A review on insight of immense nutraceutical and medicinal potential of custard apple (Annona squamosa Linn.)

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Abstract

The natural remedies and substitute medication have been used since early civilization for the treatment and wellbeing of human mankind. The medicinal plants are considered to be effective and for most important for the human health. Some of the natural medicinal plants are so common that we use them in daily life without knowing their medicinal importance. Annona squamosa belonging to the family Annonaceae is a well-known plant of natural niches is perceived as best example of it. It is a multipurpose saint tree with edible fruits. Its fruits are commonly known as etario of berries which is edible. The edible mass of custard apple is pulp entangled around the needs as sticky mass. 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 content is also significant. The custard apple is reported to possess various beneficial chemical compounds such as alkaloid, isomeric hydroxyl ketones from leaf, acetogenin, samaquasine, annonacin and annonastatin from seeds, acetogenin, and squamone from bark of it. Various studies envisaged that custard apple possesses an antibacterial, antidiabetic, antitumor, antimarial, anthelmintic, anti-genotoxic potential and hepatoprotective activity. The multifaceted uses of custard apple leaves include protein properties having vermicidal action for treating cancerous tumors, abscesses, insect bites and other skin diseases. The crushed leaves are sniffed in tribal areas to overcome the hystera and fainting spells and they are also applied as medication for treatment of ulcers and wounds. Scrapings of root-bark are used for toothache. Powdered seeds are used to kill head-llice and fleas but excessive precaution should be taken that the powder does not come in contact with the eyes as this causes great pain. The crude extracts of different parts and pure isolated phytochemical constituents of custard apple fruit was reported to possess anti-diabetic, antiviral, antioxidant activity, respiratory stimulant, during pregnancy and diuretics properties being potent for the improvement of the immune system, nervous system and also for the development of the brain in the foetus. Custard apple can be the most effective available of choice among fruits for controlling various diseases and disorder and new paradigms in focusing the nutraceutical and valuable therapeutic potential will definitely help mankind to lead a disease free and healthy life.

Keywords: nutraceutical, medicinal potential, custard apple, Annona squamosa, vitamin C, annonaceae

Introduction

Management of poor health through medication under burgeoning population explosion across the globe has entered an era of rapid ascent in nutritional deficiencies for the mankind. The plant kingdom still holds potential among different unknown species, containing chemical constituents of therapeutic and nutraceutical value, which have yet to be ascertained. Fruits and vegetables are a ‘power house’ for a plethora of nutritional compounds. The modern pharmaceutical industries need a large quantity of genuine plants for the manufacturing of drugs in view of developed resistance among the present drags. Extraction of active constituents and production of drug formulations is a sophisticated technology and require intensive effects with attractive remuneration. Annona squamosa Linn. (Annonaceae) is a small, semi deciduous tree, 3 - 7 m in height, with a broad, open crown or irregularly spreading branches, widely available in different agro-climatic zones of India. Different constituent parts of plant like fruit, leaves, bark, and root are used in the treatment of various diseases and gaining acceptance for its medicinal and nutraceutical values. It is native to the New World Tropics, particularly northern South America - Columbia, Ecuador, and Peru. It was cultivated by natives in the Andes and was first planted in California in 1871(Kirtikar and Basu). It is believed that it was first introduced into Brazil as “fruta do conds” It was later taken to the Philippines and Asia via West Indies. In India, there is very large and good
Commercial importance so considered as potential underutilized fruit as natural gene sanctuary in various niches. However, this is a secondary centre of diversity, created during the last 500 years. This fruit has an interesting history attached to it in respect to its name i.e. Sitaphal. Mythologically it is said that Sita, wife of Lord Rama during her Vanvaas used to eat this fruit. While some texts says that when Ravana was abducting Sita, at that time the tears of her eyes and nose fell onto the ground and they gave birth to Sitaphal trees in the wilderness. Although, many people believe that sitaphal has nothing to do with Sita. Its origin is in Sanskrit i.e. “sheet” in hindi means cold and “phal” is fruit and having excess of it can give you cold and also it has a cooling effect on your body so hence the name is Sitaphal. Annona is semi- evergreen shrub species of Annona and native to the tropical America and India. It is a fast growing tree producing, 6 - 10 cm diameter fruits with a thick, scaly or knobby skin that gives them a pine-cone appearance, commonly known as ‘Custard apple’ Sharifa or Sitaphal and Krishnaguru in Sanskrit. It is widely distributed in the tropics and abundantly present in the central and northern regions of India. It is a terrestrial coarse-gained, woody, deciduous, perennial tree with characteristic odour rough, ash gray colored bark with visible leaf scars and smooth to slightly fissured into plates, inner bark light yellow and slightly bitter, twigs become brown with light brown dots. The leaves are brilliant green above and bluish green below; with petioles 0.7 to 1.5 cm; elliptical ovate to lanceolate; lamina measures about 10 × 5 cm; alternated to spirally arrange with zigzag pattern. Flowers of the plant is 2.0 to 2.5 diameter; somewhat fragrant, solitary or in fascicles with 2 to 4 flowers, with three green sepals and six petals arranged in two containers. The flowers have several conglomeration and spirally arranged stamens below and around with upper globes shaped dome shaped of numerous united carpels. The fruit flesh is high fragrant, sweet, and white to pale yellow in color with texture greatly or mealy. Fruits are divided into 20 - 38 segments, each generally containing a hard, shiny brownish-black, seed, entangled in the flesh, although some trees produce seedless fruit. The fruits are generally eaten fresh, or used to make juice beverages or sorbet, and are a good source of iron, calcium, and phosphorus (Morton et al.2013) [40]. Seeds are shiny brownish-black, black color with ovoid shape, numerous scattered over the white pulp. 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. Annonaceae, the custard apple family is a family of flowering plants consisting of trees, shrubs, or rarely lianas, (Germplasm Resource Information Network (GRIN). The family is concentrated in the tropics, with few species found in temperate regions. About 900 species are Neotropical, 450 are Afro-tropical, and the other species Indo Malayan (Wunderlin et al. 2009). Under Annonaceae family 130 genera are available, out of that genera are widely available Annona, Anonidium, Rollinia, Uvaria, Melodorum, Asimina, Stelieochocarpus, as described by (Raj et al. 2009 and Crane et al. 1994) [58, 10]. At present, many commercial fruit products are exist in the market hence the present review will probably act as connection between nutraceutical food and industrial pharmaceutical potentials of Annona squamosa (Arif et al. 2016) [4].

Traditional Uses: The custard apple is used by indigenous as an insecticidal and antitumor agent, anti-diabetic; antioxidant, anti -lipidemic, and anti-inflammatory agent which may be characterized due to the presence of the cyclic peptides. An infusion with 2 handfuls of fresh leaves in 1 liter of water is prepared to fight against heart failure and palpitations (1 cup after meal). This infusion is also effective for proper digestion and has antispasmodic activities. The seeds are reported to possess anti-parasitic activities (against lice). A cream consisting of 3 cl bee wax, 12 cl almond oil, 3 cl coconut oil, 6 cl of water, 6 cl glycerin, and 1 handful of crushed plant’s seeds is prepared and heated over a water bath for 3 h before applying to the hair. In India, the crushed leaves are applied on ulcers and wounds and a leaf decoction is taken in cases of dysentery. In Aligarh district of Northern India, villagers used to consume a mixture of 4 - 5 newly grown young leaves of Annona squamosa along with black pepper (Piper nigrum) for management of diabetes. It is documented that this may ensure up to 80% of the positive results with continued therapy. The bark decoction is given as a tonic and to halt diarrhea. Throughout tropical America, a decoction of the leaves is imbibed either as an emmenagogue, febrifuge, tonic, cold remedy, digestive, or to clarify urine. The leaf decoction is also employed in baths to reduce rheumatic pain. Sitopaladi churna is an ayurvedic medicine for cough and cold and sneezing nose. Administration of the aqueous extract of the leaves also improved the activities of plasma insulin and lipid profile and reduced the levels of blood glucose and lipid peroxidation, indicating that the high levels of triglyceride and total cholesterol associated with diabetes can also be significantly managed with the extracts the custard apple fruit comes under low glycemic index. 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. The wood is valued as firewood yellow and brown dyes (Crane et al. 1994) [10]. A recent study suggests that the alcoholic seed extract contains antitumor compounds as envisaged by (Cochrane et al. 2008) [9]. Leaf extract have anti-nociceptive effect, Gonzalez et al. 2009 [19]. Roots were found to have anticonvulsant effect as reported by (Eva et al. 2006) [15]. In Mexico, the juice is used for chills and fever (CBS Publisher Edition 5, 2007) [13]. Pulp was found to have mutagenic property (Dragona et al. 2010) [12]. It is mainly used as ornamental plant and it is cultivated along with banana plantation. It is an orange skin fruit native of Brazil, it is rarely available (Oliveira et al. 2010) [51]. Leaves are used to treat hysteria, fainting spells and juice is used as vermifuge. Unripe dried fruits used in diarrhoea and dysentery treatment. Root, bark is used in toothache. Seeds leaves, young fruits have got insecticidal activity. Seeds are used in folk for their insecticidal activity, parasitic activity (Agro Forestry Tree Database. 2008) [11]. Roots are reported to have apomorphine alkaloids: Reomemerine, anoninine and dehydroremerine produce skeletal muscle relaxant effect. Yellow resin extracted from seeds exhibits sympathetic action such as dilatation of pupil, dryness of mouth, decreases secretions. It is found to have in-vitro, in vivo studies exhibiting anti-tumor activity (Morton et al. 1999) [47]. Fruits and fruit juice are taken for worms and parasites, to cool fevers, to increase mother's milk after childbirth, as an astringent for diarrhea and dysentery. The crushed seeds are used against internal and external parasites, head lice, and worms. The bark leaves, and roots are considered sedative, ulcer treatment and a nerve tonic and a tea is made for various disorders towards those effects (Churchill et al. 1880) [8]. Leaf decoction is used in the treatment of cold, cough, intestinal infections and acidity condition. Bark decoction is used in diarrhea, roots are

~ 1238 ~
used in dysentery. Fruit is used in making of ice creams and milk beverages. Crushed leaves are used in internal and external wounds, boils and in gastritis (Pandya et al. 2011) [53].

**Phytochemistry:** Patel et al. (2008) [54] studies and investigated biochemistry and reported that the custard apple pulp is very sweet and contains up to 28% sugar in which sucrose (2.53%) percentage are pre- dominant sugar along with dextrose (5.05%) percent laevulose (0.04%) in rich with aromatic flavours. It contains significant quantities of Vitamin C, iron, calcium, thiamine, amino acid, potassium, carotene, riboflavin, niacin and ascorbic acid, magnesium and dietary fibres. Despite its high sugar content, the glycemic index of custard apple is low and the glycemic load moderate. Specific chemicals extracted include aliphatic ketones like palmitone. Organic acids like hexanoic and octanoic acid and purines. Pandey et al. (2011) [52] conducted GC-MS analysis of leaf and oil yielded 59 compounds. Main components were β-caryophyllene (31.4%) (Natural bicyclic sesquiterpene) δ-cadinene (6.7%), α-murolene (5.5%), α-cadinol (4.3%) and isoquinoline alkaloids. Two acetogenins, annonetin and isoannonetin isolated from the leaves were found to be selectively cytotoxic to certain human tumors. The leaves and stems also gave alkaloids dopamine, salsolinol and coacinarine. Others are anonaine, aporphine, coryline, isocorydine, norkorydine, and glaucine. The alkaloid isolated from the plant was samoquinine, aporphine, benzyloquinoline, protobererine and tetrahydro isoquinoline. Other constituents of plant are oxopoebeine, reticuline, atidine, histidine, hidetidine, hidetinine, heterophylline, heterophylline, heterophylline, isoatitine, dihydroatitine, histidine neand benzoyl heteratitine. In root and stem, bark ooxaporphines compound like liridione, oxoanabolone were identified by NMR spectra. Different chemical constituents like borneol, camphene, camphor, car-3-ene, carvone, β-caryophyllene, eugenol, farnesol, geraniol, 16- hexatriacontan, hexacontanol, higenamine, isocorydine, limonine from stems root extracts of plant (Perez et al. 2004) [44]. The isolation studies on stem bark yielded one acetogenin, solamin, two triterpenoids, stigmasterol, sitosterol and different bullatacin, bullatacinone. About 30 acetogenins were isolated from the seeds namely squamocins B to N, coumarinoligans, annotemoyin-1, annotemoyin-2, squamocin and cholesteryl, glucopyranoside. These compounds showed remarkable antimicrobial and cytotoxic activities as reported (Li et al. 1990. and Yu et al. 2005) [37].

**Pharmacological activity**

**Antioxidant Activity:** Yang et al. (1970) [74] demonstrated the antioxidant potential of custard apple leaf on rat’s brain through various medical investigations the free radical scavenging potential of the leaves of Annona squamosa Linn. was studied by using different antioxidant models of screening. The ethanolic extract at 1000 μg/ml showed maximum scavenging of the radical cation 2, 2-azinobis-(3- ethylbenzothiazoline- 6- sulphonate) (ABTS) observed to the level of (99.07%) followed by the scavenging of the stable radical 1, 1-diphenyl, 2-picryl hydrazyl (DPPH) (89.77 %) and nitric oxide radical (73.64%) at the same level of concentration. However, the extract showed only moderate scavenging activity of superoxide radicals and anti-lipid peroxidation potential, which was performed using rat-brain homogenate. The findings justify the antioxidant activity of plants. The studies were conducted to analyze the antioxidant effect of oral administration of aqueous extract of plant’s leaf on blood glucose, haemoglobin, glycosylated hemoglobin, plasma insulin, antioxidant enzymes and lipid peroxidation in liver and kidney to streptozotocin (STZ)-induced diabetic rats. Oral administration of aqueous extract to diabetic rats for 30 days significantly reduced the levels of blood glucose, lipids and lipid peroxidation, but increased the activities of plasma insulin and antioxidant enzymes like catalase, superoxide dismutase, reduced glutathione and glutathione peroxidase. The present studies the fact that the aqueous extract supplementation is useful in controlling the blood glucose level, improves the plasma insulin, lipid metabolism and is beneficial in preventing diabetic complications from lipid peroxidation and antioxidant systems in experimental diabetic rats. Results from previous studies showed that polar extracts were found to be better free radical scavengers compared with those less polar. The leaves extracts of the two parts showed high flavonoid content.

**Anti-tumor Activity:** Ranjan et al. (2009) [59] the plant Annona squamosa traditionally known as custard apple possesses potent bioactive principles in all components of parts. The effect of aqueous and organic extracts from defatted seeds of plant was studied on a rat histiocytictumor cell line AK-5. Both the extracts caused significant apoptoticum tumor cell death with enhance caspase-3 activity. Down regulation of anti-apoptotic genes Bel-2 and Bclxi and enhance 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 tumor cells through the oxidative stress. Aqueous extract of plant’s seeds possessed significant antitumor activity in-vivo against AD-5 tumor. The seed extracts of custard apple have revealed significant anti-tumor activities against human hepatoma cells in-vitro and in-vivo, indicating a potential for developing the extract as a novel anti-cancer liver drug. Aqueous extracts of the seeds possess significant anti-tumor activity in-vivo against AD-5 tumor.

**Antimalarial Activity:** Rahman et al. (2005) [56, 57] demonstrated the potential of Annona extracts against virulent mosquitoes killing. The significant activity suggests 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 plant were the most active achieving 100 to 90% mortality at 50. 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 plant showed a dose dependant (p ≥ 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. The studies on plant collected from Brazil indicated larvicidal effect against Aedes adopictus and C. quinquefasciatus and against Anopheles stephensi. Present larvicidal activity result supports the reports and demonstrated that extract of Annona species are potential antimosquito agents. In the recent studies on Annona squamosa all compounds showed moderate activity against a chloroquine sensitive strain and a chloroquine resistant strain of Plasmodium falciparum.

**Anthelmintic Activity:** Gupta et al. (2005) [20, 21] investigated the anthelmintic activities of the Annona squamosa and its
leaf extract by conducting studies 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.

**Anti-genotoxic effect:** Gupta et al. (2005) [20, 21] investigated the antigenotoxic effects of aqueous and ethanolic bark extracts of Annona squamosa was assessed by determining the frequency of micro nucleated polychromatic erythrocytes (MnPCEs) and chromosomal aberrations. The frequency of MnPCCs 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 MnPCEs and chromosomal aberration in DMBA treated hamsters. Although both extracts have shown anti-genotoxic effects, the effects of ethanolic extract was found to be more prominent than the aqueous extract. The present study demonstrates the anti-genotoxic effects of plant’s bark extracts in DMBA induced genotoxicity in Golden Syrian hamsters. Studies on the genotoxicity potential of plant have shown that the plant extract treatment significantly altered serum enzyme levels in oxidative stress conditions.

**Antulcer activity:** Yadav et al. (2011) [71] investigated the synthesis of specific compound namely 1-(4-β-D-glucopyranosyl oxy phenyl) – 2 - (β – D - glucopyranoslyoxy)-ethane which was isolated naturally first time from the Annona squamosa twigs. The compounds which were isolated from the twig of plants were subjected to screening for antulcer activity. Models used for the screening were cold restraint, pyloric ligation, aspirin, alcohol induced gastric ulcer and histamine induced duodenal ulcer model. The result was compared with the standard drug omeprazole. The result through screening demonstrated anti-secretory activity in-vivo through reduced, total acidity and pepsin in pyloric ligation, confirmed by in-vitro inhibition of H (+) K (+)-, ATP ase activity with corresponding decrease in plasma gastrin level. Cytoprotection of plant was apparent with protection in alcohol induced, aspirin models and enhanced mucin level in pyloric ligation model.

**Hepatoprotective activity:** Saleem et al. (2008) [60] investigated that aqueous and alcoholic extract of leaves 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 promoted 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 treated extracts on group of animals showed minimal inflammation with moderate portal triaditis and their lobular architecture was normal. The study 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.

**Anti-bacterial and wound healing activity:** Shenoy et al. (2009) [63] demonstrated the studies of custard apple leaves of the plant were exhaustively extracted by soxhlet apparatus with different solvents like petroleum ether, solvent ether, chloroform, alcohol and chloroform water in ascending order of the polarity. All the five extracts were subjected to antibacterial screening by using the cup plate method. The petrol ether, alcoholic and chloroform water extract showed maximum zone of inhibition. So these extracts were taken for wound healing activity. The petrol ether extracts of Annona squamosa leaves were used in all models showed significant results. All the results were significant for different parameters in wound healing activity when compared with control group.

**Anti-arhritic, anti-inflammatory and analgesic activity:** Singh et al. (2011) [65] demonstrated the medical finding and beneficial properties of custard apple leaf extracts. The above activities were screened using combined extract of Annona squamosa and Nigella sativa was evaluated and validated in various animal models. Arthritis was induced by complete Freund’s adjuvant (CFA) injection in metatarsal footpad of Sprague-Dawley rats. Degree of inflammation was evaluated by hind paw swelling and body weight, estimation of AST, ALT and TP supported by histopathology of knee joint. The result of combine extract was significant decrease in paw volume, increase body weight and reduction in elevated levels of ALT, AST and TP. For antiarthritic activity the histopathological revealed the fact that there was significant reduction in neutrophils infiltration, pannus formation and bone of the animal treated with plant extract. The extract revealed that it has analgesic and anti-inflammatory activity in dose dependent manner when compared to comparable with the reference standard drugs, pethidine sulfate and indomethacin.

**Anti-HIV:** Saleem et al. (2008) [60] demonstrated the immune properties of custard apple leaf extracts as life savours against treated disease HIV. There was a positive result exhibited by the extract of Annona squamosa 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, 16β, 17-dihydroxy-ent- kauran-19-oic acid showed significant activity against HIV replication in H9 lymphocyte cells with an EC50 value of 0.8 µg/ml.

**Cytotoxic activity:** Two new compounds have been isolated and were evaluated for the above activity. The extract of seed was used for the isolation of the compound. The study was carried out against HCT, human lung carcinoma (A-549), human breast carcinoma (MCF-7), and human prostate adenocarcinoma (PC-3) with Adriamycin as positive standard using MTT method.

**Hypoglycemic and anti-diabetic activity:** Mujeeb et al. (2009) [49] conducted studies to demonstrate hypoglycemic and anti-diabetic potential of custard apple. 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 GTT (Gonzalez et al. 2009) [19]. In the same way, the aqueous extract of the roots of plant at a dose of 250 mg/kg and 500 mg/kg body weight was tested for the antidiabetic activity in the Streptozotocin (STZ) – induced hyperglycemic rats which cause a reduction in the blood glucose in STZ- induced diabetic rats from 285.52 to 208.81 mg/dl.

**Larvicidal activity:** Kaushik et al. (2009) [32] demonstrated the potential of ethanolic leaf extracts of Annona squamosa as a potential, eco- friendly, biodegradable, larvicidal in mosquito control programme. Mosquitoes possess a great threat to the human health by means of the transmission of the serious diseases in the changing menace climate scenario. Development of the resistance, cross-resistance, and also the rising cost as well as the possible toxicity hazards arises 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 *A. 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 identified.

**Stress and depression:** Kaur et al. (2015) [31] in her investigation found that sitaphal is enriched to be a good source of Vitamin B complex which helps in controlling the GABA neuron chemicals in the brain. This relaxes the mind and helps to calm down stress, tension, irritability and depression.

**During pregnancy:** The amazing benefits of custard apple to pregnant woman are described by Kaur et al. (2015) [31] sitaphal is helpful in the development of the brain, nervous system and immune system of a foetus. Regular consumption of sitaphal during pregnancy reduces the chances of miscarriage and minimizes the extent of labour pain during delivery. It is termed by some as the pregnancy wonder fruit that helps in coping with morning sickness, nausea and mood swing. It is a good source of copper. Generally pregnant women need to take 1000 µg of copper. Low copper in the body can cause premature birth. So consuming this fruit can be really helpful. It has Vitamin C and Vitamin A which is very useful for the foetus in the womb. It is brilliant for the development of eyes, skin, hair and also haematic blood tissues.

**Prevent ageing:** Vohora et al. (1975) [69] in her investigation found that sitaphal is a rich source of L-lysine and L-proline, the amino acids that help to create collagen in the body. Collagen is a substance that provides structure and elasticity of the skin tissues. The high levels of antioxidants in custard apple immune the cell membranes from the free radical damage, allowing the body to fight the signs of ageing. Sitaphal boosts the growth of new cells, making the skin look young. It helps to reverse the discoloration and wrinkles associated with ageing. It also tones and firms the skin shining. Sitaphal is also helpful in increasing the production of breast milk after the childbirth.

**For a stronger digestive system:** Kaur et al. (2015) [31] investigated the flushes out the toxins from the intestine, aiding in proper functioning of the bowels. It also prevents stomach related diseases like heartburn, ulcer, gastritis and acidity. This delicious fruit is very effective for treating indigestion. Custard apple in its unripe form is further dried and crushed to treat diarrhea and dysentery. One medium sized custard apple contains 6 grams of dietary fiber, amounting to almost 90% of the recommended amount. Fiber adds bulk to the stools, relieving constipation.

**Anti-hyperlipidemic activity:** Tiangda et al. (2000) [68] investigated the antihyperlipidemic activity for curing diabetics in rats through application of aqueous extract administration of custard apple for studies on reduction of blood glucose in rats. The studies in effect of Polyherbal formulation of *Annona squamosa* on blood glucose, plasma insulin, tissue lipid profile, and lipidperoxidation in streptozotocin induced diabetic rats. Aqueous extract of Polyherbal formulation of the plant fruit was administered orally (200 mg/kg body weight) for 30 days. The different doses of polyherbal formulation on blood glucose and plasma insulin in diabetic rats were studied and the levels of lipid peroxides and tissue lipids were also estimated in streptozotocin induced diabetic rats. The effects were compared with tolbutamide. Treatment with Polyherbal formulation and tolbutamide resulted in a significant reduction of blood glucose and increase in plasma insulin. Polyherbal formulation also resulted in a tremendous decrease in tissue lipids and lipid peroxide formation. The phenomenal decrease in lipid peroxides and tissue lipids clearly showed the antihyperlipidemic and antiperoxidative effect of polyherbal formulation apart from its antidiabetic effect.

**Anti-head lice effect:** Kumar et al. (2010) [34] through chromatographic techniques and isolated two potential compounds an anti-head lice effect. The present study focused on the separation and identification of the active compounds against head lice from the hexane extract of *Annona squamosa* seed, the chromatographic and spectroscopic techniques revealed that two major compounds of the hexane seed extract were oleic acid and triglyceride with one component 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. The triglyceride, oleate ester and the crude hexane extract diluted with coconut oil. These compounds were found to kill all tested head lice in 49, 11 and 30 min respectively. The triglyceride ester can be used as a marker for quantitative analysis of the active compound for quality control of the raw material plant’s 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.

**Insecticidal activity:** Magadula et al. (2009) [39] through primary investigation identified various bio-organic compounds in leaf extracts against *Sitophilus oryzae*. The present study investigated insecticidal activity of ethanolic extract of *Annona squamosa*. The preliminary phytochemical investigation was carried out to identify the various constituents present in the extract. It was found that the plant contain alkaloids, protein, amino acid, carbohydrate, glycosides, phytosterols, tannins and phenolic compounds.
The ethanol extract of plant produced significant Knockdown” (KD50) in the concentration 1% w/v and 5% w/v tested 23.1 min and 11.4 min for respectively. The mortality (100%) was achieved at 39.6 ± 1.4 and 14.5 ± 1.1 min for 1% w/v and 5% w/v concentration respectively. No mortality of the insects was found in any of the controls up to 100 hours. The ethanolic extract of plant showed potent activity against *Sitophilus oryzae* pest. The finding of new insecticidal activity is of great economic importance both from the agronomic and preventive medicine point of view. The reason for using new natural insecticides is that these are active at highly acceptable levels, biodegradable and do not leave toxic residues while the commonly used phosphorous and chlorinated insecticides contaminate the environment.

Mosquitocidal activity: Haque et al. (2003) [23] investigated the potential efficiency of custard apple leaf extracts as anti Mosquitocidal action against anophelines species. The significant activity demonstrated by extracts of *Annona squamosa* suggests 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 plants were the most active achieving 100 to 90% mortality at 50. 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 plant showed a dose dependant (p ≥ 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. 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.

Antithyroidic activity: Santos et al. (2001) [61] exhibited the ameliorating potential of *Annona squamosa* seeds extracts against antithyroidic activity. 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, i.p.), which increased the levels of serum triiodothyronine (T3) and thyroxine (T4), activity of hepatic G-6-Phosphatase, 5'-monodeiodinase (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 anti-peroxidative nature.

Molluscicidal activity: Ahir et al. (1999) [1] demonstrated the comparative anti molluscidal potential of *Annona* seeds as compared to leaf extracts. In search for plant molluscicides for the vector control of schistosomiasis, ethanolic extracts from *Annona squamosa* Linn. root was evaluated against adult forms and egg masses of Biomphalaria glabrata. Results from extensive studies indicate that the analyzed extracts possess properties lethal to *Biomphalaria glabrata* (Mrita et al. 2001). [48, 62] The molluscicidal activity of leaves, bark and seed of *Annona squamosa* against the snail *Lymnaea acuminate* was studied. The toxicity of powder from leaves, bark, and seed of custard apple against the snail was time and dose-dependent. After 24 h the toxicity of the seed (LC50=377.8 mg/l) was higher than that of the leaf (LC50=381 mg/l) and bark (LC50=458 mg/litre). The acetogenins extracted from the seed were highly toxic against the snail (LC50=2 mg/l at 96 h).

**Anti-plasmodial activity:** Morita *et al.* (2006) [42] conducted clinical trials to exploit the needs of unrevealed therapeutic efficiency. The anti-plasmodial activity of methanolic extracts of plant *Annona squamosa* Linn. was tested on chloroquine sensitive strain 3D7 and chloroquine resistant strain Dd2 of *P. falciparum*. The methanolic extract of *Annona squamosa* leaves showed high anti-plasmodial activity with IC50 values of 2 and 30 μg/ml on 3D7 and Dd2, respectively. While stem bark showed moderate activity with IC50 values of 8.5 and 120 μg/ml on Dd2.

**Vasorelaxant activity:** Yang *et al.* (1970) [74] through multitude of experiments revealed that 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 Ca++ channels.

**Anti-platelet activity:** The ent-kaurane diterpenoids, which are isolated from stem of *Annona squamosa* Linn. are investigated for anti-platelet activity. The ent-kauranederpenoids ‘ent-Kaur- 16-en-19-oic acid’ and ‘16alpha-hydrox- 19 -al-ent-kauran- 17-oic acids’ showed complete inhibitory effects on rabbit platelet aggregation at 200 μM (Misha *et al.* 1979) [41] reported that Annona species can be exploited for preparation of medicinal products with high value.

**Antifertility activity:** Fabricant *et al.* (2001) [16] investigated the medicinal utilization of seeds of *Annona* for anti-fertility. The seed extract of *Annona squamosa* Linn. was investigated for post coitus antifertility activity. The seed extract of plant Linn shows anti-implantational and abortifacient activities.

**Drug interactions:** Handling the fruit may produce a skin rash in sensitive individuals. There are no interactions documented.

**Recipes of sitaphal:** This seasonal fruit has several health benefits like enhancing vision, fighting fatigue, treating arthritis/rheumatism and many more disorder. Apart from taking the fruit as such, which is the most common form of intake of the fruit; there are certain preparations which make it more palatable especially for the children.

**Ice-Cream:** Fruit is used in making of ice creams and milk beverages. The fruit is generally eaten out of hand with a spoon or incorporated into fruit salads. It may be blended with orange juice, lime and cream to make a delicious ice-cream.

**Juice:** Custard Apple (Sitaphal) Powder, which is one of the most enjoyed fruits that cultivate in the latter half of monsoon
Sitaphal firni: Milk thickened with rice flour is flavoured with custard apple pulp and refrigerated to enhance the flavour and get the perfect consistency. It is served enough chilling for a fruit luscious experience, which is much healthier than regular custards and puddings.

Sitaphal rabdi: Mix saffron, cardamom after shimming almonds, pista in stove. Combine with the pulp of sitaphal and can be served hot or cold.

Sitaphal kheer: It is a mixture of cooked rice and sitaphal in specific proportions with added flavor with cardamom.

Other Uses

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.

For pimple-prone: Consumption of custard apple decreases skin sebum production, controlling acne and pimples. Mix custard apple paste with lemon juice and use it three times a week to control sebum production. The anti-inflammatory properties of custard apple fight acne and clear the pores to prevent further breakout. Soursop tea is used in traditional medicine to heal wounds, for soothing knee pain and for reducing mucous in colds and in sinuses (Singh et al. 2011) [65]. Leaves-insecticide (see powder, mixed with leaf juice is used for removing lice from scalp). Seeds - abortifacient. Root-purgative, used in blood dysentery. Fruit invigorating, sedative to heart, antibilious, antiemetic, expectorant. Dried powdered unripe fruits-used for treating ulcers. Ripe fruit made into paste with betel leaves is applied to tumor to hasten suppuration. Leaves, bark, unripe fruit-strongly astringent; used for diarrhoea and dysentery.

Natural detoxifying agent: Junya et al. (2006) [30] investigated for natural detoxifying agents to improve the health status of consumers. Sitaphal is embedded with soluble fiber and antioxidants, making it an excellent laxative. Regular consumption of custard apple helps to get rid of toxins and waste, giving you a healthy and glowing skin. Drinking custard apple juice even out the skin tone and makes it firm by rejuvenating its appearance. The multifaceted plant bears some amazing medicinal qualities, that protect or promote health whether delivered from raw laundry use; cleaning, polishing, scouring and abrasive preparations; soaps, perfumery, essential oils, cosmetics, hair lotions. Sitaphal protects and preserves the cells of the skin, making it more supple and radiant. It glows the skin by removed of oxidative stress. This creamy fruit helps to even out the skin tone and rejuvenates the appearance. The antioxidants also shield the skin from the sun rays, thereby reducing sun damage. Facial application of custard apple pulp can lighten the appearance of dark spots, freckles and other skin imperfections. The fruit penetrates to the deep layers of the skin, transporting the important nutrients into it. The fruit is being widely used in the Himalaya products like pimple creams, anti-stress massage oil, ayur slim capsules, cold balms, foot care creams, and pain massage oils and for overall improvement of skin texture.

Seed oil for better hair growth: It inhibits scalp inflammation, preventing hair fall. It also facilitates the absorption of nutrients, providing nourishment to the hair. The considerable amount of iron in custard apple improves blood circulation in the scalp, stimulating the follicles to promote hair growth. This oil has a slight almond-like odor and a very mild, pleasant taste.

Shampoos: Bhakuni et al. (1972) [6] investigated that Mediker, from Marico, pioneered the switch from the traditional lice comb, which is painful to use, to an easy and effective way of treating lice using shampoo. The shampoo contains coconut, Neem and camphor. Mediker anti-lice treatment has transformed lice removal into a painless activity, replacing the traditionally-painful lice comb with a wash-off format. Mediker contains active such as Neem, camphor and sitaphal extracts.

Conclusion

The edible fruits from the natural gene sanctuaries of India were investigated for their nutraceutical and therapeutic potential. A through consumption of this fruit has potential benefits in the human health as this fruit has demonstrated in terms of overall value being it as a source of energy, phenolic compounds, natural antioxidants and minerals. It is a major source of ascorbic acid, calcium, phosphorus and other nutrients. The current study explains the nutritional as well as medicinal utility of the fruit which is a rich source of minerals and antioxidants such as phenols and flavonoids. The custard plant is easy to cultivate, free of serious pest and disease, utilized as food or parts of tree may provide medical health benefits including the prevention and or treatment of diseases. The nutritional value and health related benefits of custard apple fruit depends upon the bioactive ingredients of the plant that protect or promote health whether delivered from raw fruits, leaves, flowers or processed foods, dietary supplements, extracts, beverages or other products. The ingredients of this plant in the form of residues have tremendous impact on the health care system and may provide medical health benefits including the prevention and or treatment of diseases. The studies reported by several co-workers have supported the view that phytoconstituents of the fruit have potential of organic acid, minerals, flavonoids and vitamins which can act against allergies, ulcers, tumors, platelet aggregation, and controlling hypertension. Over the centuries, this plant used by folklore has served as a major source of medicines for treating dysentery, diarrhea and prevention of diseases of mankind. The phyto-chemicals present in the custard apple provide protection from several

and rainy seasons. This fruit is soft and juicy and has a sweet taste. Moreover, custard apple is widely used at homes, hotels and restaurants to make fruit salads. Spray dried apple powder is extensively used to make juice, milk shakes, mango flavored yoghurt and in many other applications.
diseases as they possess antioxidant properties. The natural antioxidant play a pivotal role in the prevention of chronic and degenerative disease particularly DNA damage and ageing. The free radicals are metastable chemical species, which tends to trap electron in the chemical surrounding there is an information gap on utilization, development and diversification required for commercial exploitation in Asian and African countries. There is a need to identify and scientific screening for various useful metabolites available in the custard apple trees for their utilization in food, beverages and in preparation of phytopharmaceuticals. The demand for this fruit is limited mainly due to lack of awareness on food value of the fruit, its uses and non-availability of organized supply. Therefore it is necessary to promote large scale cultivation units in India where sizable quantities are made available for market promotion. Market promotion should focus mainly to create health awareness on quality attributes particularly nutritional value, therapeutic and value multiple medicinal uses. Research and development should go in consonance to make the product to cater nutritional standards. The Annona fruits have played a key role in the diet and medicine of human beings, particularly in the tribal and rural areas of the country from inception of civilization. If educated/ uneducated and unemployed youth of this region engage themselves fully in the preparation of quality food and other related products from Annona fruits as a source of income, the employment generation could be envisaged through food industry, pharmaceuticals, nutraceutical and cosmetics.

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