Review Article

Annona squamosa L.: A brief review on biological activities and their phytochemicals

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Abstract

Although numerous civilizations have used plants extensively in traditional medicine since the dawn of time, more research is still needed to ascertain the effectiveness, security, and calibre of these cures. The plant *Annona squamosa* has long been used by people in traditional medicine. *A. squamosa* is often grown in tropical and subtropical regions. All parts of *A. squamosa*, including the bark, leaves, and roots, contain biological qualities like antioxidant, antifungal, and anticancer capabilities, with the leaves being especially potent in these areas, according to earlier studies. Young leaves of *A. squamosa* have long been used as an anti-diabetic by Indians, while South Chinese people utilise the seeds to minimize the effects of cancer on the body. *A. squamosa* leaves have pharmacological actions that include hepatoprotective, neuroprotective, cytoprotective, antibacterial, antifungal, anti-inflammatory, anti-cancer, anti-ulcer, antidiabetic, antidiarrheal, antiplatelet, and antioxidant characteristics. Coumarins, tannins, cardiac glycosides, flavonoids, sugars, and saponins are only a few of the phytochemicals found in *A. squamosa* leaves. Nutritional investigations reveal that the leaves of *A. squamosa* are rich in calcium, ash, fibre, protein, and lipids.

Keywords: *Annona squamosa*, traditional medicinal plant, medicine, phytochemistry, pharmacology

Introduction

In today's world, a better existence through the use of natural ingredients is greatly sought. Plants are the best source for traditional medicine because they are so common. According to the World Health Organisation, 80% of individuals worldwide have tried herbal remedies for medical conditions (Silva et al., 2022). The second-largest genus in the Annonaceae family after Guatteria is Annona. *A. squamosa*, also referred to as custard apple, is one of the medicinal herbs (Mudau et al., 2022). Previous studies have demonstrated that it has a range of advantageous pharmacological effects on the body.

Worldwide, including in Brazil, the West Indies, and the US, *A. squamosa*has been cultivated. Another name for *A. squamosa*, commonly referred to as custard apples, is sharifa in Hindi, sitappalam in Tamil, sitaphala in Kannada, and sita phalamu in Telugu.

Cone-shaped fruit, dual-colored leaves that are brilliant green on top and bluish green on the underside, and a petiole that can grow to a height of 0.7 to 1.5 cm are all characteristics of the *A. squamosa* tree. The tree can grow between three and eight metres tall. 5 An important tropical fruit that can withstand harsh climatic conditions among annonaceous fruits is *A. squamosa* (Anand et al., 2022).

A. squamosa leaves include active substances like flavonoids, glycosides, phenolics, tannins, phytosterols, alkaloids, and saponins. Only a few of the therapeutic advantages these chemicals display include antioxidants, anticancer, antibacterial, antiviral, anti-melanogenic, and anti-inflammatory properties (Sulaiman et al., 2022).

Plant description

Custard apple, also referred to as *A. squamosa*, is a member of the Annonaceae family of garden plants. 14 Tiny tree *A. squamosa* has thin, grey bark and a flat or rounded bloom crown. This plant's dormancy may be triggered by variations in temperature, illumination, or precipitation. The leaves of *A. squamosa* are up to 15 cm long, 3-5 cm broad, and green. *A. squamosa* is a distinct species of plant with bisexual flowers that appear in clusters of two to four and can reach lengths of up to 2.5 cm. One of the animals involved in pollinating *A. squamosa* is the nitulid beetle. After pollination, tuberculous fruit with a sweet and aromatic smell

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is produced. According to Kharchoufa et al. (2018), each carpel contains an oval-shaped, smooth seed that is either black or dark brown in colour.

Trees

A. squamosa can bloom in the spring to the beginning of the summer, but it can bloom all year long in areas with constant humidity. The blooms are described as actinomorphic, protogynous, pedicillate, spirocyclic, bracteate, and bisexual. Six petals and a sepal structure in disrepair make up the *A. squamosa* flower (Pascual et al., 2022).

The stems of branches

A. squamosa is a black, amorphous plant that contains compounds such roemerolidine, nitroso xylophone, and duguevalline alkaloid. Fruit production in *A. squamosa* begins between the ages of 3 and 4. In India, *A. squamosa* normally bears fruit from July to August. Custard apples are ripe when they have a sweet flavour akin to sugar and a pleasant aroma. *A. squamosa* seeds are commonly found 30 to 40 per fruit and range in colour from dark brown to black. The genetic marker 2n-14 is present in the plant species *A. squamosa* (Podsiedlik et al., 2020).

Geographical distribution

Although *A. squamosa*, commonly known as sugar apple or custard apple, is widely distributed throughout tropical and subtropical countries in Asia, including Malaysia, Laos, Thailand, and Vietnam, it is believed to be native to tropical America. They proliferate rapidly in Rajasthan's Aravalli Hills, which are found all over India (Leite et al., 2020).

Phytochemistry

Phytochemicals are present in all fruits and vegetables. People should eat all kinds of them since they can balance out free radicals in the body. The phytochemical makeup of this plant's leaves can help prevent some diseases including cancer and heart disease because free radical molecules in the body interact with antioxidants. Food can be kept from spoiling by using leaf extracts' antibacterial and antioxidant qualities. The leaves of *A. squamosa* contain a wide variety of common phytochemical compounds, including coumarins, tannins, cardiac glycosides, flavonoids, polysaccharides, and saponins. The most common substances found in *A. squamosa* are annonaceous acetogenins, diterpenes, alkaloids, and cyclopeptides, according to earlier investigations. In *A. squamosa* extracts, leaves, and seeds, four alkaloids were found, including anonaine, asimilobine, nur nuciferine, liriodenine, corypalmine, and reticuline. Numerous phytochemical compounds, including (E)-caryophyllene, bicyclogermacrene, caryophyllene oxide, germacrene D, spathulenol, -pinene, limonene, and -elemene, have been discovered in essential oils from the genus Annonaceae. Fantastic antiparasitic and antimalarial activity can be seen in *A. squamosa* basic oil. Base oil is produced in the lowlands of the Himalaya with a hydrostillation rate of 0.13%. According to the results of the extraction technique, which utilised a total oil content of 88.6%, about 40 components from *A. squamosa* have been discovered. According to ASLEO GC-flame ionisation finding investigations and gas chromatography-mass spectrometry, sesquiterpenoids (21.8% oxygenated sesquiterpenes and 63.4% hydrocarbon tarred sesquiterpenes) predominated the sesquiterpenoids, followed by 1.4% oxygenated monoterpenes and 2.0% monoterpenes. *A. squamosa* is claimed to have altered the restorative impact, quantifying the anticancer, insecticidal, antiovulatory, and abortive effects, in research that primarily focus on assuring the of *A. squamosa* constituents. studies on leaves using GC-MS. Approximately 43-54% of hydrogen peroxide may be linked by *A. squamosa* leaf extract, exhibiting antioxidant activity (Leite et al., 2021).

Nutritive value

Numerous minerals are present in sufficient amounts in the leaves of *A. squamosa*. Minerals are essential for the protection of the human body because they can help with a variety of physiological processes, including blood pressure regulation, immune system function, blood clotting, nerve function, muscle contraction and relaxation, metabolism energy, maintenance of healthy bones and teeth, and regulation of many enzymes. One of the vitamins in *A. squamosa* extract is vitamin C. Vitamin C is used by the body for a variety of processes, including immune response, maintaining healthy skin, bone development, wound healing, and connective tissue strength. Additional vitamins that functioned as co-factors in enzymes involved in oxidation-reduction reactions and carbohydrate metabolism include vitamins B1, B2, and B3 (Barros et al., 2016).

In comparison to its fruit and seeds, the *A. squamosa* plant's leaves contain the highest protein content, according to an Egyptian study. Both humans and animals can use *A. squamosa* leaf extract, which has a higher protein content than other *A. squamosa* variants, to increase the nutritional value of meals. Significant amounts of protein and amino acids are present in the methanol and water-based leaf extracts of *A. squamosa*. The Biuret test, which confirmed the presence of amino acids and proteins in the aqueous *A. squamosa* leaf extract, and the Milon test, which confirmed their presence in the methanolic *A. squamosa* leaf extract, provided support for these conclusions.

Traditional uses

The majority of nations in the world embrace herbal

treatment, according to the WHO. In Asia, Latin America, and Africa, herbal medicine is utilised in addition to conventional medicine. One such plant with numerous traditional uses is *A. squamosa*. The *A. squamosa* tree is extensively distributed in Indomalaya, the Caribbean, South America, and Australia. All parts of *A. squamosa* are frequently used by communities to treat a variety of acute and chronic ailments, including cancer, skin conditions, and insect bites. *A. squamosa* leaves have antibacterial and wound-healing properties. In America, India, and Thailand, *A. squamosa* leaf is used to treat diarrhoea and UTIs. In Indonesia, *A. squamosa* leaves are quite popular, especially now that research is beginning to suggest they can treat really serious diseases like cancer. The leaf is crushed and applied to wounds as a traditional treatment even in India. The decoction of *A. squamosa* leaves or its combination with other plants can also be used as an alternative to treat rheumatic pain in the bath and is well absorbed by the body in traditional American medicine (Barros et al., 2016).

Medicinal value

Alternative medicine has been practised for aeons and relies on organic ingredients produced from healing plants. Plant-based alternative medicine is regarded as beneficial and essential for preserving human health.

Numerous studies on the benefits of *A. squamosa* leaves have been done, and the findings show that these leaves have a number of health benefits related to their phytochemical makeup. Proanthocyanidins are among the phenol-based compounds discovered in *A. squamosa* leaves, along with 18 other phenolic compounds. According to Podsiedlik et al. (2020), *A. squamosa* leaf extract exhibits biological qualities that include anticancer, hepatoprotective, lipidlowering, antidiabetic, and antioxidant.

A. squamosa leaves are also claimed to contain various chemical compounds that are beneficial to the body, including hydroxyl isomers of ketones and alkaloids. The leaves of *A. squamosa* can be used as a vermicide and as a remedy for skin diseases, cancer, abscesses, and insect bites. *A. squamosa* leaves that have been broken down into smaller compounds have been used to treat wounds and skin ulcers. Laxatives and an alternate treatment for cases of sticky diarrhoea are made from dried and powdered *A. squamosa* leaves (Freitas et al., 2008).

The methanol extract of *A. squamosa* leaves has the potential to be used as a substitute for antioxidants or as a natural component in the creation of various treatments that can delay or even prevent damage to human cells. Methanol extract from *A. squamosa* leaves is now used as a dermatological anti-hyperpigmentation treatment but has the potential to be turned into skin-lightening cosmetic products. According to the results of the tests, *A. squamosa* leaf methanol extract can decrease MITF, TRP1, TRP2, and tyrosinase. MITF, TRP1, TRP2, and tyrosinase may all decrease as a result of its ability to promote p38 phosphorylation (Duarte et al., 2016).

Pharmacological activities

Medicinal plants play a significant role in the development of new drugs because they can be produced at relatively low cost and because the side effects of using drugs containing ingredients from medicinal plants are typically less severe than those of using synthetic drugs.

Antimicrobial activity

Based on research done by Neethu et al. (2016) using clinical isolates of P. aeruginosa and E. coli to test the antibacterial activity of ethanol extract from *A. squamosa* leaves and DMSO, it was found that the treatment with *A. squamosa* leaf ethanol extract had a mechanism of inhibiting the growth of these two microbes.

In this study, an ethanol extract of *A. squamosa* leaf at a concentration of 25 showed no zone of inhibition. While isolates of E. coli had an inhibition zone measuring mm at a concentration of, isolates of P. aeruginosa had none, and at a concentration of 100 l, isolates of E. coli had an inhibition zone measuring 17 mm and isolates of P. aeruginosa had 15 mm. *A. squamosa* is used as an antibacterial agent because it contains secondary metabolites like phenols, terpenoids, alkaloids, and flavonoids.

Antifungal activity

A. squamosa leaf extract has been shown to inhibit the growth of *Fusarium oxysporum* and *Colletotrichum capsici* (Venkatesan 2009; Ansori et al., 2021).

Anti-inflammatory activity

In terms of maintaining urolithiasis, the ethanolic extract of *A. squamosa* is essentially equivalent to the therapeutic treatment. Urinary tract inflammation discomfort can be reduced by the pharmacological effectiveness of anti-inflammatory and analgesic components from *A. squamosa* leaf extract. It has been shown that decreasing urinary tract smooth muscle spasms can be achieved by enhancing kidney function, restoring injured cells, and adjusting serum and urine parameters. Leukocyte migration decreased as a gauge of inflammatory activity in relation to the evaluation of Atemoya's ethanol extraction takes off (*Annona squamosa* L. x *Annona cherimola* Mill.). A peritoneal cavity check is followed by a subcutaneous discussion package test to ascertain whether movement has abated. The production of mediators is inhibited by the inflammatory activity, which results in the cyclooxygenase action. By inducing the migration of defense cells, carrageenan, IL-1, IL-8, IL-6, plasma exudation, and TNF-

can all contribute to inflammation (Korah et al., 2020).

Anticancer activity

Ethnic cultures have long employed all parts of *A. squamosa* to treat a wide range of problems, including cancer tumours, skin conditions, insect stings, and other maladies. But the seeds of this plant contain a deadly substance that can be used to treat lice and head lice. *A. squamosa* leaves, on the other hand, possess hepatoprotective and immunomodulatory qualities (Khar et al., 2004).

There has previously been investigation on *A. squamosa*'s resistance to anti-cancer-related non-alkaloidal moieties, specifically the acetogenin. After studying the alkaloids of *A. squamosa*, two benzylisoquinoline alkaloids were found. A number of Alkaloids I provide good activity for both colon cancer cells (HTC116) and human breast cancer cells (MCF-7) in regard to the activity of benzylisoquinoline alkaloids in cancer cells (Khar et al., 2005).

Antiulcer activity

Effective antiulcerants can be found in the leaves of *A. squamosa*. Male albino-Wistar rats were used as experimental subjects in a recent study, and indomethacin was used to induce ulcers. The findings demonstrated that aqueous extract dosages of 175 mg/kg and 350 mg/kg significantly decreased free acidity, stomach volume, and ulcer index when compared to the control group. Because the plant's safety and lack of negative side effects were established in the acute oral toxicity testing for its aqueous extract, *A. squamosa* leaves can be utilised to treat peptic ulcers (Yadav et al., 2011; Ibrahim et al., 2015).

Antioxidant activity

By blocking or suppressing ROS synthesis, which is a sign of unregulated ROS production, antioxidants work to protect living things from harm. 53 Among the disorders brought on by oxidative stress include conditions like diabetes, cancer, and inflammatory diseases. Antioxidants in this scenario contribute to the fight against oxidative stress by scavenging free radicals. There is proof that some phenolic substances, such as flavonoids, act as natural antioxidants and protect cells from free radicals (Mariod et a., 2012).

According to the results of numerous studies on the amount of antioxidant compounds in the ethanol extract of *A. squamosa* leaves, flavonoids are present in the form of rutin and hyperoside in *A. squamosa* leaves.

A. squamosa leaf extract showed potent free radical scavenging activity in chloroform solution, with an IC50 of 308.3 mg/mL. On the other hand, when employed in a methanol solution, its leaf extract showed IC50 342.5 mg/mL free radical scavenging activity. Its extract has a relatively low IC50 of 439.6 mg/mL when mixed with an aqueous solution, which denotes a low amount of free radical scavenging activity. The extract using ascorbic acid revealed the highest level of free radical scavenging activity (Vikas et al., 2017).

Antidiabetic activity

These compounds may be the reason why *A. squamosa* leaf extract has anti-diabetic and anti-oxidant properties. The specific islet cell damage induced by streptozotocin induction results in an increase in blood glucose levels. Gliclazide is routinely used as the reference drug in STZ-induced models of mild diabetes to assess the anti-diabetic effects of different medications because it is well known that it causes hypoglycemia. After diabetic rats induced with STZ were given *A. squamosa* leaf extract, blood glucose levels considerably dropped (Kaleem et al., 2006; Shirwaikar et al., 2004).

Anti infertility activity

Animal subjects who received *A. squamosa* leaf extract had considerably lower average testicular indices. Loss of testicular mass, a sign of antifertility action, was the cause of this. The caudal epididymal sperm count is decreased by *A. squamosa* leaf extract, which influences the hormonal systems that regulate spermatogenesis. Anomalies in spermatozoa, such as bent tails, spermatozoa without tils, headless spermatozoa, and spermatozoa with two heads, were plainly visible when the ethanol extract was administered (Varghese et al., 2013).

Anti platelet activity

Ent-kaurane diterpenoids, which are extracted from the stem of *A. squamosa*, are being studied for their potential anti-platelet effects. According to Yang et al. (2002), the ent kaurane diterpenoids "ent-Kaur- 16-en-19-oic acid" and "16alpha-hydro19-al-entkauran- 17-oic acids" showed how Annona species might be abused to create highly valued restorative goods.

Hepatoprotective activity

A. squamosa leaves include lipid peroxidation inhibitors, which protect the liver, as well as exceptionally potent antioxidant activity, which fights free radicals. Researches found that giving a dose of *A. squamosa* leaf extract (1000 mg/kg body weight) could effectively protect liver cells by raising protein levels and causing levels of glutamate oxaloacetate and glutamate pyruvate transaminase to significantly drop in the blood (Raj et al., 2009; Uduman et al., 2011; Mehta et al., 2017).

Anti diarrhea activity

The leaves of *A. squamosa* contain a variety of compounds, including alkaloids, tannins, steroids, flavonoids, and saponins. Diarrhoea and dysentery can be treated with

tannin because of its astringent properties. The compound leaves include alkaloids, specifically 6, 7-dimethoxy-1-(hydroxy-4-methoxybenzyl)-2-methyl-1, 2, 3, and 4-tetrahydroisoquinoline. 61 This study proved that an ethanolic extract of *A. squamosa* leaves has antidiarrheal properties (Afroz et al., 2019).

Neuroprotective activity

The leaf of *A. squamosa* has a number of benefits. The sugar apple leaf extract, which contains anonaine, can be used to treat epilepsy, mood disorders, and memory problems, according to Reddy et al.'s (2020) study on neuron protection.

The phytochemical analysis of *A. squamosa* leaf extract using petroleum and ethanol revealed that the leaf contains phenolic compounds.

Hypolidemic activity

Researchers have found that diabetic mice have higher levels of TGs and total cholesterol than healthy mice. Both aqueous and ethanolic treatments with *A. squamosa* leaf extracts decreased mean cholesterol, triglyceride, and LDL cholesterol levels while raising HDL cholesterol. Activation of the lipoprotein lipase enzyme and stimulation of beta cells, which release large amounts of insulin to eliminate triglycerides from plasma, may be the causes of this (Wen et al., 2019).

Immunomodulatory activity

A. squamosa leaf aqueous extract may function as a strong immunostimulant with a wide immunological mechanism. The immunomodulatory effect of leaf extract seen in *A. squamosa* in haematological parameters was demonstrated in Clarias batrachus fish. The concentration of the extracts (10 ml, 50%) and (15 ml, 100%) dramatically increased. The TEC, haemoglobin levels, TLC counts, and Differential Leukocyte numbers in fish blood were found to have increased at the time when haematological parameters were evaluated. Haematological parameters including haemoglobin and blood cell counts (RBC and WBC) significantly changed when *A. squamosa* leaves and fruit were used as an ethanol extract. The fact that treated animals in this study had significantly higher WBC counts than untreated mice shows that the immune system may have been activated (Soni et al., 2012; Sultana et al., 2008).

Nephroprotective activity

At the expense of the animals, kidney tissue from rats that had been paracetamol-impaired for 24 hours was removed for histological examination. Severe tubular epithelial necrosis and degradation were found during an inspection. The majority of these alterations are histological in nature and imply significant tubular necrosis along with cell degeneration. No significant edoema or direct necrosis was present in the pretreatment ethanolic extract of *A. squamosa* leaves (200 and 400 mg/kg), but urate significantly lowered the levels of BUN, creatinine, and urate corrosive. At that dose, the capacity for kidney cell regeneration is demonstrated (Neelima et al., 2020).

Conclusion

The *A. squamosa* plant was discovered for the first time in Mexico and is now found extensively in India. *A. squamosa* plants flourish in the tropics and lowlands. The leaves of the plant species *A. squamosa* are still scarcely ever used. The leaves of *A. squamosa* have a high nutritional value, which has numerous benefits for human health, according to earlier study. However, additional research on *A. squamosa* leaves is needed in order to convince people of their advantages, notably in the prevention and treatment of disease.

References

Abd-Elghany AA, Ahmed SM, Masoud MA, Atia T, Waggiallah HA, El-Sakhawy MA, Mohamad EA. 2022. Annona squamosa L. Extract-Loaded Niosome and Its Anti-Ehrlich Ascites' Carcinoma Activity. ACS Omega. 7(43):38436-38447.

Afroz N, Ahsanul Hoq M, Jahan S, Mainul Islam M, Ahmed F, Shahid-Ud-Daula AFM, Hasanuzzaman M. 2019. Methanol soluble fraction of fruits of Annona muricata possesses significant antidiarrheal activities. Heliyon. 6(1):e03112.

Ali SH, Jafar ZJ. 2022. Comparison of antibacterial efficacy of *Annona squamosa* mouthwash with chlorhexidine for children. Journal of Research in Medical and Dental Science, 10:87–94.

Anand U, Tudu CK, Nandy S, Sunita K, Tripathi V, Loake GJ, Dey A, Prockow J. 2022. Ethnodermatological use of medicinal plants in India: From ayurvedic formulations to clinical perspectives – A review. Journal of Ethnopharmacology, 284: 1–28.

Ansori AN, Fadholly A, Proboningrat A, Antonius Y, Hayaza S, Susilo RJ, et al. 2021.Novel Antiviral Investigation of Annona squamosa Leaf Extract against the Dengue Virus Type-2: In vitro Study. Pharmacognosy Journal. 13(2):456-462.

Barros FJ, Costa RJO, Cesario FRAS, Rodrigues LB, Costa JGM, Coutinho HDC, Galvao HBF, Menezes IRA. 2016. Activity of essential oils of Piper aduncum Anf and Cinnamomum zeylanicum by evaluating osmotic and morphologic fragility of erythrocytes. European Journal of Integrative Medicine, 8: 505–512.

Baskaran R, Pullencheri D, Somasundaram R. 2016. Characterization of free, esterified and bound phenolics in custard apple (*Annona squamosa* L) fruit pulp by UPLC-ESI-MS/MS. Food Research International, 82:121–127.

Chen Y, Cao Y, Li F, Zhu X, Peng C, Lu J, Chen J, Li X, Chen

Y. 2017. Studies on anti hepatoma activity of *Annona squamosa* L. pericarp extract. Bioorganic & Medicinal Chemistry Letters, 27:1907–1910.

de Freitas MV, Netto Rde C, da Costa Huss JC, de Souza TM, Costa JO, Firmino CB, Penha-Silva N. 2008. Influence of aqueous crude extracts of medicinal plants on the osmotic stability of human erythrocytes. Toxicol In Vitro. 22(1):219-24.

Dholvitayakhun A, Trachoo N, Sakee U, Cushnie TP. 2013. Potential applications for *Annona squamosa* leaf extract in the treatment and prevention of foodborne bacterial disease. Nat Prod Commun. 8(3):385-8.

Duarte AE, Waczuk EP, Roversi K, da Silva MA, Barros LM, da Cunha FA, de Menezes IR, da Costa JG, Boligon AA, Ademiluyi AO, Kamdem JP, Rocha JB, Burger ME. 2015. Polyphenolic Composition and Evaluation of Antioxidant Activity, Osmotic Fragility and Cytotoxic Effects of Raphiodon echinus (Nees & Mart.) Schauer. Molecules. 21(1):E2.

Kaleem M, Asif M, Ahmed QU, Bano B. 2006. Antidiabetic and antioxidant activity of *Annona squamosa* extract in streptozotocin-induced diabetic rats. Singapore Med J. 47(8):670-5.

Kharchoufa L, Merrouni IA, Yamani A, Elachouri M. 2018. Profile on medicinal plants used by the people of North Eastern Morocco: Toxicity concerns. Toxicon. 154:90-113.

Korah MC, Rahman J, Rajeswari R, Sherief H, Lalitha V, Sengottavelu S, Sivakumar T. 2020. Evaluation of diuretic efficacy and antiurolithiatic potential of ethanolic leaf extract of *Annona squamosa* Linn. in experimental animal models. Indian J Pharmacol. 52(3):196-202.

Leite DOD, Camilo CJ, Nonato CFA, Carvalho NKG, Salazar GJT, de Morais SM, Costa JGMD. 2021. Chemical Profile and Evaluation of the Antioxidant and Anti-Acetylcholinesterase Activities of Annona squamosa L. (Annonaceae) Extracts. Foods. 10(10):2343.

Leite DOD, de F A Nonato C, Camilo CJ, de Carvalho NKG, da Nobrega MGLA, Pereira RC, da Costa JGM. 2020. Annona Genus: Traditional Uses, Phytochemistry and Biological Activities. Curr Pharm Des. 26(33):4056-4091.

Lira AB, Montenegro CA, de Oliveira KM, de Oliveira Filho AA, da Paz AR, de Araújo MO, de Sousa DP, de Almeida CLF, da Silva TG, Lima CMBL, Diniz MFFM, Pessôa HLF. 2018. Isopropyl Caffeate: A Caffeic Acid Derivative-Antioxidant Potential and Toxicity. Oxid Med Cell Longev. 6179427.

Londershausen M, Leicht W, Lieb F, Moeschler H, Weiss H. 1991. Molecular mode of action of annonins. Pesticide Science, 33 (4):427–438.

Mariod AA, Abdelwahab SI, Elkheir S, Ahmed YM, Fauzi PN, Chuen CS. 2012. Antioxidant activity of different parts from *Annona squamosa*, and Catunaregam nilotica methanolic extract. Acta Sci Pol Technol Aliment. 11(3):249-58.

Mehta SD, Paliwal S. 2007. Hepatoprotective activity of hydroalcohilic extract of *Annona squamosa* seeds, Int J Pharm Phyto Res, 9:997-1000.

Mudau TE, Olowojo JO, Amoo SO. 2022. Ethnobotanical assessment of medicinal plants used traditionally for treating diabetes in Vhembe district, Limpopo Province. South Africa. S. Afr. J. Bot. 146:304–324.

Neelima S, Dwarakanadha Reddy P. Kothapalli Bannoth CS. 2020. Nephroprotective activity of *Annona squamosa* leaves against paracetamol-induced nephrotoxicity in rats: in vitro and in vivo experiments. Futur J Pharm Sci. 6:131.

Oršolić N, Sirovina D, Odeh D, Gajski G, Balta V, Šver L, Jazvinšćak Jembrek M. 2021. Efficacy of Caffeic Acid on Diabetes and Its Complications in the Mouse. Molecules. 26(11):3262.

Pardhasaradhi BV, Reddy M, Ali AM, Kumari AL, Khar A. 2004. Antitumour activity of Annona squamosa seed extracts is through the generation of free radicals and induction of apoptosis. Indian J Biochem Biophys. 41(4):167-72.

Pardhasaradhi BV, Reddy M, Ali AM, Kumari AL, Khar A. 2005. Differential cytotoxic effects of Annona squamosa seed extracts on human tumour cell lines: role of reactive oxygen species and glutathione. J Biosci. 30(2):237-44.

Pascual LMC, Macahig RAS, Rojas NRL. 2022. Comparative toxicity, phytochemistry, and use of 53 Philippine medicinal plants. Toxicol. Rep. 9:22–35.

Podsiedlik M, Markowicz-Piasecka M, Sikora J. 2020. Erythrocytes as model cells for biocompatibility assessment, cytotoxicity screening of xenobiotics and drug delivery. Chem Biol Interact 332:109305.

Raj DS, Vennila JJ, Aiyavu C, Panneerselvam K. 2009. The hepatoprotective effect of alcoholic extract of *Annona squamosa* leaves on experimentally induced liver injury in Swiss albino mice, Interl J Inte Biol, 5:182-186.

Reddy, KS, Bhupalam P, Akkiraju S, Mallela V. 2020. Effect of *Annona squamosa* Linn against Aluminium Chloride Induced Alzheimer's Disease in Rats. Egyptian Pharma J. 19: 330-337.

Rodrigues FFG, Boligon AA, Menezes IRA, Galvão-Rodrigues FF, Salazas GJT, Nonato CFA, Braga NTTM, Correia FMA, Caldas GFR, Coutinho HDM, Siyadatpanah A, Kim B, Costa JGM, Barros ARC. 2021. HPLC/DAD, Antibacterial and Antioxidant Activities of Plectranthus Species (Lamiaceae) Combined with the Chemometric Calculations. Molecules. 26(24):7665.

Shirwaikar A, Rajendran K, Dinesh Kumar C, Bodla R.

2004. Antidiabetic activity of aqueous leaf extract of *Annona squamosa* in streptozotocin-nicotinamide type 2 diabetic rats. J Ethnopharmacol. 91(1):171-5.

Silva RF, Carneiro CN, Sousa CBC, Gomez FJV, Espino M, Boiteux J, Fernandez MA, Silva MF, Dias FS. 2022. Sustainable extraction bioactive compounds procedures in medicinal plants based on the principles of green analytical chemistry: A review. Microchem. J. 175 (1–21): 07184.

Soni VK, Yadav DK, Bano N, Dixit P, Pathak M, Maurya R, Sahai M, Jain SK, Misra-Bhattacharya S. 2012. N-Methyl-6, 7-dimethoxyisoquinolone in Annona squamosa twigs is the major immune modifier to elicit polarized Th1 immune response in BALB/c mice. Fitoterapia. 83(1):110-6.

Sulaiman AN, Arzai AH, Taura DW. 2022. Ethnobotanical survey: A comprehensive review of medicinal plants used in treatment of gastro intestinal diseases in Kano state, Nigeria. Phytomed. Plus. 2: 100180.

Sultana N. 2008. Lipoxygenase inhibition by novel fatty acid ester from *Annona squamosa* seeds, J Enzyme Inhib Med Chem, 23:877-881.

Suwalsky M, Colina J, Gallardo MJ, Jemiola-Rzeminska M, Strzalka K, Manrique-Moreno M, Sepúlveda B. 2016. Antioxidant Capacity of Gallic Acid in vitro Assayed on Human Erythrocytes. J Membr Biol. 249(6):769-779.

Tadeg H, Mohammed E, Asres K, GebreMariam T. 2005. Antimicrobial activities of some selected traditional Ethiopian medicinal plants used in the treatment of skin disorders. Journal of Ethnopharmacology, 100:168-75.

Thattakudian Sheik Uduman MS, Sundarapandian R, Muthumanikkam A, Kalimuthu G, Parameswari S A, Vasanthi Srinivas TR, Karunakaran G. 2011. Protective effect of methanolic extract of Annona squamosa Linn in isoniazid-rifampicin induced hepatotoxicity in rats. Pak J Pharm Sci. 24(2):129-34.

Vikas B, Akhil B S, P R, Sujathan K. 2017. Free Radical Scavenging Properties of *Annona squamosa*. Asian Pac J Cancer Prev. 18(10):2725-2731.

Wen W, Lin Y, Ti Z. 2019. Antidiabetic, Antihyperlipidemic, Antioxidant, Anti-inflammatory Activities of Ethanolic Seed Extract of Annona reticulata L. in Streptozotocin Induced Diabetic Rats. Front Endocrinol (Lausanne). 10:716.

World Health Organisation. 1993. Summary of WHO guidelines for the assessment of herbal medicines. Herbal Gram, 28:13–14.

Yadav DK, Singh N, Dev K, Sharma R, Sahai M, Palit G, Maurya R. 2011. Anti-ulcer constituents of *Annona squamosa* twigs. Fitoterapia. 82(4):666-75.

Yang YL, Chang FR, Wu CC, Wang WY, Wu YC. 2002. New ent-kaurane diterpenoids with anti-platelet aggregation activity from Annona squamosa. J Nat Prod. 65(10):1462-7.

Yonathan D, Yeshitila A, Tadesse M, Mathewos A. 2015. Extraction and physico-chemical characterization of Cordia africana Lam seed oil. J Adv Bot Zoology, 4:8.

Zabihullah Q, Rashid A, Akhtar N. 2006. Ethnobotanical survey in Kot Manzary Baba Valley Malakand Agensy, Pakistan. Pakistan Journal of Plant Sciences, 12:115–21.

Zeleke E, Enbiyale G, Mamo G, Giday M, Luelseged A. 2019. The In Vitro Antibacterial Sensitivity Test of Selected, Medicinal Plants. Journal of Genomic Medicine Pharmacogenomics, 5(1):402-12.