Shikha Srivastava et al. / Journal of Pharmacy Research 2011,4(12),4596-4598

Review Article
ISSN: 0974-6943

Available online through
www.jpronline.info

Medicinal potential of *Annona squamosa*: At a glance

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Received on:20-08-2011; Revised on: 15-09-2011; Accepted on:10-11-2011

ABSTRACT

From ancient days, medicinal plants are useful for the treatment of several diseases and disorders. Our traditional system or in Ayurvedic Industry is purely depend on the medicinal plants. Day to day many fruitful result came in the treatment of disease from Ayurvedic research which are having benefit of no side effects. One of the tropical medicinal Plants is *Annona squamosa*; it has been used in various Asian traditional medicines. In this review we revealed the Phytochemical and medicinal potency of *Annona squamosa* at a glance.

KEYWORDS*: Annona squamosa*, Medicinal properties of *Annona squamosa*, Traditional uses,Phytochemical of *Annona squamosa*, Pharmacological activities of *Annona squamosa*

INTRODUCTION

Annona squamosa or Sugar apple is also known as Sitaphal. Literatures of many Research work conducted so far proves that every parts of *A.squamos*a possess wide medicinal properties.

In Ayurveda the fruits are used as tonic that enriches blood; ripe fruit is used along with salt against malignant tumors to hasten suppuration. The seeds are powerful irritant of conjunctives and produce ulcers in the eye. Leaves used as poultice over boils and ulcers and also to kill the lice [1].

Scientific Classification:
Kingdom: Plantae – Plants
Division : Magnoliophyta – Flowering Plants
Family : Annonaceae – Custard apple Family
Genus : Annona L – annona
Species : *Annona squamosa* L-Sugar apple

Morphology

Annona squamosa is a small well branched tree or shrub belongs to family Annonaceae. Leaves occur singly, lanceolate or oblong lanceolate thin, dull green to dark green on top surface, and pale blue-green and covered with bloom on underside; apex short or long pointed; base short pointed or rounded; petioles 0.6-1.3 cm long, green, sparsely pubescent. Flowers greenish-yellow, fragrant, on slender hairy stalks, sepals pointed, hairy, green, about 16 mm long; 3 outer petals oblong, thick and rounded at the tips, yellow-green, slightly hairy, inside light yellow and keeled with a purplish or reddish spot at the thin, stamens very numerous, crowded, white, less than 16 mm long; ovary light green, styles white, crowded on the raised axis. Fruit is round, ovate or conical, 5-10 cm in diameter, with many round protuberances; greenish-yellow when ripe, the pulp is white, edible and sweetly aromatic. seed oblong, shiny and smooth, blackish or dark brown, 1.3-1.6 cm long, numerous [2].

Traditional uses of various parts

The plant is traditionally used for the treatment of epilepsy,dysentry,cardaic problem,warm infection, constipation,hemorrage,antibacterial infection, dysuria, fever and ulcers. It also has antifertility, antitumour and abortifacient properties [3-6].

In Ayurveda, Fruits are considered as a good tonic, enriches food, used as an expectorant, increases muscle strength, cooling, lessens burning sensation and tendency to biliousness, sedative to heart and relieves vomiting. Ripe fruit mixture along with salt is used against malignant tumours to hasten suppuration. Dried unripe fruit is used to destroy vermin [15].

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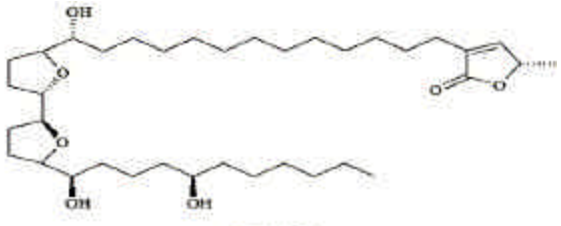
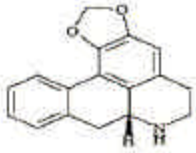
Seeds are used as an abortifacient and good to destroy lice in hair in unani medicine. Seeds are powerful irritant of conjunctivitis and produce ulcers in the eye. Leaves are used as polutice over boils and ulcers and also to kill lice. The whole tree is a good source of fire wood [15]Roots are traditionally used as a purgative [7] .

PHYTOCHEMICALS

The seed of *Annona squamosa* L. contains Annonaceous acetogenins: annonins VI, VII, VIII, IX, XIV[8], annonacin, annonacins A[9] , I, II, annonastatin, asimicin[8] , neoannonin B[10] , squamocins A, B, C, D, E, F, G, H, I, J, K, L, M, N[11], O1, O2 [12] .squamostatins A, B, C, D, E, squamosten A [12]annotemoyins 1, 2[13] . squamocenin, reticulatain 2, motrilin, cherimolins 1, 2 [14] .squamostolide[15], neo-desacetyluvaricin, neo-reticulatacin A[10] , bullatacinone[16], squamostanal A[17] , annonsilin A[18] , mosin B[19] ; cyclopeptides: annosquamosin A[20] , cyclosquamosins A, B, C, D, E, F, G[21] , squamins A, B[22] , squamtin A[23] ; alkaloids: samoquasine A[24], anonaine[25].The fruit contains kaurane diterpenoids: annosquamosins A, B[26] ; alkaloids: liriodenine, oxoxylopine, reticuline, coclaurine, N-methylcoclaurine, anonaine, nornuciferine, asimilobine[27] . The root contains alkaloids: anonaine, michelalbine, liriodenine, reticuline, anolobine[28]. The stem and leaf contain alkaloids: annosqualine, demethylsonodione, liriodenine, annobraine, thalifoline[29]lignans and neolignans: squadinorlignoside, 1-methoxyisolariciresinol, isolariciresinol, secoisolariciresinol, urolignoside[30], podophyllotoxin, 4'-demethylpodophyllotoxin[31] ; amines: dihydrosinapoyltyramine, dihydroferuloyltyramine[29] , squamosamide, moupinamide[32] ; kaurane diterpenoids: annomosin A, 16a-methoxy-(-)-kauran-19-oic acid, sachanoic acid, (-)-kauran-19-al-17-oic acid, annosquamosins B, C, D, E, F, G[33] , 16ß,17-dihydroxy-ent-kauran-19-oic acid[34].



squamocin A



anonaine

Young leaves of *Annona squamosa* conatins streoids, alkaloids, saponins,terpenes,phenoicssubstances,carbohydrates,volatile oils,mucilages and flavonoids. Leaves conatins 4-(2-nitroethyl)-1-(6-o-ß-D- xylopyranosyl –ß-D –glucopyranosyl)-oxy) benzene. Anonaine, Benzyl tetrahydro-isoquinoline,Borneol,Cmphene,Camphor,Car-3-ene,carvone,ß Caeyophellene,Eugenol,Farnesol,Geraneol,6-Hentriacontanone, Higenamine, Hexacontanole,Linalool,Limonene,Linalool acetate,Menthone, Methyl-anthranilate,Methylsalicylate,Methylheptenone,p-(hydroxybenzyl)-6,7-(2-hydroxy,4-hydro)isoquinoline,,-octanasanol,a-pinene,ß-pinene,Rutin, Stigmaasterol,ß-sitosterol,Thymol,and n-tricontanol.Several other compounds -like Aporphine alkaloids,squamosamide,16-alpha-methoxy-(-)-kauran-19-oic acid,Sachanoic acid,(-)-kauran-19-al-17-oic acid,dauosterol, linodenine, moupinamide-(-)kauran-16 alpha-ol-19-oic acid,16 beta,17-dihydroxy-(-)-kauran-19-oic acid,16alpha,17-dihydroxy-(-)-kauran-19-oic acid,have been isolated from the plant.

The stem bark contains Annonaceous acetogenins: bullatacin, bullatacinone, squamone[35] , squamolinone, 9-oxoasimicinone, bullacin B[36] , 4-deoxyannoreticuin, squamoxinone[37] , mosinone A[38] ; alkaloids: corydine, isocorydine, anonaine, glaucine[39] .The leaf contains alkaloids: xylopine, lanuginosine[40] ; flavonoids: rutin, hyperoside, quercetin[41] . Leaves conatins 4-(2-nitroethyl)-1-(6-o-ß-D- xylopyranosyl –ß-D –glucopyranosyl)-oxy) benzene. Anonaine, Benzyl tetrahydro isoquinoline,Borneol, Cmphene, Camphor,Car-3-ene,carvone,ß Caeyophellene, Eugenol, Farnesol,Geraneol, 6Hentriacontanone, Higenamine, Hexacontanole, Linalool,Limonene, Linalool acetate,Menthone,Methyl-anthranilate,Methylsalicylate, Methylheptenone, p-(hydroxybenzyl)-6,7-(2-hydroxy,4-hydro)isoquinoline,,-octanasanol, α-pinene,ß-pinene,Rutin,Stigmaasterol,ß-sitosterol,Thymol,and n-tricontanol,squamosamide,16-alpha-methoxy-(-)-kauran-19-oic acid, Sachanoic acid,(-)-kauran-19-al-17-oic acid,dauosterol,linodenine, moupinamide-(-)kauran-16 alpha-ol-19-oic acid,16 beta,17-dihydroxy-(-)-kauran-19-oic acid,16alpha,17-dihydroxy-(-)-kauran-19-oic acid,have been isolated from the plant. Several other compounds -like Aporphine alkaloidsThe aporphine alkaloids anonaine, roemerine, norcorydine, corydine, norisocorydine, isocorydine and glaucine have been isolated from *Annona* squamosa[42,43].

THERAPEUTIC CLASSIFICATION INDEX

CNS

Plant is traditionally used in the treatment of CNS disorder epilepsy.Chemical constituent Corydine,Magnine shows CNS deppresent activity, Borneol, Camphor, Reticulline act as an CNS Stimulant.One of the active constituent Tryptophan possess antimanic,antidepressent property,Thiamine possess anti alzimer activity[42] .

Studies revealed that *Annona squamosa* is potentially used in Parkinsonian diseases.Hydroalcoholic extract of *Annona squamosa* shows neuroprotective effect against 6-hydroxydopamine induced Parkinsonian disease at a dose of 200 and 400 mg/kg and significantly increase the dopamine level [44] .

Blood and Haemopoetic tissue

Fruits of *Annona squamosa* is considered as a good tonic to enriches the blood [45].

Antidiabetic

It has been shown through research that *Annona squamosa* exhobit potential antidiabetic activity. Oral administration of hot water extract of leaves of *Annona squamosa* at a dose of 350 mg/kg body weight reduce the fasting blood glucose level by 6.5% in the STZ induced diabetes rats. The same dose shows significant reduction in Fasting Blood Glucose level by 24.4% in alloxan induced diabetes rabbits. It seems to act by enhancing insulin level from pancreatic islets, increasing the utilization of glucose in muscle and inhibition of glucose output from live. Water extract inhibit the activity of glucose 6-phosphatase in isolated rat microsomes. *Annona squamosa* act more than site pancreas, muscle and intestine. The margin of safety is also high [46].

It has been observed through various literatures that the Antidiabetic effect of *Annona squamosa* leaf extract is possibly mediated through the insulin stimulating and free radical scavenging properties of its active constituents Quercetin-3-O-glucoside[47].Streptozotocin inhibit the free radical scavenging enzymes causing ß cell cytotoxic effect .It has also been observed that young leaves of the plant contain phenol and flavonoid which possess an antioxidant and free radical scavenging ability. Antihyperglycemic activity of the plant may be due to the antioxidant activity of phenol and flavonoid which reduces ß cell cytotoxicity and restores the ß cell.

Reduced glutathione is a potent free radical scavenger GSH within the islet of ß cell and is an important factor against the progressive destruction of the ß cell following partial pancreatectomy .Depletion of GSH result in enhanced lipid per oxidation. This can cause increased GSH consumption and can be co-related to the increase in the level of oxidized Glutathione (GSSG).Treatment with *Annona squamosa* resulted in elevation of GSH levels which protect cell membrane against oxidative damage by regulation the redox status of proteins in the membrane [48] .

Anticancer

As it is known that oxidative stress have been implicated in the pathology of many diseases such as cancer, diabetes, because *Annona squamosa* shows effective antioxidant activity .So it may possess anti carcinogenic property [40] . Extract of *Annona squamosa* fruit pericarp was tested for cytotoxic activity against Dalton's lymphea cells and He La cells. The chloroform extract was found to be cytotoxic to different cells lines tested and suggested the potential for *Annona squamosa* fruit pricarp for the developement of anticancer activity. It has been shown in research in literatures that active costituent Bullatacein possess anticancer activity in the treatment of breast and kidney [49] . Other phytochemical that have been documented with antitumor activity are Limonene,Liridenine,ß-carotene,citric acid,corydiene,mallic acid and tannin[42] .There has been no dearth of scientific literature that genotoxic agents have a causative effect in the pathogenesis of carcinomas. 7,12dimethylbenz(a) anthracene (DMBA) which is, a potent organ specific carcinogen has been found to produce mutagenic effects on cells. *Annona squamosa* has a long history in traditional indian medicine for being used to treat several diseases including cancer. Genotoxicity was induced in golden Syrian hamsters by single intraperitonial injection of DMBA (30 mg/kg body weight). The antigenotoxic effect of aqueous and ethanolic bark extracts of *Annona squamosa* was assessed by determining the frequency of micronucleated polychromatic erythrocytes (MnPCEs) and chromosomal aberrations.The frequency of MnPCEs and chromosomal aberrations in bone marrow were higher in DMBA treated animals as compared to control animals[50] . Oral administration of aqueous and ethanolic bark extracts significantly reduced the frequency of MnPCEs and chromosomal aberration in DMBA treated hamsters. Although both extracts have shown antigenotoxic effect, the effect of ethanolic extract was found to be more prominent than the aqueous extract[50]The functional groups of Annonaceous acetogenins include the terminal ?-lactone ring and the tetrahydrofuran ring, which could inhibit cell energy metabolism by inhibiting the respiratory chain of cellular mitochondria. Annonaceous acetogenins could inhibit cancer cell growth, but at the same dose, could not inhibit the growth of non-cancer cells[51] . In vivo and in vitro Annonaceous acetogenins had antitumour effects against leukemia, liver, prostate, pancreatic, and cervical carcinoma, with the constituent polyphosphorus bullatacin G having the most potent activity. In cell growth inhibition experiments, in vitro Annonaceous acetogenins and polyphosphorus bullatacin G had potent anti-tumour effects against larynx and breast cancer cells in human. In addition, Annonaceous acetogenins also inhibited mitochondrial NADH oxidoreductase and the transmission of the respiratory chain of mitochondria, resulting in the rapid decrease of cell energy, causing function loss of P-glycoprotein, overcoming multidrug resistance (MDR) [52] .

Cardiovascular system

Leaves of Annona squamosa considerd to possess Hypotensive activity.Leaves conatin (-)-kaur-16-en-19-oic acid,(-)-xylopine showed effective hypotensive activity[42].A tetra hydroisoquinoline alkaloid isolated from leaves of *Annona squamosa* known to possess cardiotonic activity[53] .Relax blood vessel Cyclosquamosin B diminished norepinephrine (NE)-induced aortic contraction in the rat, inhibited depolarized aortic contraction under high K+, and moderately inhibited NE-induced blood vessel contraction with the presence of nicardipine. The mechanism could due to the inhibition of voltage-dependent calcium channels, causing the decrease of Ca2+ influx to the cells [54].

Liver and Biliary system

Leaves of the plant are use in sub acute cases of liver. Further studies reported that Alcoholic and water extract of leaves shows potential hepatoprotective activity in rats[55] . It has been clinically demonstrated that administration of methanolic extract of *Annona squamosa* at a dose of 250 and 500 mg/kg significantly prevented the isoniazid–rifampicin induced elevation in level of serum marker enzyme, ALT,AST and ALP & ¥ GT serum bilirubin in rats. The effect of extract was compared with standard drug Silymarin[56] . Studies reported that hepatoprotective effect of the extract may be due the flavonoid component having free radical scavenging activity lead to heptoprotection so it could be due to anti oxidative effect of flavonoid present in leaf of *Annona squamosa*.Research studies also shows that *Annona squamosa* is potential hepatoprotective drug against diethylnitrosoamine induced liver injury in swiss albino mice[57] .

GIT / Digestive system

Roots of *Annona squamosa* is drastically used as purgative. Decoction of bark

of the plant is used as tonic and is used in diarrhoea. The study revealed that *Annona squamosa* showed promising gastro protective effect. Compound Isocorydine, N- methylcorydaline were evaluated for H+K+ATP ase activity and also compared with standard drug Omeprazole for its activity[58] .Chloroform and hexane fraction attenuated ulcer formation in cold restraint Pyloric ligation model and displayed ant secretary activity .The bark and leaves extract contain annonaine which is effective in curing diarrhoea and clarifying urine.

Analgesic and Antiinflammatory activity
18-acetoxy - ent-kaur-16-ene isolated from petroleum ether extract showed promising analgesic and Antiinflammatory activity at a dose 12.5 mg and 25 mg/kg body weight[59] .

Studies also demonstrated that Caryophyllene oxide was isolated from an unsaponified petroleum ether extract of the bark of *Annona squamosa* possess 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[60] . cyclic peptide cyclosquamosin H&I, Squamin A and B, cyclosquamosin A,D,E and cherimolacyclopeptide B isolated from seeds inhibit the Proinflammatory cytokines.

Skin
Psoriasis is a chronic inflammatory skin disorder by rapid prolifleration of keartonocytes .It has been observed that ethanolic extract of *Annona squamosa* possess potential Anti psoriatic activity and clinically demonstrated by using HaCaT Keratonocytes cell lines as in vitro model[61] .

Reproductive system

As an abortifacient
Annona squamosa is used as a traditional medicine in fertility and health problems .Roots of the plant is used to induced the abortion in the women. Dried root powder is taken orally in morning for five days from one to fifth months of pregnancy[62,63] .

Thyroid Hormones.
Leaf extract of *Annona squamosa* were found to be thyroregulatory medicine. Previous findings proved that plant exhibit thyroid inhibitory effect in mice but alter the hepatic LPO in a dose dependent manner.

Studies revealed that at low concentration leaf extract found to be anti thyroidic as well as antiperoxidative where as at higher concentration it is found to be thyroid inhibitory but show hepatotoxicity by enhancing the LPO. So it suggesting the unsafe nature of highest dose.

Circulating thyroid harmone T4 is senial from the thyroid gland where as T3 is considered as most metabolically active harmone formed in liver by monodeiodination of T4.Leaf extract of *Annona squamosa* decreases the T4 concentration by direct inhibition of T4 synthesis or release at Thyroid level and decrease the T3 by the inhibition of monodeiodination of T4 and also increases the utilization of harmone by body[64] .

Sexully transmitted diseases
One of the study demonstrated that *Annona squamosa* shows effective potential against Neisseria gonorrhoeae[65] .

Anti-head lice activity
The human head louse (Pediculus humanus capitis) is a small insect causing a public health problem especially in poor sanitory condition .Researchers has shown that anti head lice activity of *Annona squamosa* seeds extract in coconut oil at the ratio of 1: 2 can kill 98% of head lice.It has been found that the petroleum ether extract of leaves and seeds dissolved in coconut oil at the ratio of 1:1 kill 90 % of head lice in vitro by 53 and 26 min respectively.

Phytochemical studies documented that the compound responsible for antihead lice activity is oleic acid and triglycerides with one oleate ester isolated from hexane extract of seed of the plant[61] .

Anti microbial activity

Antibacterial
Previous studies revealed that there are some phytoconstituents such as Linalool,Borneol,Eugenol and Geraneol in the extract which provide antibacterial activity. Different solvent extract of leaves of custard apple were studied for its antibacterial activity with the help of Agar difussion method against two gram positive and two gram negative bacteria and concluded that highest inhibition showed by methanol extract against Pseudomonas aeruginosa(MIC: 130 µg/ml) followed by Petroleum ether extract against P.aeruginosa(MIC: 165µg/ml) and methanol extract E.coli (MIC: 180µg/ml).*Annona squamosa* contain flavonoid which expose strong antibacterial activity[43,67] .

Anti-malaria
In vitro plant leaf methanol extract exhibited potent inhibition against the chloroquine-sensitive strain 3D7 and chloroquine-resistant strain Dd2 of malignant plasmodium, and the stem skin methanol extract had moderate inhibitory effect against Dd2[68] .

Antiviral
Ent-16ß,17-dihydroxykauran-19-oic acid extracted from fresh Annona fruit exhibited potent inhibition against human HIV activity in lymphatic cell H9[26]

Anthelminthic
Studies demonstrated that the methanolic extract of seeds of *Annona squamosa* possess anthelminthic activity against earthworm Pheritima posthum and compared with standard drug Albendazole.It was found that the *Annona squamosa* seeds extract was effective at all concentration tested against standard drug Albendazole in causing the death of earthworm *Annona squamosa* seeds extracts showed anthelmintic activity against *Haemonchus contortus*, the main nematode of sheep and goat in Northeastern Brazil. A compound was isolated from ethyl acetate extract and inhibited the egg hatching of *H. contortus* at 25 mg ml-1. The structure of compound was determined as a C37 trihydroxy adjacent bistetrahydrofuran acetogenin based on spectroscopic analysis[69] .

Insecticidal
The reason for using natural pesticide is that these are active at highly acceptable levels, biodegrable and do not leave toxic residue. while commonly use phosphate and chlorinated pesticide contaminate the environment that's why the finding of new insecticidal is of great economic importance both from agronomic and preventive medicine point of view.

Crude ethanolic seed extracts of *Annona muricata*, *A. squamosa* were screened for inhibition of larval growth against the polyphagous lepidopteran *Spodoptera litura* (Noctuidae). Extracts of *A. squamosa* were significantly more active (20-fold) than those of *A. muricata*[70] .

Studies revealed that ethanol extract of *Annona squamosa* possess insecticidal activity and clinically tested and concluded that the mortality (100%) was achieved at 39.6±1.4 and 14.5±1 for min 1% w/v and 5%w/v concentation respectively. The ethanolic extract produce significant "Knockdown" (KD50) in the concentration of 1% w/v and 5%w/v tested 23.1 min and 11.4 min respectively. It has been established that ethanolic extract at concentration of 5%w/v showed significant knockdown and mortality rate [71] .

Warning
Pregnant women should not eat Sugar apple as it may abort the foetus.

Conclusion
We concluded from above review studies that*Annona squamosa* is a potential plant in the world. Further studies are required both phytochemically and pharmacologically to find many more activities of the plant and the phytoconstituents responsible for that particular activity.

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Source of support: Nil, Conflict of interest: None Declared