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Annona squamosa: Seetaphal: A review

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Abstract

Alterative medication and natural remedies have been used from ancient time for the treatment and wellbeing of human. Medicinal plants are considered to be effective and for most important for the above purposes. The Mother Nature has provided us with a huge count of flora and fauna. Some of the natural medicinal plants are so common that we use them in daily life without knowing their medicinal importance. Plants have been one of the important sources of medicines since the beginning of human civilization. There is a growing demand for plant based medicines, health products, pharmaceuticals, food supplements, cosmetics etc. *Annona squamosa* Linn is a multipurpose tree with edible fruits & is a source one of the medicinal & industrial products. *Annona squamosa* Linn is used as an antioxidant, antidiabetics, hepatoprotective, cytotoxicactivity, genetoxicity, antitumour activity, antilice agent. It is related to contain alkaloids, carbohydrates, fixed oils, tannins & phenolic. A review of pharmacognostical, chemical constituent present in various parts of *A. squamosa* Linn & their pharmacological actions in given in the present article.

Keywords: *Annona squamosa* Linn, Pharmacognostical, Phytochemical constituent, Pharmacological actions, Toxicity.

Introduction

The history of herbal medicine starts with human civilization. The documents which are of great antiquity, revealed that plants were used medicinally in China, India, Egypt and Greece long before the beginning the Christian era. The knowledge of healing power of plants became a special calling of the priest and magicians, and this knowledge became a source of power. For thousands of years, the role of the priest and physician were combined and exists today in the form of witch, doctor, shaman, exorcist's medicine man.

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. *A. squamosa* has been named botanically from Jamaica.[1]

Plant part used: Fruit, bark, seed, Root, Leaf.[95]

Synonyms:[1,2,95]

English : Custard apple, Sugar apple, sweet sop
Sanskrit : Seetaphalam, Sudha, Subha
Hindi : Seetaphal, Sharifa, Ata
Malayalam: Athachakka, Atha, Seetapazham
Kanda : Sitaphal
Telgu : Sitaapandu
Tamil : Sitapplam
Bengali : Ata
Arabic : Ghista
Italian : Pomo canella
French : Corossolier, Cachiman canelle, Pomme de cannelle, Attier
Portuguese: Atta, Fructa do conde
Malay : Nona sri kaya, Sri kaya, Buah nona

Classification:[4]

Kingdom: Plantae
Order : Magoliales
Family : Annonaceae
Genus : Annona
Species : *Annona squamosa*

Plant Description

The Seetaphal tree ranges from 10 to 23 ft (3-7 m) in height with open crown of irregular scattered branches, and some-what zigzag twigs. Deciduous leaves, alternately arranged on short, hairy petioles, are lanceolate or oblong lanceolate, blunt tipped, 5 to15 cm long and 2 to 5 cm wide; dull-green on the upper side, pale, with a bloom, below; slightly hairy when young; aromatic when crushed. Along the branch tips, opposite the leaves, the fragrant flowers greenish-yellow, fragrant on slender hairy stalks, produced singly or in short lateral a bunch about 2.5 cm long, 2 to 4 flowers but not at the base of the leaves. Sepals pointed, hairy green, about 16 mm long; 3 fleshy outer petals oblong, thick and rounded at the tips, fleshy, 1.6 to 2.5 cm long, 0.6 cm wide, never fully open; yellow-green, slightly hairy, drooping stalks, pale-yellow inside with a purple or dark-red spot at the base. The 3 inner petals are merely tiny scales. The compound fruit is nearly round, ovate, or conical; 5-10 cm in diameter; its thick rind composed of knobby segments, pale-green, gray-green, bluish-green, or, in one form, dull, deep-pink externally (nearly always with a bloom); separating when the fruit is ripe and revealing the mass of conically segmented, creamy-white, powdery bloom; glistening, delightfully fragrant, juicy, sweetly aromatic, delicious flesh. Many of the segments enclose a single oblong-cylindrical, black or dark-brown seed about 1.3 to 1.6 cm long. There may be a total of 20 to 38, or perhaps more, seeds in the average fruit. Some trees, however, bear seedless fruits.[22,23]

Propagation

Sugar apple seeds have a relatively long life, having kept well for 3 to 4 years. They germinate better a week after removal from the fruit than when perfectly fresh. Germination may take 30 days or more but can be hastened by soaking for 3 days or by scarifying. The percentage of germination is said to be better in unsoaked seeds. While the tree is generally grown from seed, vegetative propagation is practiced where the crop is important and early fruiting is a distinct advantage. Seedlings may be budded or grafted when one-year old.[23]

Soil

The sugar apple is not particular as to soil and it grows in rich, well-drained, deep rocky soils, limestone and heavy loam. Water-logging is intolerable. The tree is shallow-rooted and doesn't need deep soil.[22,23]

Products

- **Food:** Fruits are normally eaten fresh. The pulp can be used as a flavoring in ice cream. 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 fiber is also significant.[22]
- **Fuel:** The tree is a good source of firewood.
- **Timber:** The light yellow sapwood and brownish heartwood are soft, light in weight and weak.
- **Poison:** Green fruits, seeds and leaves have effective vermicidal and insecticidal properties.
- **Medicine:** Leaves, shoots, bark and roots have been reported to have medicinal properties. The unripe fruit is astringent, and the root is a drastic purgative.[22]

Uses: Due to the presence of alkaloid higenamine it is recommended in heart disorder, and precursor of other isoquinolines.(t), Annona fruits provide good carohydratesnutrition, acting as excellent sources of energy, minerals, such as calcium, phosphorus and potassium. They are important in biological function, such as helping to protect bones and teeth, providing strong muscles and improving health. Annona plant parts used in folk medicine contain chemical compounds such as tannins, alkaloids and flavonoids found in roots, leaves, bark, fruits and seeds. Acetogenins, (great potential in anti-cancer treatment) are present in seeds, roots, bark, stem and fruits. Boiled water infusions of leaves help to control convulsions and digestive problems, and also diabeties. Roots of sugar apple can be used to treat acute dysentery and depression while leaves have been used in case of anal prolapsed, sores and swelling. Tea made from roots is highly purgative, Tea of leaves are mild laxative, Wild soursop roots, leaves and bark are used to treat cancer, convulsions, venereal disease, diarrhea and dysentery, fever, filariosis and male impotence.[147,148]

Ayurvedic Properties:

Rasa : Madhura, Kashaya
Guna : Guru, Snigdha
Virya : Seeta[164]

Annona squamosa

Fig. of *Annona squqmosa* Bark

Morton, (1987) analysed the food value of edible portion per 100 g of to be calories (88.9-95.7g), moisture (69.8-75.18g), fat (0.26-1.10g), carbohydrates (19.16-25.19g), crude fiber (1.14-2.50g), protein (1.53-2.38g), vitamins-carotene (5-7 I.U.), The amine (0.100-0.13mg), riboflavin (0.113-0.167mg), niacin (0.654-0.931mg), ascorbic acid (34.7-42.2mg), amino acid- tryptophan (9-10mg), methionine (7-8mg), lysine (5.4-9mg). Minerals-ash (0.55-1.34mg), phosphorus (23.6-55.3 mg), calcium (19.4-44.7mg), iron (0.28-1.34mg). The average sugar content is 14.58% and is about 50-50 glucose and sucrose.[5]

Kawazu *et al.*, (1989) isolated neoannonin, a novel insecticidal from the seed of *Annona squamosa*, which were found to be toxic to fruit fly.[6]

Born *et al.*, (1990) and Mukhlesur *et al.*, (2005) isolated A new natural compound squamosamide and two bis- tetrahydrofuran acetogenins, squamocin-O (1) and squamocin-O (2) from the methanolic extract of seeds of *Annona squamosal.*[7,8]

Li. *et al.*, (1990) isolated annotemoyin-1, annotemoyin-2, squamocin, cholesteryl glycopyranoside, anonin I and anonin VI from seeds of *Annona squamosa*. annonain I is identical with that of squamosin.[9]

Lieb *et al.*, (1990) and Morita *et al.*, (2002) investigated samaquasine A, benzoquinazoline, annonacin, annonacin-A and annonastatin alkaloid from the seeds of *Annona squamosal.*[10, 11]

Bhagawan *et al.*, (1992) studied the depletion in free amino acids had an adverse effect on protein turnover, resulting in delayed metamorphosis.[12]

Reddy et al., (1993) applied topically seed extract of *Annona squamosa* in laboratory caused a steady decline of all free amino acids in freshly emerged 5th-instar larvae of *Dysdercus koenigii.*[13]

Epino and Chang (1993) found repellent and anti-oviposition properties when *A. squamosa* seed extracts to *Ceratitis capitate*.[14]

Saxena *et al.*, (1993) isolated alkaloids from *Annona squamosa* which on concentrations of 50 to 200 ppm showed larvicidal growth-regulating and chemosterilant activities against *Anopheles stephensi* at Adults exposed as larvae to different treatments showed reduced fecundity and fertility in females. Mortality in the larvae, pupae and adults produced about a 52-92% decrease in the laboratory experiment.[15]

Sahai, *et al.*, (1994) reported that the petroleum ether extract of the seeds of *Annona squamosal* yielded 13 known adjacent, and 4 non-adjacent bistetra hydrofuranic acetogenins, and the compounds squamocin and squamostatin A.[16]

Fujimoto *et al.*, (1994) isolated four non-adjacent bis-tetrahydrofuranic acetogenins, named squamostatins-B to -E, from the petroleum ether extract of *A. squamosa* seeds.[17]

Hussain *et al.*, (1995) reported that the adults *T. castaneum* were repelled by contact with food medium treated with 2 and 5 g leaf dust/10 g flour, for *A. squamosal.*[18]

Malek and Wilkins (1995) recorded seed extract at 1.5 percent concentration the highest mortality in *H. armigera* (43.33%) and 36.66 per cent mortality at 1% concentration in *S. litura*. Larval development of FSS II and CTC-12 strains of *T. castaneum* significantly affected by the seed oil of *A. squamosal.*[19]

Hopp *et al.*, (1996) isolated a new bioactive acetogenin, squamotacin and a known compounds mluizarin from the bark of *Annona squamosa*, which showed cytotoxic selectively for the human prostate tumor cell line (PC-3), with a potency of over 100 million times that of Adriamycin.[20]

Wu *et al.*, (1996) performed phytochemical analysis of the fruits of *Annona squamosa* yielded 12-known kuarane derivatives and two new kaurane diterpenoids, annosquamosin-A and annosquamosin-B. The structures of these two compounds were established by spectral analysis and chemical evidences.[21]

Hopp *et al.*, (1997) isolated the new mono-tetahydrofuran (THF) ring acetogenins, mosinone-A, mosin-B and mosin-C from the bark of *Annona squamosa* by using the brine shrimp lethality assay and elucidation of the structure of these compounds was by spectroscopic & chemical methods.[22]

Babu *et al.,* (1998) reported insecticidal and abortifacient properties of the seeds of *A. squamosa*. The leaf damage caused by larvae were reduced significantly at 2.5 percent concentrations of crude oils obtained from seeds of *A. squamosal.*[23]

Hopp *et al.,* (1998) discovered three new annonaceous acetogenins, (2,4-cis and trans)-squamolinone (1), (2,4-cis and trans)-9-oxoasimicinone (2), and bullacin B (3) from the bioactivity-directed fractionation of the bark of *Annona squamosa.* These compounds are all adjacent bis-THF ring acetogenins with 2 representing the first bis-ring acetogenin to contain a carbonyl along its aliphatic chain. Compound 3 was selectively cytotoxic in a panel of six human tumor cell lines with a potency of nearly a million times that of adriamycin against the MCF-7 (human breast adenocarcinoma) cell line.[24]

Hopp *et al.,* (1998) represented three new annonaceous acetogenins, 4-deoxyannoreticuin, cis- 4-deoxyannoreticuin and (2,4-cis and trans)-squamoxinone was directed by the brine shrimp lethality test (BST) from the bark of *Annona squamosa*. A hydroxylated mono-THF ring with respective threo/trans/ threo and threo/cis/ threo relative stereochemistries were found there. The latter compound is a ketolactone mixture which has the same relative stereochemistry around the THF ring and the same spatial relationship between the THF ring and the hydroxyl group along the aliphatic chain as 4-deoxyannoreticuin, but is two methylene units longer. Additionally, the isolated hydroxyl group is at C-11, while the THF ring starts at C-17, instead of at C-9 and C-15, respectively, as for the first two compounds. All three compounds showed moderate but significant, cytotoxicities against a panel of six human tumor cell lines with (2,4 cis and trans)-squamoxinone showing promising selectivity against the pareatic cell line (PACA – 2).[25]

Sonkamble *et al*. (2000) found the acetone extract of *Annona squamosa* seed was less active against adults of *T. castaneum.*[26]

Boreddy and Chitra (2001) observed that petroleum ether extract of seeds reduced the weight and length of *S. litura.*[27]

Dash *et al.,* (2001) evaluated the aqueous & ethanolic extract of *Annona squamosa* leaves for analgesic & anti-inflammatory activity. The significant oedema suppressant activity against carrageenan and histamine induced paw oedema similar to that of ibuprofen and equal to the pentazocin were shown by aqueous extract of *Annona squamosa*, whereas ethanolic extract did not produce significantly result.[28]

Dharmasena *et al*. (2001) extracted acetone extracts from fresh and stored leaves of *Annona squamosa* were toxic to adult *C. maculatus*, whereas the ethanol extracts were not active.[29]

Kuruppasamy R., (2001) examined inhibitory effect of seed extract of *Annona squamosa* on digestive enzyme at sub lethal dose (0.4 ml) of 4% concentration of LD50, Which shows inhibition of amolytic, proteolytic and lipolytic enzyme.[30]

Damasceno *et al.,* (2002) observed effect on early pregnancy in rats using aqueous extract of *Annona squamosa* from the seeds, which have been administrated by gavage during days 1 to 5 of pregnancy (pre-implantation period) at a dose of 300-600mg/kg, Showed anti-ovulatory and abortifacient effect and did not interfere with reproductive performance of pregnant rat.[31]

Araya*et al.,* (2002) discovered the bioactivity-directed fractionation on the bark of *Annona squamosa* resulted in the of three new annonaceous acetogenins, (2, 4-cis and trans)-squamolinone (1), (2, 4-cis and trans)-9-oxoasimicinone (2), and bullacin B (3).[32]

Jaswanth *et al.,* (2002) prepared a liquid mosquito insecticide formulation with the methanolic extract of leaves of *Annona squamosa* using deodorized kerosene as the solvent and investigated for its mosquitocidal effect against *C. quinquefasciatus*. The extract formulation produced dose-dependent activity and the results suggest the potential mosquitocidal effect of *Annonasquamosa* on *C. quinquefasciatus.*[33]

Jaswanth *et al.,* (2002) evaluated methanolic extract of *Annona squamosa* for its insecticidal activity against *Sitophilus oryzae* at 1 and 5% w/v concentration. The extract showed significant activity against *Sitophilus oryzae* in both the concentration with 'knock down' (KD50), 23.1 and 11.4 min. for 1 and 5 % w/v concentration. The mortality had achieved at 39.6 +- 1.4 and 14.5 +- 1.1 min. for 1 and 5% w/v of the extract.[34]

Ji *et al.,* (2002) investigated diterpenoids annomosin A, annosquamosin C, annosquamosin D, annosquamosin E, annosquamosin F, annosquamosin G. from the stem of the *Annona squamosal.*[35]

Kotkar *et al.,* (2002) isolated flavonoids from aqueous extracts which showed antimicrobial activity against all the common microbial contaminants of pulses and 80% insecticidal activity against *C. chinensis* at a concentration of 0.07 mg ml-1.[36]

Yang *et al.,* (2002) concluded six new ent-kaurane diterpenoids annomosin A, annosquamosin C, annosquamosin D, annosquamosin E, annosquamosin F, annosquamosin G were isolated from stem of the *Annona squamosa*. The structures of these six compounds were elucidated by NMR spectroscopy data interpretation.[37]

Dwivedi *et al.,* (2003) evaluated the toxicity of *Annona squamosa* acetone/ pet. ether extracts to various stages of *Trogoderma granarium*. The acetone extract was found to be more toxic than the pet. ether extract at 100% concentration.[38]

Kukarni *et al.,* (2003) investigated the anti-feedant activity of *Annona squamosa* leaves against *Crypsiptya coclesalis* in laboratory. Petroleum ether and hexane fraction proved best with over 90% leaf protection.[39]

Gupta *et al.,* (2005) illustrated The ethanolic extract of *Annona squamosa* leaves showed Anti-diabetic effect orally at different dose to normal against streptozotocin (STZ) induced diabetic rats and Alloxan induced diabetics rabbits. The various doses of extract here shows reducing its fasting blood glucose level and fall in total cholesterol level with increasing HDL and decreasing the LDL & Triglyceride level respectively.(40)

Garg *et al.,* (2005) investigated the oil of *Annona squamosa* extracted from leaves, made up of monoterpene hydrocarbon, sesquiterpene hydrocarbons and oxygenated sesquiterpenes in this β-Caryophyllene, germacrene, bicyclogermacrene & β-elemene were the major constituents of the oil, by GC and GC MS.(41)

Mukhlesur *et al.,* (2005) given detail of isolation of Annotemoyin-1, Annotemoyin-2, Squamocin and cholesteryl glycopyranoside and plant seed extracts of *Annona squamosa* evaluated antimicrobial & cytotoxic activities.(42)

Yu *et al.,* (2005) first time isolated the squamocenin, a new acetogenin, annotemoyin-2 and reticulatain-2 from ethyl alcohol extract of *Annona squamosa* plant andisolated eleven compounds from ethyl alcohol extract of *Annona squamosa* which shows antitumor activity.(43)

Khalequzzaman and Sultana, (2006) reported in the experiments that *T. castaneum* larval mortality was the most in petroleum spirit extract of seed, whereas ethyl acetate and acetone extracts were moderately toxic and methanol extract was the least toxic for Raj and FSS-II strains, but it remained toxic for CR-1 and CTC 12 strains. In adults acetone extracts showed less toxic to all strains used. Petroleum spirit extract remained most toxic for FSS-II and CTC 12 strains, whereas methanol extract was most toxic for other two strains i. e., Raj and CR-1 strains.(44)

Chavan *et al.,* (2006) isolated and identified essential oil from the bark of *Annona squamosa* when subjected to GC / GC-MS, six major compounds. The oil was also evaluated for its antimicrobial activity, which exhibited a significant activity against *Bacillus subtilis* and *Staphylococcus aureus*.(45)

Intaranongpai *et al.,* (2006) performed a comparative study of the crude hexane extract diluted with coconut oil (1:1) and isolated compound i.e. oleic acid and triglyceride with one oleate ester carried out in vitro against head lice and the studies showed that these compounds were found to be effective against. 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* seed and its extract.(46)

Morita *et al.,* (2006) isolated and investigated a cyclic octapeptide, cyclosquamosin B from the seed of *Annona squamosa* showed a vasorelaxant effect on rat arota. It showed a slow relaxant activity against norepinephrine (NE) induced concentration of rat arota.(47)

Baskar *et al.,* (2007) used different in-vitro models to study the antioxidant potential of leaves of three different species of Annona. The ethanolic extract of *Annona muricata*at 500 µg/ml showed maximum scavenging activity (90.05%) of ABTS radical, hydroxyl radical (85.88%) and nitric oxide (72.60%). *Annona reticulata* showed better activity in quenching DPPH and superoxide radical (89.37%) & (80.88%) respectively. *Annona squamosa* extract display the least inhibition in all in vitro antioxidant models excepting hydroxyl radical.(48)

Shanker *et al.,* (2007) compared the antimicrobial activity of the isomeric hydroxy ketones against gram (+) ve and gram (-) ve bacterial strain and also some selected fungal strains and with Palmitone. The antimicrobial activity of Palmitone was notably higher than those of the isomeric hydroxy ketones but their antifungal activity was comparable and reported the nearness of 10-hydroxy-16-hentriacontanone from *Annona squamosa* by phytochemical examination.(49)

Magadula *et al.,* (2009) revealed that the leaf extracts of *A. squamosa and A. senegalensis* possess cytotoxic and larvicidal activities. Their potential application in managing mosquito larvae would, therefore, be a promising undertaking.(50)

Chavan *et al.,* (2010) isolated Caryophyllene oxide from an unsaponified petroleum ether extract of the bark of *Annona squamosa* and studied for its analgesic and anti-inflammatory activity. Caryophyllene oxide at the doses of 12.5 and 25mg/kg body wt. and unsaponified petroleum ether extract at a dose of 50mg/kg body wt. showed significant central as well as peripheral analgesic, along with anti-inflammatory, activity. These activities of caryophyllene oxide were comparable with the standard drug used in the respective experiments.(51)

Kamaraj *et al.,* (2010) assessed the larvicidal activity of hexane, chloroform, ethyl acetate, acetone and methanol extracts of ten medicinal plants tested against fourth instar larvae of malaria vector, Anopheles stephensi Liston and lymphatic filariasis vector, Culex quinquefasciatus Say(Diptera: Culicidae). Ethyl acetate of Annona squamosa was in the range of 70.38-210.68 ppm. Results that bark ethyl acetate extract of A. squamosa from Southern India have the potential for use to control mosquitoes. Therefore, this study provides the larvicidal activity against An. stephensi and Cx. quinquefasciatus of plant extracts.(52)

Bagavan *et al.,* (2011) extracted ten plants with ethyl acetate and methanol and treated for their antimalarial activity against chloroquine (CQ)-sensitive (3D7) and fluorescence-based SYBR Green assay was performed. Moderate activity (30-75 µg/mL) was found in the ethyl acetate and methanol extracts of *Annona squamosal*.(53)

Chavan *et al.,* (2011) collected *Annona squamosa* L. bark from Ahmednagar district, India and isolated 18-Acetoxy-ent-kaur-16-ene from petroleum ether extract (PE) and evaluated for its analgesic and anti-inflammatory activities. 18-Acetoxy-ent-kaur-16-ene at the quantity of 12.5 and 25 mg/kg, and PE at a quantity of 50 mg/kg present notable analgesic along with anti-inflammatory activity.(54)

Kamaraj *et al.,* (2011)assessed the role of larvicidal activities of hexane, chloroform, ethyl acetate, acetone, and methanol dried leaf and bark extracts of *Annona squamosa* L., *Chrysanthemum indicum* L., and *Tridax procumbens* L. against the fourth instar larvae of malaria vector, *Anopheles subpictus* Grassi and Japanese encephalitis vector, Culex tritaeniorhynchus Giles (Diptera: Culicidae).(55)

Kamaraj and Rahuman (2011) searched for alternatives to control gastrointestinal nematodes of small ruminant's imperative due to the development of anthelmintic resistance. The leaf and seed of ethyl acetate, acetone and methanol extract of *Annona squamosa*, showed complete inhibition (100%) at the maximum concentration tested (50 mg/ml).(56)

Uduman *et al.,* (2011) investigated the protective effect of methanolic extract of *Annona squamosa* on isoniazid-rifampicin-induced hepatotoxicity in rats. The administration of methanolic extracts of *Annona squamosa* significantly prevented isoniazid-rifampicin-induced elevation in the levels of serum diagnostic liver marker enzymes (alanine amino transferase (ALT), aspartate amino transferase (AST), alkaline phosphatase (ALP) and gamma glutamate transpeptidase (γ-GT)), serum bilirubin, and TBARS level in experimental groups of rats. Moreover, total protein and reduced glutathione (GSH) levels were significantly increased in the treatment group. The effect of the extract was compared with a standard drug, silymarin. The changes in biochemical parameters were supported by histological profile. It is to be concluded that the methanolic extract of Annona squamosa protects against isoniazid and rifampicin-induced oxidative liver injury in rats.(57)

Yadav *et al.,* (2011) investigated phytochemically the *Annona squamosa* twings, and isolated and identified of twelve known (1-12) compounds among them one 1-(4-β-D-glucopyranosyloxyphenyl)-2-(β-D-glucopyranosyloxy)-ethane (11) is synthetically known but first time isolated from natural sources. The given study showed the gastroprotective effect of *A. squamosa* (AS) and identified the active constituents. Cytoprotection of AS was apparent with protection in AL, ASP models and enhanced mucin level in PL.(58)

Deshmukh *et al.,* (2011) treated Nephrectomized rats (5/6) showed a significant rise in plasma urea and creatinine levels with a stable fall in urine creatinine. Treatment with *A. squamosa* extracts (300 mg/kg bw) lead to a significant fall in the plasma urea and creatinine values with partial restoration to normal values along with a significant rise in the activity of SOD. *A. squamosa* therapeutic strategies against oxidative stress could be effective in renal diseases.(59)

Chen *et al.,* (2011) isolated three new bistetrahydrofuran annonaceous acetogenins (1-3) from a 95% EtOH extract of *Annona squamosa* seeds. Four known annonaceous acetogenins, uvarigrandin A (4), bullatacin (5), squamostatin-A (6), and squamostatin-D (7), were also isolated. These all compounds exhibited significant cytotoxic activity in vitro against five human tumor cell lines.(60)

Dholvitayakhun *et al.,* (2012) described uses of Leaf of *Annona squamosa* in traditional Thai medicine to treat dysentery and other diseases. This study investigated the antibacterial activity of these plants against six species of foodborne pathogen. The *A. squamosa* extract contained flavonoids, terpenes, tannins, and alkaloids, and had the broadest spectrum of antibacterial activity, inhibiting Bacillus cereus, *Listeria monocytogenes*, *Staphylococcus aureus* and *C. jejuni* between 62.5 and 500 µg mL(-1). MBCs were 2 to 4fold higher than MICs against *B. cereus* and *C. jejuni*, proposed the extracts are bactericidal against these species. *A. squamosa* could potentially be used in modern applications aimed at the treatment or prevention of foodborne diseases.(61)

Madhumitha *et al.,* (2012) extracted *Annona squamosa* (Annonaceae) immersion method exhibited adulticidal activity against *Haemaphysalis bispinosa* (Acarina: Ixodidae) and the hematophagous fly, *Hippobosca maculata* (Diptera: Hippoboscidae), and larvicidal activity against the cattle tick Rhipicephalus (Boophilus) microplus (Acari: Ixodidae), *Anopheles subpictus*, and *Culex quinquefasciatus* (Diptera: Culicidae). The major chemical constituent of peel aqueous extract of *A. squamosa* was 1H-cycloprop[e]azulen-7-ol decahydro-1,1,7-trimethyl-4-methylene-[1ar-(1aα,4aα, 7β, 7 a, β, 7bα)] retinal 9-cis-(12.61%), 3,17-dioxo-4-androsten-11alpha-yl hydrogen succinate (6.86%), 1-naphthalenepentanol decahydro-5-(hydroxymethyl)-5,8a-dimethyl-y,2-bis(methylene)-(1α,4aβ,5α,8aα) (14.83%), 1-naphthalenemethanol decahydro -5-(5-hydroxy-3-methyl-3-pentenyl)- 1,4a-di methyl - 6-methylene -(1S-[1α, 4aα, 5α(E), 8aβ] (4.44%), (-)-spathulenol (20.75%), podocarp-7-en-3-one13β-methyl-13-vinyl- (5.98%), and 1-phenanthrene carboxaldehyde 7-ethenyl-1,2,3,4,4a,4,5,6,7,9,10,10a-dodecahydro-1,4a,7-trimethyl-[1R-(1α,4aβ.4bα,7β, 10aα)]-(5.98%). the eco-friendly and biodegradable compounds from fruit peel aqueous extract of *A. squamosa* may be an alternative to conventional synthetic chemicals, particularly in an integrated approach for the control of *Haemaphysalis bispinosa*, *Hippobosca maculata*, R. *microplus*, and the medically important vectors *A. subpictus* and *C. quinquefasciatus.*(62)

Ponrasu *et al.,* (2012) examined the efficacy of an ethanolic extract of *A. squamosa* leaves on wound

repair in streptozotocin-nicotinamide-induced diabetic rats. The back of rats an Open excision wounds were made. The drug at a dosage of 100 mg/kg body wt was reconstituted in 200 µl of phosphate buffered saline and applied topically once daily for the treated wounds. The control wounds were left untreated. Wound tissues formed on days 4, 8, 12 and 16 (post-wound) were used to estimate DNA, total protein, total collagen, hexosamine and uronic acid. Levels of lipid peroxides were also evaluated along with tensile strength and period of epithelialisation. *A. squamosa* L. an increased cellular proliferation and collagen synthesis at the wound site as evidenced by increase in DNA, protein and total collagen. The treated wounds were observed to heal much faster as proved by enhanced rates of epithelialization and wound contraction, which was also confirmed by histopathological examinations. The results strongly substantiate the beneficial effects of the topical application of *A. squamosa* L. in the acceleration of normal and diabetic wound healing.(63)

Chen *et al.,* (2012) investigated the chemical constituents and the anti-tumor activity of the standardized *A. squamosa* seeds extract in vitro and in vivo. The presence of annonaceous acetogenin compounds in the extract by FT-IR spectroscopy. Two major annonaceous acetogenins: bullatacin and 12, 15-cis-squamostatin-A was identified and quantified by HPLC. It has been concluded thatA. Squamosa seed extract showed significant anti-tumor activities against human hepatoma cells in vitro and in vivo, indicating a potential for developing the extract as a novel anti-liver cancer drug.(64)

Mariod *et al.* (2012) extracted phenolic compounds from *Annona squamosa* (leaves, bark, roots and seedcake), and *Catunaregam nilotica* (leaves, bark, and seedcake) using methanol and their antioxidant activity was evaluated employing various established in vitro systems. The total phenolic content was determined by Folin-Ciocalteu method and the highest amounts were 171.5, 170.4, 169.5, and 167.9 g/kg plant extract as GAE for *A. squamosa* roots, *C. nilotica* bark, *C. nilotica* leaves, and *A. squamosa* bark, respectively. The different parts extracts from two trees showed good antioxidant activity evaluated by oxygen radical absorbance capacity and MTT assay systems. *Annona squamosa* and *Catunaregam nilotica* phenolic compounds could be utilized as a natural antioxidant.(65)

Thang *et al.,* (2013) identified the volatile compounds from four species of Annona from Vietnam. The oils were obtained from *Annona squamosa* L., comprised mainly of α-pinene (1.0-11.9%), limonene (0.8-11.7%), β-cubebene (0.5-13.0%), β-caryophyllene (11.6-24.5%), spathulenol (0.8-9.0%), caryophyllene oxide (1.0-10.6%) and α-cadinol (3.3-7.8%).(66)

Nandha KE and Indumathi P. (2013) evaluated the antioxidant activity of the fruit of Annona squamosa. The antioxidant properties of the extract were determined by scavenging 1, 1-diphenyl-2-picrylhydrazyl radical (DPPH), lipid peroxidation (LPO), nitric oxide (NO), superoxide anion (O2 (-)), hydroxyl radical (OH(•)), reducing power and total antioxidant. The results showed that, compared to aqueous extract, a methanolic fruit extract of *A squamosa* has a higher percentage of inhibition of DPPH radical scavenging activity (97.99%), LPO (94.15%), NO scavenging activity (70.96%), O2(-) scavenging activity and OH(•) scavenging activity (78.68% and 85.25%, respectively), total antioxidant activity (206 µg α-tocopherol/g) and reducing power (56.0 µg of ascorbic acid/g). The results obtained in the in vitro models clearly suggest that methanol extract has higher antioxidant activity than the aqueous extract due to a higher presence of phenolic and flavonodal constituents in the methanol extract.(67)

Wu *et al.,* (2014) isolated two new cyclic peptides, fanlizhicyclopeptide A, cyclo (Pro(1) – Pro(2) – Tyr (3) – Leu (4) – Pro (5) - Gly(6) – Val (7)) (1), and fanlizhi cyclopeptide B, cyclo(Pro(1) –Ile (2) - Tyr (3) – Ala (4) – Gly (5)) (2), along with six known kaurane diterpenoids and a known clovane sesquiterpene from the exocarps of sugar-apples, the fruit of *Annona squamosa*. In the anti-inflammatory assay, both 1 and 2 showed in vitro inhibitory effects on the production of pro-inflammatory cytokines, TNF-α and IL-6, in LPS-stimulated RAW 264.7 macrophages.(68)

Yang *et al.,* (2015) found the inhibitory rate of TAAs in mice was 50.98% at 4 mg/kg dose. The IC50 of TAAs on Bel-7402 was 20.06µg/mL (15.13-26.61µg/mL). Effective mechanisms of TAAs were confirmed as both of arresting cell cycle at G1 phase and inducing apoptosis dose- and time-dependently. Mitochondrial and recipient pathways involved in apoptotic actions of TAAs. TAAs are effective for hepatocarcinoma, via inhibiting proliferation and inducing apoptosis.(69)

Miao et al., (2016) isolated and evaluated four new annonaceous acetogenins (ACGs), squamocin-I (1), II (2) and III (3) and squamoxinone-D (4), together with seven known ACGs (5-11), from the seeds of *Annona squamosa*. Compounds 1-4 were evaluated for their cytotoxicity's against Hep G2, SMMC 7721, BEL 7402, BGC 803 and H460 human cancer cell lines. Compound 1 exhibited better potent activity than the positive compound and compound 3 shows selectively cytotoxic activity against H460 with IC50 values of 0.0492 µg/ml.(70)

Panda and Kar (2015) evaluated the protective effects of 5,7,4'-trihydroxy-6,3'dimethoxy-flavone 5-O-α-l-rhamnopyranoside (THDMF-Rha); in l-thyroxine (l-T4)-induced thyrotoxicosis in rats. Administration of l-T4 at 500µg/kg body weight for 12days increased the levels of serum thyroid hormones, the activity of 5'-monodeiodinase-I (5'DI) and hepatic glucose-6-phosphatase (G-6Pase) as well as lipid peroxidation (LPO); with a parallel decrease in the levels of cellular antioxidants and serum lipids. However, administration

of the isolated THDMF-Rha at a pre-standardized dose for 15days ameliorated the l-T4-induced alterations in the levels of thyroid hormones, hepatic LPO, G-6-Pase, 5'DI activity, and cellular levels of antioxidants and improved the status of different serum lipids, suggesting its antithyroidal and antioxidative potential. As compared to standard antithyroid drug, propylthiouracil, THDMF-Rha appeared to be more promising.[71]

Tu *et al.,* (2016) had first isolated a new water-soluble polysaccharide, designated as ASPW80-1, from the fruit pulp of *Annona squamosa*. Another novel modified polysaccharide, the sulfated derivative of ASPW80-1 namely as ASPW80-M1, was also synthesized. Showed that ASPW80-M1 might be proposed to be developed as a potential value-added product with the activities of immuno modulator and free-radical inhibitors.[72]

Conclusion

Annona squamosa which is commonly known as custard apple in English and sitafal in Hindi having various pharmacological activity such ad antidiabetic, analgesic, anti-inflammatory, wound healing, antimalarial, cytotoxic, anti-oxidant, anti-microbial and few more. Some compounds have been isolated and reported from the extract of various part of the plant possessing good pharmacological activity. The studies performed on the seed extract also evidenced for anti HIV activity and reporting with new isolated compound. More pharmacological investigation should be performed using latest technique to discover the potential of the plant.

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