pommier cannelle in french etc.

English	Custard apple
Sanskrit	sitaphala
Hindi	Sitaphal
Urdu	Sharifa
Tamil	Sithapalam
Kannada	Sitaphala
Konkani	Sitaphal
Malayalam	kastard aappil

Plant Description

Annona squamosa Linn is one of the garden plant that comes from the Annonaceae family known as custard apple. *Annona squamosa* Linn., a common plant worldwide and mainly grown in gardens for its delicious fruit and its great ornamentals value. It is a small (about 5-6 m in height) deciduous tree with irregular branches. Young branches and leaf are sparsely hairy, bark is light brown, smoothish to slightly fissured while pale green leaf occur singly (4). The stems of branches *Annona squamosa* Linn are irregular in shape and gray in color and contains compounds such as roemerolidine, nitroso xylophone, and duguevalline alkaloid. (8) The crown is spherical or a flattened ball. It has green leaves 10-15 cm long and 3-5 cm wide, sharp or blunt at the tip and

round or widely wedge shaped at the base. The leaves are arranged alternately. (9) The plant is monoecious and flowers are bisexual. Nitidulid beetles are the important pollinators with wind and self-pollinating being low. After pollination berries tubercled with prominent scales formed. Fruits with white pulp are edible, round or heart shaped with many round protuberances, and has a sweetly aromatic taste. After the pollination process is carried out, tuberculous fruit is formed and has an aromatic also sweet taste. Each carpel has a smooth seed, with black or dark brown in color, and has oval shape. *Annona squamosa* Linn begins to bear fruit when it is 3-4 years old. *Annona squamosa* Linn seeds are dark brown to black, and generally 30-40 seeds can be found in one fruit. *Annona squamosa* Linn is a type of plant that is classified as diploid with 2n-14. (8)



Fig No 1. *Annona Squamosa* Linn Tree



Fig no. 2 *Annona squamosa* Linn fruit

Botanical Description Of *Annona squamosa* Linn

1. Leaves

Are oblong - lanceolate, 10-15 cm long and 3-5 cm wide, alternately arranged on short petioles, young leaves are slightly hairy, solitary and clustered crystals occur in epidermal cells(10)

2. Flowers

The trees are semi-deciduous, Flowering occurs during spring to early summer, and in permanently humid regions, flowering occurs throughout the year. Inflorescences are supra-axillary. The flowers are bracteate, pedicillate, actinomorphic, protogynous (Vithanage, 1983) (pistils are mature before pollen is liberated from anthers), spirocyclic and bisexual. (9) Flower is 2-4 cm long and contains three degenerated sepals and six petals. The six petals are arranged into two whorls with three each and the petals of the inner whorl are degenerated into small scales or completely disappear. The multiple pistiles grow on the conical receptacle, in the centre of the flower with a number of stamens at the periphery. Flowers are pollinated by nitidulid beetles(11)

3. Stem

Irregular branches with thin gray bark contain N-Nitrosoxylopin, roemerolidine and duguevalline antimalarial alkaloid(12)

4. Fruits

Trees start to bear fruit when 3-4 year old. In India fruits are produced in July-August. Sugar apple, as the name says it all, is sweet as sugar. The flesh nearest to the rind, tastes like sugar crumbs too. It is usually conical in shape but sometimes, it may be almost round. It is easy to tell when it is ready to eat. The rind is thick with knobby segments but will turn soft and crack open, releasing a sweet aroma when it ripens. Normal ripening occurred at temperature between 15-30°C. (13)

5. Roots

Branched tap root(9).

6. Seeds

Are black or dark brown in colour. There are 30-40 seeds in an average fruit. The *Annona squamosa* Linn is a diploid species with $2n=14$. (14)

Geographical Distribution

Annona squamosa Linn, belonging to family Annonaceae, that was reported with 130 genus and almost 2500 species.(15) It was planted in Puerto Rico as fruit trees in 1626, spreading from cultivated areas to roadside and valleys. The Spanish probably carried seeds from the new world to the Philippines, and the Portuguese are assumed to have introduced it to southern India before 1590. (16) Today it is cultivated in almost all tropical and subtropical countries(17). The original home of *Annona squamosa* Linn also branded as sugar apple or custard apple is unknown. Its considered endemic to tropical America but is widely distributed in tropical and subtropical climates, climate of Africa, Australia, South America, West Indies, countries in Asia such as Malaysia and Indonesia Laos, Thailand and Vietnam and also distributed throughout India. It is mainly grown in gardens for its fruits & ornamental value. (4)

Phytochemistry

The therapeutic properties of medicinal plants are perhaps due to the presence of various secondary metabolites. The extraction of different parts of *Annona squamosa* in different solvents revealed the presences of alkaloids, flavonoids, phenols, carbohydrate, saponin, sterols and tannins(18,19). In research, It has been found 33 annonaceous acetogenins, 19 diterpenes, 88 alkaloids and 13 cyclopeptides as the most common constituents of *Annona squamosa* Linn.(20,21) Four alkaloids were found in both extracts, leaves and seeds of *Annona squamosa* Linn, namely anonaine, asimilobine, nur nuciferine, liriodenine, corypalmine and reticuline.(8) Research with essential oils according to the genus Annonaceae phytochemical compounds found including, (E)-



caryophyllene, bicyclogermacrene, caryophyllene oxide, germacrene D, spathulenol, α -pinene, β -pinene, limonene and β -elemene.(22) Phytochemical analysis of fruits yielded 12 kaurane derivatives and two new kaurane diterpenoids Annosquamosin A and Annosquamosin B among these 16 beta, 17-dihydroxy-ent-kaurane-19-oic acid showed anti-HIV activity.(23) Same compound isolated from the stem also showed anti-inflammatory activity(24). Flavonoids isolated from aqueous extract of *Annona squamosa* Linn have been showed antimicrobial activity (25). Podophyllotoxin (a non-alkaloid toxin lignan compound) and its demethyl derivative 4-demethylpodophyllotoxin, liriodenine and (-)-kaur-16-en-19-oic acid were also isolated from the branches(9). GC analysis of fatty acid methyl esters (FAMES) of seed oil revealed the presence of saturated fatty acids like Hexadecanoic acid (Palmitic acid), Octadecanoic acid (Stearic acid), and unsaturated fatty acids like Octadecenoic acid (Oleic acid), Eicosanoic acid (Gondoic acid)(26). Acetogenins are present in bark (27,28). An alkaloid higenamine found in leaves is a cardiotoxic active principle.(29) Seeds contain saponin, cause haemolysis of red blood cells and is a fish poison(30). Further investigation has provided with three anti-malarial alkaloids all of them exhibited moderate activity against chloroquine sensitive strain (D10) and a chloroquine resistant strain (Dd2) of *Plasmodium falciparum*. (31) Yet another study revealed the presence of another compound responsible for anthelmintic activity against *Haemonchus contortus* and identifies as C37 trihydroxy adjacent bis tetrahydrofuran acetogenin based on spectroscopic analysis(32)

Traditional Use

Herbal medicine has been widely accepted in most countries in the world, as evidenced according to WHO countries in Africa, Latin America, and Asia use herbal medicine as a complement to the

primary treatment. One such plant with extensive traditional use is *Annona squamosa* Linn. *Annona squamosa* Linn tree is widely distributed in Indomalaya, the Caribbean, South America, and Australia. In America, India, and Thailand. These fruits are normally eaten fresh. Between 50-80% of the fruit is edible. The vitamin C content is appreciable (35-42 mg/100 g) and slightly higher than in grapefruit. The nutrient value of thiamine, potassium and dietary fibre is also significant. (3) *Annona squamosa* Linn leaf is used to treat urinary tract infection and dysentery.(8) The pulp of the ripe fruit is eaten fresh or utilized as flavouring for ice-cream and milk beverages(33). Delicious products such as jam and squash can also be made from the pulp (34). It can also be used to make wine (9). The superior quality oil can be extracted from the seeds, contains fatty acids like oleic, linoleic, palmitic, and stearic (35). These acids find use in the preparation of soap and plasticizer industry as well as in alkyd manufacturing(36). Non edible seed oil is used as insect repellent(37) and the seed cake can be used as manure(38). The tree is also a good source of firewood and is grown in gardens as ornamental tree(9). The bark, leaves, and roots of some species are used in folk medicines. The strong bark is used for carrying burdens in the Amazon Rainforest and for wooden implements, such as tool handles and pegs. (39) In Indonesia leaves *Annona squamosa* Linn are very popular, especially since research has begun to prove that it can fight super dangerous diseases such as cancer. (40) Even in India the leaf as traditional medicine is also crushed and applied to wounds. (41) In addition, decoction of *Annona squamosa* Linn leaves or combination with other plants, its content can be absorbed by the body well as a febrifuge, cold remedy, and employed in the bath to alternative rheumatic pain in traditional American medicine. (42)

Medicinal Value



Between 50-80% of the fruit is edible. The vitamin C content is appreciable (35-42 mg/100 g). The nutrient value of thiamine, potassium and dietary fibre is also significant. Commonly all parts of *Annona squamosa* Linn leaves, shoots, bark and roots have been reported to have medicinal properties which can be used by communities for the treatment of different acute and chronic diseases such as insect bites, cancerous and skin complaints. In Mexico the juice is used for chills and fever (5,43). Pulp was found to have mutagenic property (44). It is found to have In vitro, In vivo studies exhibiting anti-tumor activity. Fruit and fruit juice are taken for worms and parasites, as an antipyretic, to increase lactation after childbirth, as an astringent for diarrhoea and dysentery. The unripe fruit is astringent, used to treat diarrhoea and dysentery. and the root is a drastic purgative, the seed of the plants is believed to have anti fertility activity. The roots are used as a drastic purge, were found to have anticonvulsant effect (45). Roots are reported to have apomorphine alkaloids: Reomerine, Annonine and Dehydro reomerine show skeletal muscle relaxant effect. A recent study suggests that the alcoholic seed extract contains anti-cancer compounds (46). The leaves of *Annona squamosa* Linn are used as a vermicide, for treating cancerous tumours and are applied to abscesses, insect bites and other skin complaints, and also exhibit antibacterial and wound healing activity. Leaf extract have anti- nociceptive effect used to treat hysteria, fainting spells. Scrapings of root-bark are used for tooth ache (42). The crushed seeds are used against internal and external parasites, head lice, and worms, and fleas but care should be taken that the powder does not come in contact with the eyes as this causes great pain. The bark leaves, and roots are considered sedative, ulcer treatment and a nervine tonic and a tea is made for various disorders towards those effects. Roots contain acetogenins proved to have anti-

carcinogenic effect by inhibiting DNA synthesis. Yellow resin extracted from seeds exhibits sympathetic action such as dilatation of pupil, dryness of mouth, decreases secretions. (46)

PHARMACOLOGICAL PROFILE

Antimicrobial Activity

The leaves of *Annona squamosa* Linn have reported to have antimicrobial properties. Studies have shown the high potency of antimicrobial action of the plant(7).Methanolic extract of stem bark of *Annona squamosa* possesses the invitro antimicrobial activity against *Bacillus coagulans* and *Escherichia coli* bacteria of gram-positive and gram-negative strain(47). Antibacterial potential of plant against *Bacillus subtilis*, *Staphylococcus epidermidis*, *Staphylococcus aureus* and *Vibrio alginolyticus* showed positive results(48).

To evaluate the antibacterial activity another study was performed using three different solvent extracts of leaf of *Annona squamosa* L. and *Annona reticulata* L. Agar cup and broth dilution methods were selected to test antibacterial activity using three Gram-positive (*Bacillus subtilis*, *Staphylococcus aureus* and *Staphylococcus epidermidis*) and five Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*, *Salmonella typhi*, *Vibrio alginolyticus*, *Vibrio cholerae*) bacteria. The screening results showed that highest inhibition was observed by the methanol extract followed by petroleum ether and aqueous extracts for both *Annona squamosa* and *Annona reticulata* leaf. *Bacillus subtilis*, *Staphylococcus epidermidis*, *Staphylococcus aureus* and *Vibrio alginolyticus* are the most sensitive bacterial strains among all test organisms. None of the plant extracts showed growth of inhibition against *Salmonella typhi* (7)

Antidiabetic Activity

Recent studies have reported that the root extracts of *A.squamosa* have reported anti-diabetic effects in streptozotocin (STZ) induced diabetes mellitus and insulin deficiency lead to increased glucose



level(7). The antidiabetic and antioxidant properties of *Annona squamosa* Linn leaf extract may be due to the presence of these phytochemicals. The induction of streptozotocin causes specific damage to islet cells and thereby increases blood glucose concentrations. It is well known that gliclazide produces hypoglycemia and is often used as the standard drug in STZ-induced models of moderate diabetes to compare the antidiabetic properties of various compounds. Administration of *Annona squamosa* Linn leaf extract in STZ-induced diabetic rats resulted in a significant decrease in blood glucose levels (56). Antihyperglycemic effect of aqueous extract of root of *Annona squamosa* at a dose of 250 mg/kg and 500 mg/kg body weight was studied. The study resulted dose dependant reduction of blood glucose levels 6 hour after oral treatment.(49)

Antioxidant Activity

Ethanol extract of the bark of *Annona squamosa* showed significant antioxidant activity using in vitro antioxidant models like DPPH radical scavenging activity, hydroxyl radical scavenging activity, superoxide radical scavenging activity. (50) Antioxidants are compounds that play a role in inhibiting or providing protection for living organisms from damage which is a manifestation of uncontrolled ROS production. (51) Diseases such as diabetes, cancer, and inflammatory conditions are some of the diseases caused by oxidative stress. In this case, antioxidants play a role to help fight oxidative stress by scavenging free radicals. (52) Natural antioxidants such as flavonoids as well as several phenolic compounds have been documented that have the potential to protect cells from free radicals.(53) The results of several studies on the content of antioxidant compounds in the ethanol extract of *Annona squamosa* Linn leaves show that leaves *Annona squamosa* Linn contain flavonoids in the form of rutin and hyperoside. Rutin and hyperoside are compounds that have biological activities related

to antioxidant mechanisms. (54) *Annona squamosa* Linn leaf extract using chloroform solution showed strong free radical scavenging activity of IC₅₀ 308.3 mg/mL. In the other hand, their leaf extract using methanol solution showed free radical scavenging activity of IC₅₀ 342.5 mg/mL. Meanwhile, their extract with an aqueous solution showed relatively little free radical scavenging activity, namely IC₅₀ 439.6 mg/mL. The extract using ascorbic acid showed the highest free radical scavenging activity, which was IC₅₀ 35.26 mg/mL. (8)

Hepatoprotective Activity

Aqueous and alcoholic extract of Leaves of *Annona squamosa* were used for the screening of hepatoprotective activity. The study was performed on Wistar strain of rats. Induction of experimental hepatotoxicity was induced using Isoniazid and rifampicin, the standard drug Silymarin was used for the reference. The result was significant decrease in total bilirubin along with significant increase in the level of total protein and also significant decrease in ALP, AST, ALT and γ -GT in treatment group as compared to the hepatotoxic group. In the histopathological study the hepatotoxic group showed hepatocytic necrosis and inflammation in the centrilobular region with portal triaditis. The group of animal treated with extract showed minimal inflammation with moderate portal triaditis and their lobular architecture was normal. It should be concluded that the extracts of *Annona squamosa* were not able to cure completely hepatic injury induced by isoniazid and rifampicin, but it could restrict the effect of these drugs in liver (55) The extracts of *Annona squamosa* (300 & 350 mg/kg bw) were used to study the hepatoprotective effect in isoniazid + rifampicin-induced hepatotoxic model in albino Wistar rats. There was a significant decrease in total bilirubin accompanied by significant increase in the level of total protein and also significant decrease in ALP, AST, and ALT

in treatment group as compared to the hepatotoxic group. In the histopathological study, the hepatotoxic group showed hepatocytic necrosis and inflammation in the centrilobular region with portal triaditis. The treatment group showed minimal inflammation with moderate portal triaditis and their lobular architecture was normal. In another study, the protective effect was evaluated in diethylnitrosamine induced hepatotoxicity. This study revealed that the extracts of *Annona squamosa* Linn exerted hepatoprotective effect and the plant extract could be an effective remedial for chemical- induced hepatic damage. (56)

Analgesic And Anti-Inflammatory Activity

Unsaponified petroleum ether extract of *Annona squamosa* bark extract at a dose of 50 mg/kg b.w. and carophyllene oxide isolated from the bark of *Annona squamosa* at the doses of 12.5 and 25 mg/kg b.w. exhibited significant central as well as peripheral analgesic activity, along with anti-inflammatory activity (Chavan et al., 2010). Another study showed that 18-acetoxy-ent- kaur-16-ene isolated from petroleum ether extract of custard apple bark exhibited analgesic and anti-inflammatory activity (57). The analgesic and anti-inflammatory properties of aqueous and ethanolic extracts of leaves of *Annona squamosa* Linn (1000, 2000 and 3000 mg/kg) were tested on male and female adult Wistar albino rats. The rats exhibited marked analgesia, although mortality was not observed 72 h after treatment with the extracts. The aqueous extracts of *Annona squamosa* Linn exhibited anti-inflammatory properties against carrageenan - and histamine - induced oedema , as well as analgesic properties against thermal and chemical stimuli as evidenced by the significant reduction in the number of acetic acid-induced writhing and increase in the reaction time by the thermal stimuli. The ethanolic extracts of the plant had no significant analgesic or anti-inflammatory properties (7).

Anthelmintic Activity

The anthelmintic activities of the *Annona squamosa* and its leaf extract have been studied using various models. The hexane, ethyl acetate, ethanolic extracts of the crude drug at different concentrations were tested which involve determination of paralysis time and death time (42).The aqueous and methanolic extract of *Annona squamosa* Linn was used for the study. The extraction of seeds were done by crushing the seed to form powder then soaked with water and methanol for 7 days. The extract exhibited significant Anthelmintic activity against *Haemonchus contortus*. the main nematode of sheep and goat in Northeastern Brazil. A compound was isolated and the structure was determined as a C37 trihydroxy adjacent bistetrahydrofuran acetogenin based on spectroscopic analysis. The above reported compound isolated from ethyl acetate extract and inhibited the egg hatching of *H. contortus* (58).

Antimalarial Activity

In the recent studies on *Annona squamosa* all compounds showed moderate activity against a chloroquine-sensitive strain and a chloroquine-resistant strain of *Plasmodium falcifarum* (59). Three known aporphine alkaloids were isolated from bark. Structures of compounds were identified as N- Nitroso Xylopine , Pyrrolidine and Duguevalline. The above compounds were subjected for the screening of antimalarial activity. The result concluded that the aporphine alkaloids isolated by antiplasmodial activity- guided fractionation of *Annona squamosa* Linn bark display in vitro antiplasmodial activates with IC50 values ranging between 7.8 and 34.2 $\mu\text{M}/\text{mL}$.(60) The significant activity demonstrated by extracts of *Annona squamosa* suggest that the two plants may have strong killing effects against insects particularly mosquitoes, hence giving a promising source of larvicidal agents. The EtOAc fractions of *Annona squamosa* were the most active

achieving 100 to 90% mortality at 50 µg/ml. In order to determine the active principles in the EtOAc fraction further larvicidal testing of the three sub fractions Sq-1, Sq-2, Sq-3, for *A. Squamosa* showed a dose dependant ($p \geq 0.05$) but also significantly a decreased activity from its parent fraction at the same concentration levels. This indicates that, several medium polar compounds in the extract are acting synergistically or competitively at the active sites (61). *Annona squamosa* Linn plant collected from Brazil indicated larvicidal effect against *Aedes albopictus* and *C. quinquefasciatus* and against *Anopheles stephensi*. Present larvicidal activity result supports the reports and demonstrated that extract of *Annona* species are potential anti-mosquito agents. (62).

Anti- Genotoxic Effect

Studies on the genotoxicity potential of *Annona squamosa* have shown that the plant extract treatment significantly altered serum enzyme levels in oxidative stress conditions (63).

The antigenotoxic effects of aqueous and ethanolic bark extracts of *Annona squamosa* was assessed by determining the frequency of micronucleated polychromatic erythrocytes (MnPCs) and chromosomal aberrations. The frequency of MnPCs and chromosomal aberrations in bone marrow were higher in DMBA treated animals as compared to control animals. Oral administration of aqueous and ethanolic bark extracts significantly reduced the frequency of MnPCs and chromosomal aberration in DMBA treated hamsters. Although both extracts have shown antigenotoxic effects, the effects of ethanolic extract was found to be more prominent than the aqueous extract. The present study thus demonstrates the antigenotoxic effects of *Annona squamosa* bark extracts in DMBA induced genotoxicity in golden Syrian hamsters. (7)

Anti-thyroidal Activity

Administration of *Annona squamosa* seed extract (200 mg/kg) or quercetin (10 mg/kg) simultaneously to T(4)-induced hyperthyroid animals for 10 days, reversed all these effects indicating their potential in the regulation of hyperthyroidism (Panda et al., 2007). Further research revealed that *Annona squamosa* leaf extract exhibited thyroid inhibitory effects in mice, but altered hepatic LPO in a dose dependent manner. At low concentration it appeared to be anti-thyroid as well as antiperoxidative, whereas, higher concentration showed antithyroid effect but hepatotoxicity (indicated by enhanced LPO) suggesting the unsafe nature of the highest dose (64). The methanolic extract of seeds of *Annona squamosa* Linn shows ameliorative effect in the regulation of hyperthyroidism in mouse model. Hyperthyroidism produced by L-Thyroxine (L-T4) administration (0.5 mg/kg/d for 12 days), which increased the levels of serum triiodothyronine (T3) and thyroxine (T4), activity of hepatic G-6-Phosphatase, 5'-mono- deiodinase (5'DI) and peroxidation (LPO) with a parallel decrease in superoxide dismutase (SOD) and catalase (CAT) activities. However, simultaneous administration of the *Annona* seed extract (200 mg/kg) to L-T4 induced hyperthyroid animals for 10 days, reversed all these effects indicating their potential in the regulation of hyperthyroidism. Further, the seed extract did not increase, but decreased the hepatic LPO suggesting its safe and antiperoxidative nature (65).

Anti Infertility Activity

The seed extract of *Annona squamosa* Linn was investigated for post coitus antifertility activity. The seed extract of *A. squamosa* Linn shows anti implantational and abortifacient activities (66). Animal subject that was administered by *Annona squamosa* Linn leaf extract showed a significant reduction of the average testicular index, this happened because of testicular weight shrinkage which indicates



antifertility activity. Extract of *Annona squamosa* Linn leaves affects the hormonal mechanism that regulate spermatogenesis, which decrease caudal epididymal sperm counts.(8) Administration of the ethanol extract notably showed a decrease of spermatozoa concentration and abnormalities in spermatozoa such as bent tails, spermatozoa without tails, headless spermatozoa, and spermatozoa with two heads.(67) Contraceptive effect of methanolic extract of *Annona squamosa* stem bark was studied in male albino rats. The findings of the study support contraceptive allege of *Annona squamosa* Linn however this contraceptive activity was reversible after withdrawal of the drug treatment (68)

Anti Platelet Activity

Anti-platelet movement: The ent-kaurane diterpenoids, which are separated from the stem of *Annona squamosa* Linn. are examined for anti-platelet action. The ent kaurane diterpenoids 'ent-Kaur- 16-en-19-oic acid' and '16 α -hydro-19 -al-entkauran- 17-oic acids' appeared total inhibitory impacts on rabbit platelet conglomeration at 200 M, detailed that *Annona* species can be misused for planning of restorative items with tall esteem. (8)

Anti-Tumor And Anticancer Activity

The plant *Annona squamosa* Linn traditionally known as Custard apple possesses potent bioactive principals in all its parts. *Annona squamosa* Linn seed extract have shown, in previous studies, significant anti-tumour activities against human hepatoma cells in vitro and in vivo, indicating a potential for developing the extract as a novel anti-liver cancer drug. Aqueous extracts of *Annona squamosa* Linn seeds possess significant antitumour activity in vivo against AD-5 tumour (4). The defatted seed of *Annona squamosa* was screened for the antitumor activity. The extract was of aqueous and organic solvent. The parameter which was checked for the conclusion of the activity were estimation of intracellular

ROS, estimation of intracellular GSH, DNA fragment analysis, and quantization of apoptosis. The study was carried out on rat histolytica cells tumour cell line AK-5. The study resulted significant apoptotic tumour cell death with enhanced caspase-3 activity, down regulation of anti-apoptotic gene Bcl-2 and Bcl. Enhanced the generation of intracellular ROS, which correlated well with the decreased levels of intracellular GSH. In addition, DNA fragmentation and annexin-V staining confirmed that the extracts induced apoptosis in tumour cells through the oxidative stress. Aqueous extracts of *Annona squamosa* Linn seeds possessed significant antitumor activity in vivo against AK-5 tumour (69).

Anticancer Activity

Ethnic communities use all parts of *Annona squamosa* Linn traditionally for treatment of various diseases, such as cancer tumors, skin problems, insect bites, and any others.(67) The leaves of *Annona squamosa* Linn can be used as active and immunomodulatory.(70) In previous studies, a research has been carried out on *Annona squamosa* Linn against anti-cancer related non-alkaloidal moieties particularly the acetogenins.(8) A research on the alkaloids section of *Annona squamosa* Linn yielded two benzylisoquinoline alkaloids. Isolated Alkaloids I provide excellent activity for colon cancer cells (HCT116) and also for Human Breast cancer cells (MCF-7) which is related to the activity of benzylisoquinoline alkaloids in cancer cells.(71) Seeds contain Squadiolins A and B showed high potency against human Hep G2 hepatoma cells and significant cytotoxic activity against human MDA-MB- 231 breast cancer cells (72). Yet another study revealed that acetogenin squamotacin from the bark of *Annona squamosa* Linn showed selective cytotoxicity for PC-3 (human prostate tumour cell line) with a potency greater than 100 million times that of Adriamycin (73). Further investigation has



provided that bark extracts protected the cell surface glycoconjugates during 7,12-dimethyl benz(a)anthracene (DMBA) induced hamster buccal pouch carcinogenesis. Oral administration of aqueous and ethanolic extracts at a dose of 500 mg/kg b.w. and 300 mg/kg b.w reduced the total number of tumours and normalized the levels of glycoconjugates in tumour-bearing animals (74).

Anti-Head Lice Activity

Extract of *Annona squamosa* seeds in coconut oil at the ratio of 1:2 killed 98% of head lice within two hours, while the leaf extract had less potency. The present study focused on the separation and identification of the active compounds against head lice from the hexane extract of *Annona squamosa* L seed. Chromatographic and spectroscopic techniques revealed that two major compounds of the hexane seed extract were oleic acid and triglyceride with one oleate ester. The yields of these compounds were 12.25 % and 7.74 % dry weight respectively. The compounds were tested in vitro against head lice. comparing to the crude hexane of the seed. The triglycerides with one oleate ester and the crude hexane extract diluted with coconut oil 1:1. These compounds were found to kill all tested head lice in 49, 11 and 30 minutes respectively. The triglyceride ester can be used as a marker for quantitative analysis of the active compound for quality control of the raw material *Annona squamosa* Linn seed and its extract. This first finding will be useful for quality assessment and the chemical stability of the anti-head lice preparation from this plant (75).

Vasorelaxant Activity

A cyclic octapeptide, cyclosquamosin B, isolated from the seeds of *Annona squamosa* Linn showed a vasorelaxant effect on rat aorta. It showed a slow relaxation activity against norepinephrine (NE)-induced contractions of rat aorta with/without endothelium. It showed inhibition effect on vasoconstriction of depolarized aorta with high concentration potassium, but moderately

inhibition effect on NE-induced contraction in the presence of nicardipine. These results showed that the vasorelaxant effect by cyclosquamosin B might be attributed mainly to inhibition of calcium influx from extra cellular space through voltage-dependent calcium channels (76).

Antiulcer Activity

Annona squamosa Linn leaves contain properties that have efficacy as Anti-ulcerative. Recently a study conducted on experimental animals of male albino- Wistar rats and indomethacin was used to induce ulcer presented that aqueous extract of dosage 175 mg/kg and 350 mg/kg significant reduction in free acidity, gastric volume, and ulcer index compared with the control group. Acute oral toxicity study for aqueous extract of *Annona squamosa* Linn leaves has shown that the plant leaf was safe and nothing side effects were observed so, it can be used for the management of peptic ulcers. (77) Anti-ulcer activity of twelve compounds isolated from *Annona squamosa* twigs was evaluated against cold restraint, pyloric ligation, aspirin, alcohol induced gastric ulcer and histamine induced duodenal ulcer models and further confirmed through in vitro assay of H⁺ K⁺-ATPase activity and plasma gastrin level. *Annona squamosa* and its chloroform and hexane fraction attenuated ulcer formation in cold restraint, pyloric ligation, histamine model and displayed anti-secretory activity in vivo through reduced free, total acidity and pepsin in pyloric ligation, confirmed by in vitro inhibition of H⁺ K⁺-ATPase activity with corresponding decrease in plasma gastrin level (78).

Anti-HIV

There was a positive result exhibited by the extract of *Annona squamosa* Linn when evaluated for anti-HIV screening. In the above study new chemical compound have been named and isolated. The structures of the new compounds were established by spectral analyses and chemical evidence. Among the 14 isolated compounds in the



study, 16 β ,17-dihydroxy-ent- kauran-19-oic acid showed significant activity against HIV replication in H9 lymphocyte cells with EC50 value of 0.8 μ g/mL (79).

Neuroprotective Activity

Annona squamosa Linn leaf has many benefits. Based on a study conducted by related to neuron protection, it was stated that sugar apple leaf extract contains anonaine can help in treating epilepsy, mood disorders, and memory problems. The results of the phytochemical test of *Annona squamosa* Linn leaf extract using Petroleum and Ethanolic showed that *Annona squamosa* Linn leaf contains phenols components. Phenols play an important role in preventing neurodegenerative disease conditions.(8)

CONCLUSION:

Indian literatures like Ayurveda and various ancient literature have already mentioned herbal remediation for a number of human ailments. Research on phytoconstituents has gained a special attention in recent times. The above review is a sincere effort, to provide the available synthesizing literature to obtain a holistic overview of its updated information regarding botany, phytochemistry, pharmacological profile of *Annona squamosa* Linn, a medicinal plant which is a potential species in the family of Annonaceae, used in the Indian system of medicine. *Annona* possesses terrific medicinal properties, attributed by its diverse group of secondary metabolites. The usage of herbs to treat a variety of different ailments is universal, and exists in every human culture on Earth. *Annona squamosa* Linn plants grow well in the lowlands and the tropics. The leaves of *Annona squamosa* Linn is a type of plant that is still rarely used. Several of phytoconstituent found in *Annona squamosa* show promising activity like anti-cancer, anti-inflammatory, antidiabetic, antimicrobial, antimalarial and many more. *Annona squamosa* Linn has a lot of benefits for

humans such as for health functions based on the previous studies, that have shown that *Annona squamosa* Linn leaves have high nutritive value. The studies performed on the seed extract also evidenced for anti - HIV activity and reporting with new isolated compound. This comprehensive exploration not only serves to enrich our understanding of *Annona squamosa* Linn but also underscores its significance as a valuable resource in herbal medicine and pharmaceutical research. Hence, there is enormous scope for future investigations into the phytochemistry and pharmacological aspects of the plant to render its justified position in evidence based, phyto-therapeutic medicines for the purpose of the putative cure of human ailments. However, research on *Annona squamosa* Linn leaves needs to be further developed to be able to convince and increase the information that *Annona squamosa* Linn leaves have many benefits, especially in the prevention and treatment of disease for the welfare of the mankind.

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