



## Review on: Medicinal Potential of Custard Apple Seed

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### ABSTRACT

*Annona Squamosa* L. (Custard apple or sugar apple), with family Annonaceae and it is native to subtropical and tropical regions. 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. And it is reported to possess various beneficial chemical compounds such as alkaloid, tannin, phenol, acetogenin, squamacin, annonacin and annonastatin from seeds, acetogen, chloroform. Due to its edible fruits and medicinal properties, *Annona* is the most studied genus of Annonaceae family. According to various studies, it has been shown that the seeds of custard apple seeds have considerable potential to be used as an antibacterial, anti-inflammatory, antidiabetic, antiplatelet, hepatoprotective, antioxidant and antitumor/anticancer agent. The Vitamin C content is appreciable (35-42 mg/100 g) and slightly higher than in grapefruit. The seeds of *Annona Squamosa* show the presence of tannins, vitamin E and a higher content of amino acids. Seeds are black or dark brown in color. There are 30-40 seeds in an average fruit. The *Annona squamosa* is a diploid species with  $2n=14$ .

**Keywords:** Medicinal Properties, Custard Apple, *Annona Squamosa* seed, Annonaceae.

### Introduction

The management of poor health under the explosion of population across the globe results in rapid nutritional deficiency for 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. *Annona Squamosa* is well known plant belonging to the family Annonaceae. The fruit of the common custard apple also called sugar apple is dark brown in colour and marked with depressions giving it a quilted appearance; its pulp is reddish yellow, sweetish, and very soft as it's common name.

### Botanical description:

Table shows the Botanical description of custard apple:

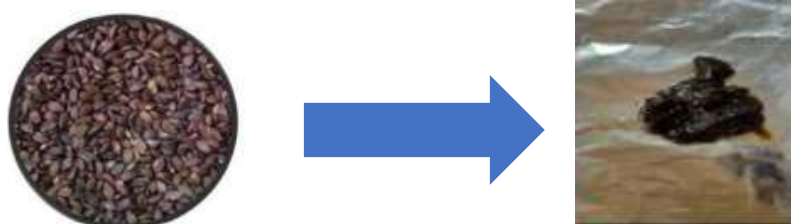
Kingdom	Plantae
Order	Magnoliales
Family	Annonaceae
Genus	<i>Annona Squamosa</i> Linn
Synonyms	<i>Annona Asiatica</i> Linn
Common name	Sugar apple, Custard apple, Sitafal, etc.

### Phytochemical (nutritional) constitution of *A. Squamosa* seeds:

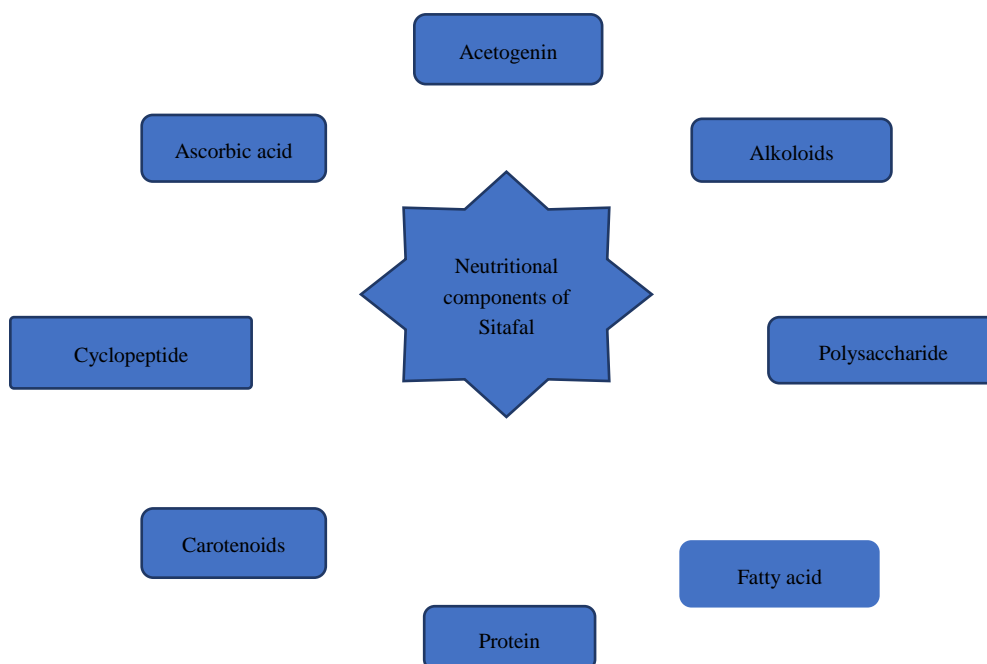
The phytochemical constitution of *Annona Squamosa* seeds are cyclopeptide and Annonaceous acetogenin as a chief constituent.[27,28]. The seeds of custard apple also found to contain acetogenin [29].



**Fig : Sitafal**



**Fig: seed extract of sitafal**



### 1. Traditional Uses:

The custard apple is used by indigenous as an insecticidal and antitumor agent, anti-diabetic, antioxidant, anti-lipidemic, and anti-inflammatory agent. It might help prevent wrinkles, acne and maintain a healthy glowing skin. It is also considered to be good for hair problems such as lice infections. The seed oil extract of custard apple may help with the growth of hair. 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<sup>[2]</sup>. Due to presence of magnesium in it, which is also helpful in removing the acid from the body joints.<sup>[3]</sup>

### 2. Anti-tumor Activity :

The plant custard apple having the potent bioactive principles in all components of parts. The effect of aqueous and organic extracts from the seeds of plant was studied on a rat histiocytic tumor cell line AK-5. Both the extracts of the plant caused significant apoptotic tumor cell death with enhanced caspase-3 activity. Down regulation of anti-apoptotic genes Bcl-2 and Bcl-x1 and enhanced the generation of intracellular ROS, which correlated well with the decreased levels of intracellular GSH. Aqueous extract of plant's seeds possessed significant antitumor activity in-vivo against AD-5 tumor. The seed extracts of plant *Annona Squamosa* have given the significant anti-tumor activities against human hepatoma cells in-vitro and in-vivo, showing the 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 [6]. The in vivo and in vitro antitumor activity of acetogenin from Custard apple seed extract were investigated. The experiments show that the two compounds from acetogenin i.e. 12,15-squamosatin-A (47.15 mg/g) and bullatacin (256 mg/g) show that considerable antitumor activity [45]. The new compounds have been isolated and were evaluated for the cytotoxic activity. For this, the extract of seed was used for the isolation of the compound. The study was carried out against human lung cancer (A-549), human breast cancer (MCF-7), and human prostate cancer (PC-3) with Adriamycin as positive standard using MTT method [2].

### 3. Antimicrobial activity:

Antimicrobial activity that inhibits growth of bacteria, prevents the development of microbial colonies and also kills the microorganisms. The microorganisms become resistant to many antibiotics which results in the difficulty in the treatment of the disease or cause more challenging for treatment. The seed extract of *Annona Squamosa* has revealed antibacterial effects against *Staphylococcus aureus* with the minimum Inhibitory Concentrations (MIC) of 50 mg/mL and also Minimum Bactericidal Concentrations (MBC) of 100 mg/mL [7]. The seed extract of *A. Squamosa* was tested against various bacterial strains including *E. coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Salmonella typhi* to check the effectiveness. The chloroform seed extract showed that having remarkable antimicrobial activity [30]. In another study the methanolic extract or the cotyledon extract of custard apple seeds was also found for its antimicrobial activity [31].

### 4. 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. These compounds are diluted with coconut oil and were found to kill all tested head lice in 49, 11 and 30 min respectively [2].

### 5. Antiplatelet activity:

Increased platelet activity is the risk of cardiovascular events in healthy men as well as in patients with coronary artery disease. The antiplatelet activity on human platelets of custard apple peel and seed extracts was studied using turbidimetry according to the methodology described by Born et al. [8]. The *Annona Squamosa* seed extracts act against platelet activations by reducing P-selectin expression. Custard apple seed extract was able to decrease the activation of GP IIb/IIIa at the highest concentration studied [9].

### 6. Antioxidant activity:

In human the skin is the most visible part in the body which plays an essential role as a barrier protecting an internal organ against physical, chemical, and biological detractors [12]. The awareness of skin aging is most highlighted issues for scientists. So there are number of studies are performed on skin aging.

In skin, this enzyme imbalance of compounds leads to the degradation of extracellular matrix (ECM) and the depletion of different important compounds such as elastin fibers, hyaluronic acid and collagen [13,14].

The decreasing of enzymes such as elastase, hyaluronidase, collagenase, tyrosinase, xanthine oxidase (XOD) and AChE is postulated as a great defensive strategy against the damaging effects of free radicals [15,16]. Less remarkable results were reported, that seed extracts against tyrosinase and hyaluronidase [17].

Phenolic compounds in plants are essential for the development of antioxidant effects. As the phenolic compounds having the ability of chelation, inactivation and prevention on different cell signalling and gene expression pathways [10]. Custard apple seed extract concluded a total phenolic content value of 3.79 mg GAE/g DE [11].

In the brain and nervous system, oxidative stress is the main cause of neurodegeneration [20]. One of the major neurodegenerative mechanisms is the overstimulation of acetylcholinesterase (AChE), which breaks down far more of the acetylcholine needed for normal brain function [15]. Other main causes of oxidative stress in the brain, and in organisms in general, is xanthine oxidase (XOD), since it plays an important role in different metabolism pathways [21]. Many diseases have been associated with XOD activity (hyperuricemia, diabetes, hypertension, ischemia, cardiovascular diseases, etc.), so it is considered an interesting target for the synergic treatment of several pathologies [22].

Wang et al. (2022) also reported anti-neurological damage caused by poncirin flavonoid through anti-inflammation mechanisms, inhibiting NOX4-mediated NLRP3 inflammasome activation [23]. This could highlight custard apple seeds as a remarkable source of different neuroprotective compounds. The most remarkable inhibitory effect of both seed and peel extracts was seen against XOD, with IC50 values lower than 10 mg/L [18,19].

### 7. Antidiabetic activity:

Diabetes is the common endocrine disorders, it is characterized by altered carbohydrate, insulin and protein metabolism as a consequence of lack of pancreatic insulin or insulin dysfunction [32]. The World Health Organization (WHO) reported that, 80–90% of people above 40 years old are more prone to non-insulin-dependent diabetes [33]. In a study, the ethanolic and methanolic seed extract of custard apple was administered to alloxan-induced diabetic rats (150 mg/kg body weight (BW)) to check its effect on blood glucose levels in diabetic rats [34]. The ethanolic (dose: 200 mg/kg) and the methanolic (dose: 200 mg/kg) seed extract of custard apple exhibited significant dose dependent 43.96% and 45.99% antihyperglycemic activity respectively. This results shows that the ethanolic extract was less effective than the standard used (gliben clamide) for hyperglycemic activity [34].

#### 8. Anti-Inflammatory activity:

Inflammation is the defensive system in human body and it is regulated by pro-and antiinflammatory mediators (chemokines, cytokines, etc.) [41]. The factors that cause inflammation in the human body are exposure to allergens, physical trauma, thermal or chemical stimuli and microbial infection [42]. The Inflammatory disorders such as chronic asthma, rheumatoid arthritis, inflammatory bowel disease and multiple sclerosis may also caused by internal or external factors which disturb the anti-inflammatory mediators [43]. The seed extract of custard apple causes a decrease in IL-6 and TNF- $\alpha$  levels in the lipopolysaccharide (LPS)-stimulated macrophage J774A.1 cell line [44]. It was shown that two parallel synthesized cyclic cyclopeptides taken out from the seeds of the *Annona Squamosa*, i.e., cyclosquamosin D and cyclopeptide B, were confirmed to have anti-inflammatory actions by slowing down the generation/production of IL-6 and TNF- $\alpha$ . From this results, it was terminated that cyclopeptides have strong anti-inflammatory effects [44]. The different studies show that, it was concluded that cyclic peptides extracted from *A. Squamosa* seeds might be utilized as an anti-inflammatory agent, though further study is needed for their anti-inflammatory effect.

#### 9. Hepatoprotective Activity:

The liver is an essential organ in vertebrates and it prone to various disorders globally, including liver harm due to alcohol, pharmaceutical drugs toxic materials [35,36]. Alcohol is the third most frequent cause of mortality caused by smoking and hypertension [37]. The long-term use of alcohol tends to alcoholic liver disease (ALD), a global problem without an effective solution, and chronic hepatotoxicity, which may develop to liver fibrosis and cirrhosis [38]. ALD has the highest impact in Europe (12%) and accounts for 4% of mortality worldwide and 5% of disabled life [39,40]. In a study, the ethanolic extract of *annona squamosa* seeds was used to treat liver damage due to alcohol in a rat animal model [29]. Oral treatment followed, with seed ethanolic extracts at a dose level of 200 and 400 mg/kg, once for the following 8 days. The antihepatotoxicity effect of the seed extract was assessed in the rat animal model via measuring alanine aminotransferase (ALT), lactate dehydrogenase (LDH), aspartate transferase (AST), alkaline phosphatase (ALP), serum bilirubin levels (SBL), total cholesterol, albumin and total protein levels. From the results, it was proposed that treatment with the ethanolic seed extract prior to ethanol administration in the tested animal model significantly reversed the effects of alcohol toxicity [29]. Thus, the seed extract of *A. squamosa* reversed the effects of liver toxicity caused by alcohol treatment in rat. From the above result, it was concluded that the seeds of custard Apple can be used against liver damage.

#### 10. Adverse effects/toxic effects:

The toxic effects of seeds extract were also observed. The juice of the *Annona Squamosa* seed extract causes the blindness when comes in contact with the eyes [24]. In some cases also observed that the seed extract when in eye contact causes conjunctival irritation and ulcers in the eye [25]. The experiment shows that the toxic extract of custard apple seeds on rabbit eyes caused conjunctival inflammation and also causes the epithelial delayed damage [26].

### 11. Conclusion:

Custard apple has increased popularity because of its recently increase reasearch and studies on the medicinal potential and it's bioactive compounds present in the difference part of the plant such as leaves, fruits, bark and its seeds. The fruits of custard apple are 50-80% edible with various neutrional values. The pulp part of the fruit is in the ice cream as the flavouring agents. The pulp is contain vitamin B1, dietary fiber, potassium and sodium. Similarly the seeds of custard apple are also rich source of phytochemical such as Annonaceous acetogenin (neurotoxin), cyclopeptide, carbohydrates, protein, lipids, oleic acid and linoleic acid. Based on various in vivo and in vitro experiment. The custard apple seed extract were found to be helpful in various bioactivities such as antitumer, antimicrobial, antifungal, antidiabetic and hepatoprotective. Based on these available studies, custard apple seeds may likely used as in neutraceutical food industry as well as nutrition industry. However, more investigational studies to be needed for the determination of the Medicinal as well as the neutraceutical potential of the custard apple seeds.

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