



PHARMACOLOGICAL ACTIVITIES OF *ANNONA SQUAMOSA*: A REVIEW

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ABSTRACT

In the present review, an attempt has been made to congregate the traditional, phytochemical and pharmacological studies done on the medicinal plant *Annona squamosa*, (Family annonaceae). Natural products were considered to be the best option as they have less harmful nature against the environment and other non-targeted organisms. The Annonaceous acetogenins were the expanding class of potential long chain fatty acid derivatives which were initially noticed only in the species of the family Annonaceae. Interest in these compounds reached worldwide due to their remarkable anti-tumor and other pesticidal activities. The pharmacological actions of the above plant include the regulation of hyperthyroidism and lipid-peroxidation. The plant also poses analgesic activity, anti-inflammatory activity, anti-microbial activity, cytotoxic activity, anti-oxidant activity, anti-lipidemic activity, anti-ulcer activity, molluscicidal properties, genotoxic effect, vasorelaxant activity, anti-tumour, hepatoprotective activity, larvicidal activity, insecticidal activity, anthelmintic activity, etc. The roots, leaves and seeds of *Annona squamosa* contain several medicinal properties. This review will be definitely helpful for the researchers as well as the clinicians dealing with *Annona squamosa* to know its proper usage, as the plant appears to be highly valuable due to its pharmacological / medicinal properties.

Keywords: *Annona squamosa*, Acetogenins, Pharmacological studies, Anthelmintic.

INTRODUCTION

Annona squamosa L. (Annonaceae), commonly known as the custard apple tree is a native of West Indies. But the cultivation is present throughout India, because of its edible nature.¹ It is a fruit tree considered as a native of Central America also and hence have a wider cultivation throughout the regions of tropics. The taste of the pulp of the fruit is really sweet because of its higher sugar content of about 58% of dry mass, and hence it is found clear that the fruit pulp possess a high calorie value. This plant was reputed to contain several medicinal properties.

Folkloric record reported the use of *Annona squamosa* as an insecticidal, an anti-tumor agent, anti-diabetic, anti-oxidant, anti-lipidemic and anti-inflammatory agent which has been characterized due to the presence of the cyclic peptides. In addition, the crushed leaves were sniffed to overcome the hysteria and fainting spells, and they were also applied on the ulcers and wounds. A leaf decoction was taken in the case of dysentery.

The previous phytochemical investigations made on the plant have proved that they possess a wide variety of compounds like acetogenins which were responsible for anti-feedant, anti-malarial, cytotoxic and the immunosuppressive activities. Diterpenes which was isolated from the *Annona squamosa* possess the anti-HIV principle and the anti-platelet aggregation activity. The partially purified flavonoids were reported from the same source as the responsible agent for the anti-microbial and othe pesticidal activities. Some lignans and other hydroxyl ketones were also found to be present in this plant. The number of alkaloids that was reported from this plant belongs to different categories such as aporphine and

benzoquinazoline. The above provided evidences suggested that the plant is known for its various medicinal values.⁸

Taxonomic Classification:

Annona squamosa L.

Kingdom : *Plantae*
 Subkingdom : *Tracheobionta*
 Super division : *Spermatophyta*
 Division : *Magnoliophyta*
 Class : *Magnoliopsida*
 Sub class : *Magnoliidae*
 Order : *Magnoliales*
 Family : *Annonaceae*
 Genus : *Annona* L.
 Species : *Annona squamosa*

Traditional uses: The plant is attributed with the medicinal properties that include anti-fertility and anti-tumour activities which were observed in mice and rats. The young leaves of *Annona squamosa* were used extensively due to its anti-diabetic activity by the tribal men who were living in and around the villages of Aligarh district which is located in the state of Uttar Pradesh, India and also by the people of Chotanagpur district which is located in the state of Bihar, India. In Aligarh district, villagers used to consume a mixture of 4–5 newly grown young leaves along with black pepper (*Piper nigrum*) of about five grains, earlier in the morning in the treatment of diabetes, with the continued therapy that ensures up to 80% of the positive results. The treatment was particularly common and was popular in the Lodha community as the plant was considered to be a sacred



fruit. The formula was successfully used and being used by some Unani and Allopathic physicians that is in existence till date. The aqueous leaf extract of *Annona squamosa* was also reported to ameliorate hyperthyroidism, which is the major causative factor for diabetes mellitus. Though there was no such scientific evidence to prove the anti-diabetic effect of *Annona squamosa*, tribal men continued to use the plant in order to manage the diabetes¹. Its leaves were used as the insecticidal and antispasmodic agents that were used in the treatment of rheumatism and painful spleen. The plant was reported traditionally to possess analgesic, anti-inflammatory, anti-pyretic, anti-ulcer, and antiseptic and abortifacient activities. Its utilization as an insecticidal agent was investigated by several workers and other various phytochemical, pharmacological, anti-bacterial and anti-ovulatory studies was carried out with the extracts obtained from the seeds.

Post-cortical anti-fertility activity of *A. squamosa* was reported from studies with the seed extract⁵. Seeds, fruits and leaves were found to be effective as an insecticide, fish poison, and as a powerful irritant of the conjunctiva. The roots were found to be effective as a drastic purgative and in the acute dysentery⁶. The hot aqueous extract of *Annona squamosa* leaves was investigated to possess a significant hypoglycemic and anti-diabetic activity and its fruit has much higher nutritional value with the biological activity of lowering blood glucose level which was tested to be positive in the experimental animals⁷. *Annona squamosa* Vell was astringent and was found to be useful for the treatment of chronic diarrhoea and estomac disease and also useful as an insecticide¹³.

Phytochemistry: Numerous acetogenins were isolated from the seeds of *Annona squamosa*. For the most part, they were found to be a mono- or adjacent bis-THF-ring bearing compounds. *Annonaceous acetogenins* were a group of compounds that were isolated so far only from the Annonaceae family, but were recently reported to be present in the family of Vitaceae. These compounds were characterized by the presence of terminal γ -methyl- γ -lactone and by the presence of a long aliphatic chain bearing tetrahydrofuranic THF and tetrahydropyranic rings, and the epoxy rings and (or) the double bonds. They were reported to inhibit the first complex of mitochondrial respiratory chain (NADH-ubiquinone oxido-reductase), and also exhibits parasiticide, insecticide and other cytotoxic activities, and were also represented as the anti-tumoral candidates.

Regained attention occurred with the recent works which shows their probable implication in the treatment of typical Parkinsonism in the tropical areas, through the consumption of the Annonaceous edible species². A new category of natural compounds, called as the *Annonaceous acetogenins*, was recently reported to inhibit the ATP production at a similar site of action and at the higher levels of potency as a rotenone, i.e., at the NADH-ubiquinone oxido-reductase, complex I in the mitochondrial electron-transport chain³.

Caryophyllene oxide was also the active agent isolated from an unsaponified petroleum ether extract of the bark of *Annona squamosa*⁵. The prolonged continuous work on the biologically active-directed fractionation of the bark of *Annona squamosa* was resulted in the discovery of new *Annonaceous acetogenins*, called as (2,4-cis and trans)-squamolone, (2,4-cis and trans)-9-oxo- asimicinone, and bullacin B⁹.

The Chromatographic purification of the seeds of n-BuOH soluble fraction was resulted in the isolation of seven cyclic peptides which were named as cyclosquamosins A - G. Cyclic peptides were the molecules possessing a wide range of biological activities. Hence, the Conformational determination of such cyclic peptides plays an important role, because of their biological activities that were known to be closely related with their conformational states. Recently, there was a report on the conformations of a list of cyclic heptapeptides, such as hymenamide, pseudostellarin D, and yunnanin A, and segetalins D and E¹⁰. Two bis-tetrahydrofuran acetogenins, squamocin-O1 and squamocin-O2, were the compounds isolated from a MeOH extract of the seeds of *Annona squamosa*¹².

The discovery of a compound uvaricin in 1982 was the first report on the *Annonaceous acetogenins*, found to act as an *in vivo* active anti-leukemia (P-388) agent that has invigorated a wide interest in the family of Annonaceae¹³. The fractionation work as directed by the brine shrimp lethality test (BST) has led to the isolation of three new bioactive acetogenins, namely 4-deoxy annoreticuin, *cis*-4-deoxyannoreticuin, and (2,4-cis and trans)-squamoxinone¹⁴.

Two more new *Annonaceous acetogenins* called as the squamostanin-C and squamostanin-D were isolated from the 95% EtOH extract of the seeds of *Annona squamosa*¹⁵. Rollicosin was the compound isolated from *Rollinia mucosa* and Squamostolide from the *Annona squamosa*. These compounds contain a partial skeleton of an ordinary *Annonaceous acetogenins* with two γ -lactone moieties on both the sides of an aliphatic chain. Rollicosin can be generated from the oxidative degradation of the ordinary acetogenins such as murisolin and/or from the *cis*-murisolin and also squamostolide from solamin and/or from the *cis*-solamin. Moreover, these compounds were found to be helpful to investigate the role of the terminal hydroxylated lactone moiety instead of the hydroxylated THF moiety with long aliphatic chain that could be seen in the ordinary acetogenins for its bioactivity¹⁸.

Physicochemical properties of sweetsop (sugar apple):

The fruits of sweetsop are found to be oval or heart-shaped with the presence of tender soft pliable spines which could breakup easily when the fruit is ripe. Sweetsop fruits normally weigh about 0.1–0.15 kg. Sweetsop fruits have been traditionally used as a food for a long time and also for making the exotic drinks. Starch usually remains as a major source of the calories in the human diet and could be found in the higher concentration in the plants main storage organs which



includes roots/tubers, stems, seeds/grains and fruits. Starch composition of sweetsop was estimated to be around 25.6%. The moisture content was about 9% and the small granules seen under the microscopic view was about 2.49–2.76 μ m. The amylose composition was about 19% and the gelatinization temperatures range from 64.12–72.99°C. The sweetsop starch was investigated and found to contain the physicochemical properties such as higher swelling power and solubility, higher paste clarity and freeze–thaw stability, lower pasting temperature, higher viscosity peak, higher viscosity breakdown and lower setback. The functionality of sweetsop starch is much comparable to those of the waxy corn and *A. hypochondriacus* starches, thus making it a candidate for the usage in the instant or as the frozen foods¹⁷.

PHARMACOLOGICAL STUDIES

Regulation of hyperthyroidism and lipid peroxidation:

Any alterations in the level of the thyroid hormones affects the basal metabolic rate and causes many health problems. Particularly, hyperthyroidism leads to diabetes mellitus and other cardio-vascular related diseases. *Annona squamosa* seeds were generally thrown away as the waste materials. But, they too were found to possess certain insecticidal, anti-ovulatory, abortifacient and anti-implantation properties.

The extract from the seeds were evaluated to know their ameliorative effect in the regulation of hyperthyroidism in the mouse model. Serum triiodothyronine (T3), thyroxine (T4) concentrations, hepatic glucose-6-phosphatase (G-6-Pase) and 5'-mono-deiodinase (5'DI) activity were determined as the end parameters to assess the alterations in the thyroid function. And also certain other parameters like hepatic lipid peroxidation (LPO), superoxide dismutase (SOD) and catalase (CAT) activities were also investigated to reveal its hepatotoxic effect. The TLC, UV spectra and HPLC analyses revealed the presence of quercetin in the given test sample. This proves that the anti-thyroidal role of *A. squamosa* seed extract could have been mediated by the quercetin. Further, the seed extract was found to decrease the hepatic lipid peroxidation which has suggested that it is safe and possess anti-peroxidative nature. Quercetin was also found to decrease the hepatic LPO⁴.

Analgesic and anti-inflammatory activity: Caryophyllene oxide which was isolated from an unsaponified petroleum ether extract from the bark of *Annona squamosa* was studied for its analgesic and anti-inflammatory activity. Caryophyllene oxide at the dosage levels of about 12.5 and 25mg/kg body weight and unsaponified petroleum ether extract at the dosage levels of about 50mg/kg body weight was found to show a significant central as well as the peripheral analgesic and the anti-inflammatory activity. Caryophyllene oxide produced an analgesic effect which is dosage dependent and also considered to be statistically significant. Further pharmacodynamic investigations were required in order to understand the

analgesic and anti-inflammatory activity exhibited by the caryophyllene oxide⁵.

Anti-bacterial and cytotoxic activity: The anti-bacterial and anti-fungal activities of the plant compounds such as Petroleum ether extract (PE), CHCl₃ extract (CE), EtOH extract (EE), annotemoyin-1, annotemoyin-2, squamocin and cholesteryl glucopyranoside showed maximum inhibition against the gram positive organisms such as *B. subtilis*, *B. cereus*, *B. megaterium*, *Staphylococcus aureus*, *S. b-haemolytica*, *Sarcina lutea* and the gram negative organisms such as *E. coli*, *S. dysenteriae*, *S. shiga*, *S. flexneriae*, *S. sonnei*, *Salmonella typhi*, *P. aeruginosa*, *Klebsiella spp.* The cytotoxicity of the plant extracts was studied by the brine shrimp lethality bioassay and the LC50 values of the petroleum ether and chloroform extracts were calculated⁶.

Anti-oxidant and anti-lipidemic activity: Anti-oxidants are the compounds responsible for the protection of living organism from the damage caused by the abnormal production of reactive oxygen species concomitant lipid peroxidation, protein damages and others including DNA strand breaking etc.. Ethnomedical literature has revealed a large number of plants like *Annona squamosa* which can be used against diabetes, in which the free radicals and ROS plays an important role. The effect of the water extract of *Annona squamosa* leaves on the antioxidant enzymes and the lipid profile of animal models of type 2, non-insulin dependent diabetes mellitus (NIDDM) was evaluated. The parameters considered as the measurement of the above activities were the increased activities of the scavenging enzymes, catalase (CAT), superoxide dismutase (SOD), reduced glutathione (GSH), glutathione reductase (GR) and glutathione-transferase (GST) and the significant decrease in the malondialdehyde levels were expressed in the various tissues. The aqueous extract of the *Annona squamosa* significantly reduced the triglyceride and total cholesterol levels with a gradual increase in the HDL cholesterol level in the treated diabetic rats when compared to that of the untreated diabetic rats (control). These changes were found to be beneficial in the prevention of the diabetic complications and also in the improvement of lipid metabolism in the diabetics⁷.

Anti-ulcer activity: Peptic ulcer is a disease that affects a large population throughout the world and it is caused mainly due to the development of gastric lesions, when there is a delicate balance between some of the gastro protective and aggressive factors is being lost. Increased secretion of the gastric acid is found to be a pathological condition, which occurs mainly due to the uncontrolled secretion of hydrochloric acid through the proton pumping H⁺ K⁺-ATPase. Anti-ulcer activity of the plant extract was evaluated against the cold restraint (CRU), pyloric ligation (PL), aspirin (ASP), alcohol (AL) induced gastric ulcer and the histamine (HA) induced duodenal ulcer models and then further confirmed through in vitro assay of H⁺ K⁺-ATPase activity and the plasma gastrin level. The plant and its chloroform and hexane fraction



attenuated the formation of ulcer in CRU, PL, HA model and also displayed anti-secretory activity in vivo with the decrease in plasma gastrin level. Cytoprotection of *Annona squamosa* was apparent with protection in AL, ASP models and enhanced mucin level in PL. (+)-O-methylarmepavine, N-methylcorydaldine, lanuginosine, were found to be the active principles of the plant which may serve as the initial point for the designing of novel semi-synthetic and synthetic compounds as the anti-ulcer agents in the future⁸.

Hypoglycemic and anti-diabetic activity: From ancient times, diabetes has been treated orally by using several medicinal plants or their extracts. These herbal remedies produce minimal effect and possess no side effects and also found to be economically low cost than the other synthetic hypoglycemic oral drugs. The ethanolic extract of *Annona squamosa* leaves when administered orally to the normal as well as the streptozotocin (STZ)-induced diabetic rats and alloxan-induced diabetic rabbits at different dose, proved that the dose of 350 mg/kg body weight was found to reduce the fasting blood glucose (FBG) level by 6.0% and the peak blood glucose during the glucose tolerance test (GTT) was also reduced by 17.1% in the normal rats. The same dose of the ethanolic extract has reduced the FBG level by 26.8% and also improved the glucose tolerance by 38.5 and 40.6% during the GTT in alloxan-induced diabetic rabbits. In STZ-diabetic rats, there was a fall of 13.0% in FBG and was an improvement in the glucose tolerance by 37.2 and 60.6% was observed during GTT¹¹. In the same way, the aqueous extract of the roots of *Annona squamosa* L. at a dose of 250 mg/kg and 500 mg/kg body weight was tested for the antidiabetic activity in the Streptozotocin (STZ) - induced hyperglycaemic rats which causes a reduction in the blood glucose in STZ- induced diabetic rats from 285.52 to 208.81 mg/dl²⁶.

Molluscicidal properties: Schistosomiasis is an endemic parasitic disease that affects mostly the tropical and subtropical regions of the world and it is caused due to the presence of the worm *Schistosoma mansoni* in the affected person's liver. The utilization of the molluscicides in the prophylactic treatment was found to promote the rupture of the worm's evolutionary cycle with the simultaneous destruction of the snail *B. glabrata* (intermediate host). The ethanolic extracts of *Annona squamosa* was evaluated against the adult forms and egg masses of *Biomphalaria glabrata*.

Annona squamosa Vell. was used from the traditional period as the toxic agent against the snail and then the experimental studies of the seed, root, stem, bark and leaf's ethanolic extract was also found to show the molluscicidal activity against the adult snail at a maximum concentration of 100 ppm¹³.

Genotoxic effect: Biopesticides replaced the potential use of the chemical pesticides due to their risk to human and the environment. Regard to this, a seed extract of *Annona squamosa* produced a compound isosquamocin which

could be used as a promising pesticide for the protection of the plants. The genotoxicity of the compound was also evaluated by the comet assay and other related studies which revealed the fact that the genotoxicity and biochemical effects of *A. squamosa* may not cause any risk to humans in a large magnitude. However, the dosages have to be further established by the development of other mutagenic tests to make the moderate usage in order to reduce the health risk of humans¹⁶.

Vasorelaxant activity: Vasodilators are the agents that are useful for the treatment of cerebral vasospasm and hypertension, and for the better improvement of peripheral circulation. A cyclic octapeptide, cyclosquamosin B which was isolated from the seeds of *Annona squamosa* was found to show a potential vasorelaxant effect on the rat aorta. The vasorelaxant effect caused by the cyclosquamosin might be attributed significantly to the inhibition of calcium influx from the extracellular space via voltage-dependent calcium channels¹⁹.

Anti-tumour activity: Twelve different acetogenins with diverse stereochemical structures and configurations namely asimicin¹⁸, squamocin¹⁸, squamocin-D¹⁸, desacetylurvaricin¹⁸, Iso desacetylurvaricin¹⁸, squamostatin-D¹⁸, squamostatin-E¹⁸, squamostatin-B¹⁸, squamostatin-A¹⁸, 12,15-cis-squamostatin-A¹⁹, 4-deoxyannoreticuin²⁰, and cis-4-deoxyannoreticuin²⁰ were evaluated for their ability to inhibit the growth of cancer cell lines using MTT method which indicated that the stereochemical factor is to be considered as an essential factor for the potent activity of the tested compounds irrespective of their bis-adjacent THF ACGs or the nonadjacent bis-THF ACGs. The ACGs with S configuration at C-24 possessed more selective cytotoxicity than the ACGs with the R configuration at C-24. ACGs showed the significant inhibitory activities against the growth of various tumor cell lines and also against the multiple drug resistant (MDR) tumor cell lines. Thus, ACGs might be considered as a promising antitumor candidates for the future clinical application²⁰.

Hepatoprotective activity: Natural remedies obtained from the medicinal plants are considered as an effective and safe alternative for the treatment of liver toxicity. The hepatoprotective effect of the alcoholic and water extract of *Annona squamosa* was evaluated in the hepatotoxic induced animals in order to explore its usage for the treatment of hepatotoxicity in the human. The experimental study suggested that the extracts of *Annona squamosa* were not capable of reverting the hepatic injury completely which was induced by isoniazide and rifampicin, but it was able to limit the effect of these drugs in the liver. The protective role of *Annona squamosa* leaf extracts might be caused due to the antioxidative effect of the flavonoids present in it²¹. The protective effect of the methanolic extract of *Annona squamosa* on isoniazid-rifampicin-induced hepatotoxicity



was also evaluated in the rats and was found that they also showed a protective effect against the liver injury²⁷.

Larvicidal activity: Mosquitoes possess a great threat to the human health by means of the transmission of the serious diseases^{22,28}. Development of the resistance, cross-resistance, and also the rising cost as well as the possible toxicity hazards arised due to the synthetic insecticides usage were some of the reasons lead to the interest in the discovery of plant based products in the recent years.

The larvicidal and the growth regulating activities of *Annona squamosa* was reported against *An.stephensi* and other mosquitoes. The high potency of *Annona squamosa* as a larvicide against mosquito species was evaluated but the active compound that possess a toxic substance against the larval species has to be identified²².

Insecticidal activity: The common housefly *Musca domestica* (Diptera: Muscidae) which is an important mechanical vector of many bacterial and pathogenic microbes of human and animals have become resistant to the chemical insecticides. *Annonaceous acetogenins* which were extracted from the tree leaves, bark and seeds possess the insect anti-feedant properties. The larvicidal activities of the ethanolic extracts of *A. squamosa* leaves against the *Musca domestica* was evaluated and was found that the LC50 values of the extract was found to be of around 282.5 and 550 mg/l. The data obtained suggested that the leaf extracts of the above plant can be utilized as the probable candidates in the development of bioinsecticides in order to control the population of *Musca domestica* for safer and economic alternative to the synthetic insecticides²⁴. Crude ethanolic seed extracts of *A. squamosa* was also screened for their inhibition of larval growth against the polyphagous lepidopteran *Spodoptera litura* (Noctuidae) in which the extracts significantly showed more active (20-fold) insecticidal effect²⁹.

Anthelmintic activity: Among the gastrointestinal nematodes, *Haemonchus contortus* is found to be the most frequent and pathogenic species that causes the high mortality rate in young animals mainly during the rainy season. Synthetic anthelmintics are often used to reduce the above losses. *Annona squamosa* seed powder is used against the insects in Northeast of Brazil due to the presence of active substances with parasitocidal effects. The anthelmintic activity of the extracts and the isolated compounds of *A. squamosa* seeds were evaluated on the egg hatching of *H. contortus*. Compound one which was isolated from the ethyl acetate extract inhibited the egg hatching of *H. contortus* at the concentration of about 25 mg /ml and the structure of compound one was determined as a C₃₇ trihydroxy adjacent bistetrahydrofuran acetogenin by the spectroscopic analysis²³. The anthelmintic activity of the *Annona squamosa* seed extract against the adult earthworm, *Pheritima posthuma* was also investigated and was found that the methanolic extract showed the

effective anthelmintic activity causing the death of earthworms²⁵.

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