

A Review of an Important Plants: *Annona squamosa* Leaf

Arifia Safira¹, Prasita Widayani¹, Dhiya An-Najaaty¹, Cinta Atsa Mahesa Rani¹, Mela Septiani¹, Yan Arengga Syah Putra¹, Tridiganita Intan Solikhah^{1,*}, Aswin Rafif Khairullah², Hartanto Mulyo Raharjo³

Arifia Safira¹, Prasita Widayani¹,
Dhiya An-Najaaty¹, Cinta Atsa
Mahesa Rani¹, Mela Septiani¹, Yan
Arengga Syah Putra¹, Tridiganita
Intan Solikhah^{1,*}, Aswin Rafif
Khairullah², Hartanto Mulyo
Raharjo³

¹Division of Veterinary Clinic, Faculty of
Veterinary Medicine, Universitas Airlangga,
Surabaya, INDONESIA.

²Doctoral Program in Veterinary Science,
Faculty of Veterinary Medicine, Universitas
Airlangga, Surabaya, INDONESIA.

³Center of Excellence Fish Infectious Disease,
Department of Veterinary Microbiology,
Faculty of Veterinary Science, Chulalongkorn
University, THAILAND.

Correspondence

TI Solikhah

Division of Veterinary Clinic, Faculty of
Veterinary Medicine, Universitas Airlangga,
Surabaya, INDONESIA.

E-mail: tridiganita-intan-s@fkh.unair.ac.id

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ABSTRACT

Plants have been utilized extensively in traditional medicine by a range of nations since ancient times, and more research into their safety, efficacy, and quality value is needed. One of the plants that have been widely used by society in traditional medicine is *Annona squamosa* L. *A. squamosa* is commonly cultivated in tropical and subtropical regions. Based on previous research, all parts of *A. squamosa* including bark, leaf, and roots have proven biological activities such as antioxidant, antifungal, and anticancer, especially on the leaves. Indian people have long history used young leaves of *A. squamosa* for antidiabetic, besides in South China, they use seeds to decrease the cancer effect in the human body. The pharmacological activities of *A. squamosa* leaves are antimicrobial, antifungal, anti-inflammatory, anticancer, antiulcer, antidiabetic, antiarrheals, antiplatelet, antioxidant, and hepatoprotective, neuroprotective, and cytoprotective. Phytochemicals in *A. squamosa* leaves include coumarins, tannins, cardiac glycosides, flavonoids, carbohydrates, and saponins. Meanwhile based on nutritional analysis shows that the *A. squamosa* leaves are water, protein, lipids, Fiber Ash and Calcium.

Key words: *Annona squamosa*, Traditional medicinal plant, Medicine, Phytochemistry, Pharmacology.

INTRODUCTION

Today's society has a high concern for a healthier life by consuming natural ingredients.¹⁻³ Plants are the best source for making traditional medicine because they live all around us. According to the World Health Organization, it is estimated that 80% of the world's population has used herbal ingredients as medicine for aspects of health care.⁴ *Annona* is the second largest genus in the *Annonaceae* family after *Guatteria*. *A. squamosa* is one of the herbal plants that can be used as medicine, also known as custard apple, and based on previous research studies it has been proven has various pharmacological effects that are good for the body.

A. squamosa has been cultivated throughout the world such as in the West Indies, America, and Brazil. Besides custard apples, *A. squamosa* can also be referred to as sharifa (Hindi), sitappalam (Tamil), sitaphala (Kannada), and sita phalamu (Telugu).⁴

The *A. squamosa* tree can grow up to 3-8 m tall, has cone-shaped fruit, has leaves consist of two colors, namely brilliant green on the top and bluish green on the underside of the leaves, also has petiole that can reach 0.7 - 1.5 cm, while the leaf shape can be oval or elliptical.⁵ *A. squamosa* is an important tropical fruit that can withstand harsh climatic conditions and is widely distributed among annonaceous fruits.⁶

A. squamosa leaves contain active substances such as flavonoids, glycosides, phenolics, tannins, phytosterols, alkaloids, and saponins. These compounds show therapeutic effects such as antioxidants, anticancer, antimicrobial, antiviral, anti-melanogenic, and anti-inflammatory activities.^{4,7-11}

TAXONOMY

Kingdom: Plantae

Division: Magnoliophyta

Class: Magnoliopsida

Order: Magnoliales

Family: *Annonaceae*

Genus: *Annona* L.

Species: *Annona squamosa*¹²

PLANT DESCRIPTION

A. squamosa is one of the garden plant that comes from the *Annonaceae* family known as custard apple.¹⁴ *A. squamosa* is a small tree with thin gray bark, has flower crown that resembles a flat or round ball. *A. squamosa* leaves are green with a width of 3-5 cm and a length of up to 15 cm, this plant dormancy can be caused by fluctuations in temperature, light, or rainfall. *A. squamosa* is also a type of plant with bisexual flowers with the groups of 2 to 4 and can reach a length of about 2.5 cm. One of the animals that plays a role in the pollination process of *A. squamosa* is the nitulid beetle. After the pollination process is carried out, tuberculous fruit is formed and has an aromatic also sweet taste. Each carpel has a smooth seed, with black or dark brown in color, and has oval shape.¹⁵

Trees *A. squamosa* can flower in spring to early summer, but in areas with permanent humidity levels, *A. squamosa* can flower throughout the year. The flowers are actinomorphic, protogynous, pedicellate, spirocyclic, bracteates, and bisexual. The *A. squamosa* flower has six petals and a degenerated sepal formation.

The stems of branches *A. squamosa* are irregular in shape and gray in color and contains compounds

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such as roemerolidine, nitroso xylophone, and duguevalline alkaloid.¹⁶ *A. squamosa* begins to bear fruit when it is 3-4 years old. In India, usually *A. squamosa* bear fruit around July-August. Custard apple has a sweet taste like sugar, their ripe fruit is indicated by the sweet aroma of the fruit. *A. squamosa* seeds are dark brown to black, and generally 30-40 seeds can be found in one fruit. *A. squamosa* is a type of plant that is classified as diploid with $2n-14$.¹⁵

GEOGRAPHICAL DISTRIBUTION

A. squamosa also branded as sugar apple or custard apple is considered endemic to tropical America but is widely distributed in tropical and subtropical countries in Asia such as Malaysia, Laos, Thailand and Vietnam.^{17,18} In India it is scattered all over Rajasthan where they grow wild in the Aravalli hill region.¹⁹

PHYTOCHEMISTRY

Phytochemicals can be found in all fruit and vegetables. That's why people should consume any kind of them because they can remove free radicals in the human body. Some forms of disease such as heart disease and cancer can be prevented by the phytochemical content in the leaves of this plant, free radical molecules react with antioxidants in the body.²⁰ Food decomposition can be prevented by using the antibacterial and antioxidant components of leaf extracts.²¹ In the leaves of *A. squamosa* various kinds of common phytochemical compounds can be found including coumarins, tannins, cardiac glycosides, flavonoids, carbohydrates and saponins.¹⁸ In other research, It has been found 33 annonaceous acetogenins, 19 diterpenes, 88 alkaloids and 13 cyclopeptides as the most common constituents of *A. Squamosa*.²² Four alkaloids were found in both extracts, leaves and seeds of *A. squamosa*, namely anonaine, asimilobine, nur nuciferine, lirioidenine, corypalmine and reticuline.²³ Research with essential oils according to the genus Annonaceae phytochemical compounds found including, (E)-caryophyllene, bicyclogermacrene, caryophyllene oxide, germacrene D, spathulenol, α -pinene, β -pinene, limonene and β -elemene.²⁴ The fundamental oil extricated from *A. squamosa* shows fabulous antiparasitic and antimalarial movement. 0.13% base oil is produced in the Himalayan lowlands by hydrodistillation strategy. The number of constituents that have been identified is around 40, from *A. squamosa*, the results obtained with a total oil of 88.6% in the extraction process. ASLEO GC-flame ionization discovery investigations and gas chromatography-mass spectrometry showed that the sesquiterpenoids were dominated by sesquiterpenoids (21.8% oxygenated sesquiterpenes and 63.4% hydrocarbon tarred sesquiterpenes) taken after by 1.4% oxygenated monoterpenes and 2.0% monoterpenes.²⁵ *A. squamosa* is said to have altered the restorative effect, quantifying the antitumor, insecticidal, antioviulatory and abortive effects according to studies which mainly focus on guaranteeing the of *A. squamosa* constituents. leaves by GC-MS studies.²⁶ About 43-54% Hydrogen peroxide can be linked by *A. squamosa* leaf extract so that it shows antioxidant activity.²⁷

NUTRITIVE VALUE

A. squamosa leaves contain sufficient concentrations of several minerals. Minerals are needed to protect human's body because they can help to carry out various activities inside the body, such as regulating blood pressure, the immune system, blood clotting, nerve function, muscle contraction and relaxation, metabolism energy, maintenance of healthy bones and teeth, and regulate many enzymes.²⁸ One of vitamins that contained in *A. squamosa* extract is vitamin C.²⁹ Vitamin C is involved in various activities in the human body such as immune response, maintaining healthy skin, bone development, wound healing, bone development, and strengthening connective tissue. Other vitamins that functioned as co-factors in enzymes involved in oxidation-reduction reactions and carbohydrate metabolism are vitamins B1, B2, B3.

In a study conducted in Egypt, suggested that the highest protein content was in the leaves of *A. squamosa* when it compared to the fruit and seeds of *A. squamosa* plant. *A. squamosa* with a higher protein content, that is *A. squamosa* leaf extract, can be used in humans and also animals to increase the value of food.³⁰ High amounts of protein and amino acids are found in the methanol and water extracts which from the leaves of *A. squamosa*. These results were proven by the Biuret test which confirmed that there were amino acids and proteins in the aqueous *A. squamosa* leaf extract, also the Milon test confirmed that there were amino acids and proteins in the *A. squamosa* methanol leaf extract.

TRADITIONAL USE

Herbal medicine has been widely accepted in most countries in the world, as evidenced according to WHO countries in Africa, Latin America, and Asia use herbal medicine as a complement to the primary treatment. One such plant with extensive traditional use is *A. squamosa*. *A. squamosa* tree is widely distributed in Indomalaya, the Caribbean, South America, and Australia. Commonly all parts of *A. squamosa* can be used by communities for the treatment of different acute and chronic diseases such as insect bites, cancerous and skin complaints. Antibacterial and wound healing activity of the leaves of *A. Squamosa*.³¹ In America, India, and Thailand *A. squamosa* leaf is used to treat urinary tract infection and dysentery.³² In Indonesia leaves *A. squamosa* are very popular, especially since research has begun to prove that it can fight super dangerous diseases such as cancer.³³ Even in India the leaf as traditional medicine is also crushed and applied to wounds.³⁴ In addition, decoction of *A. squamosa* leaves or combination with other plants, its content can be absorbed by the body well as a febrifuge, cold remedy, and employed in the bath to alternative rheumatic pain in traditional American medicine.³⁵

MEDICINAL VALUE

Medicine using natural ingredients from medicinal plants has been used as an alternative medicine since ancient times. The use of medicinal plants as alternative medicine is considered effective and important for human health.³⁶

Research on the benefits of leaves *A. squamosa* has been widely carried out, and research studies examining the benefits of *A. squamosa* leaves show that leaves *A. squamosa* have many health benefits related to phytochemical diversity. The compounds contained in *A. squamosa* leaves include phenol-based compounds such as proanthocyanidins and 18 different phenolic compounds. The biological activities of *A. squamosa* leaf extract includes anticancer, hepatoprotective, lipid-lowering, antidiabetic, anti-obesity, antioxidant.²⁵

A. squamosa leaves are also reported to have various chemical compounds that are beneficial for the body such as hydroxyl isomers of ketones and alkaloids. *A. squamosa* leaves have potential for vermicide action, treatment of tumors, cancer, insect bites, abscesses, and skin diseases. *A. squamosa* leaves that have been crushed into smaller compounds have been used to treat wounds and ulcers on the skin.³⁷ Leaves *A. squamosa* which have been in the form of dry powder are considered as an alternative medicine for cases of slimy diarrhea and can also be used for laxatives.¹⁹

Leaf methanol extract *A. squamosa* can be a natural ingredient that is used as an alternative material that can be developed into various types of drugs that can delay or even prevent damage to body cells or in other words, *A. squamosa* leaf has the potential as an alternative antioxidant material.³⁸ *A. squamosa* leaf methanol extract can be used as a dermatological anti hyperpigmentation agent and has the potential to be developed into cosmetic products that can lighten the skin. This is based on the test results that *A. squamosa* leaf methanol extract can



Figure 1: Twigs of *A. squamosa* showing fruit and leaf.¹³

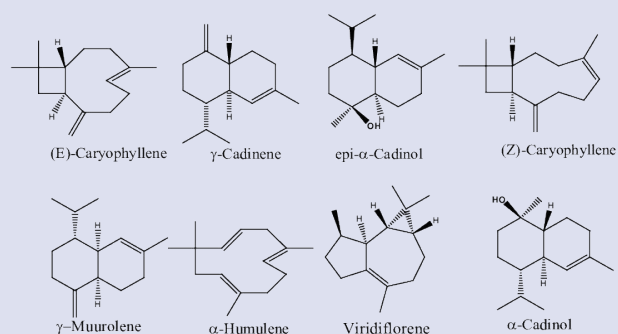


Figure 2: Structure of major constituents of *A. squamosa* leaf essential oil.¹³

inhibit MSH-induced melanogenesis in B16F10 cells and can also induce p38 phosphorylation which can lead to a decrease in MITF, TRP1, TRP2, and tyrosinase.³⁹

PHARMACOLOGICAL ACTIVITY

Medicinal plants have an important role in the process of developing new drugs,⁴⁰ this is because, medicinal plants have relatively cheap manufacturing costs⁴¹ and the side effects arising from the use of drugs with medicinal plant ingredients are relatively less when compared to the side effects arising from the use of synthetic drugs.⁴²⁻⁴⁴ The pharmacological activity of leaves *A. squamosa* can be described in below:

Antimicrobial activity

Based on research on the antibacterial activity of the ethanol extract of *A. squamosa* leaves and DMSO which were tested in vitro with the agar plate method against clinical isolates of *P. aeruginosa* and *E. coli* by Neethu *et al* (2016),⁴⁵ it was shown that there was a mechanism of inhibition of the growth of these two microbes due to the treatment of *A. squamosa* leaf ethanol extract.

In this study, *A. squamosa* leaf ethanol extract at concentration of 25µl was shown no zone of inhibition. However, at a concentration of 50µl, there was an inhibition zone of 11 mm on isolates *E. coli* and no inhibition zone on isolates *P. aeruginosa*. and at a concentration of 100 µl, there was an inhibition zone of 17 mm on isolates *E. coli* and 15 mm on isolates *P. aeruginosa*. *A. squamosa* is used as an antibacterial agent

because it has secondary metabolites such as essential oils, phenols, alkaloids, terpenoids, and flavonoids.⁴⁵

Antifungal activity

A. squamosa leaves extract is revealed to be capable of inhibiting the growth of *Fusarium oxysporum*⁴⁶ and especially *Colletotrichum capsici*.⁴⁷

Anti-inflammatory activity

Maintenance of urolithiasis using the ethanolic extract of *A. squamosa* have almost the same comparison than the clinical treatment. Pain in urinary tract inflammation can be reduced by the pharmacological activity of anti-inflammatory and analgesic compounds from *A. squamosa* leaf extract. Smooth muscle contractions of the urinary tract have been shown to be relaxed by restoring impaired kidney function, normalizing urine and serum parameters, and restoring damaged cells.²¹ In association with the assessment of The ethanol extricate of atemoya takes off (*Annona squamosa* L. x *Annona cherimola* Mill.), There was a reduction in leukocyte relocation as a parameter of inflammatory activity. Examination of the peritoneal cavity is carried out and then a subcutaneous discussion package test is carried out so that the decrease in movement can be known. Barriers to the pathway This cyclooxygenase effect occurs because the inflammatory activity inhibits the synthesized mediators. Inflammation can occur due to involvement of the relocation of defense cells by carrageenan, IL-1β, IL-8, IL-6, plasma exudation and (TNF-α).²⁰

Anticancer activity

Ethnic communities use all parts of *A. squamosa* traditionally for treatment of various diseases, such as cancer tumors, skin problems, insect bites, and any others.⁴⁸ But there is a part of this plant that is poisonous located in the seeds which can be used to kill lice and head lice,³⁴ while the leaves of *A. squamosa* can be used as hepatoprotective and immunomodulatory.⁴⁹

In previous studies, a research has been carried out on *A. squamosa* against anti-cancer related non-alkaloidal moieties particularly the acetogenin.⁵⁰ A research on the alkaloids section of *A. squamosa* yielded two benzyloquinoline alkaloids. Isolated Alkaloids I provide excellent activity for colon cancer cells (HTC116) and also for Human Breast cancer cells (MCF-7) which is related to the activity of benzyloquinoline alkaloids in cancer cells.⁵¹

Antiulcer activity

A. squamosa leaves contain properties that have efficacy as Anti-ulcerative. Recently a study conducted on experimental animals of male albino- Wistar rats and indomethacin was used to induce ulcer presented that aqueous extract of dosage 175 mg/kg and 350 mg/kg significant reduction in free acidity, gastric volume, and ulcer index as compared with the control group. The acute oral toxicity study for aqueous extract of *A. squamosa* leaves has shown that the plant leaf was safe and nothing side effects were observed so, it can be used for the management of peptic ulcers.⁵²

Antioxidant activity

Antioxidants are compounds that play a role in inhibiting or providing protection for living organisms from damage which is a manifestation of uncontrolled ROS production.⁵³ Diseases such as diabetes, cancer, and inflammatory conditions are some of the diseases caused by oxidative stress. In this case, antioxidants play a role to help fight oxidative stress by scavenging free radicals.⁵⁴ Natural antioxidants such as flavonoids as well as several phenolic compounds have been documented that have the potential to protect cells from free radicals.⁵⁵

The results of several studies on the content of antioxidant compounds in the ethanol extract of *A. squamosa* leaves show that leaves *A. squamosa* contain flavonoids in the form of rutin and hyperoside. Rutin and hyperoside are compounds that have biological activities related to antioxidant mechanisms.⁵⁴

A. squamosa leaf extract using chloroform solution showed strong free radical scavenging activity of IC₅₀ 308.3 mg/mL. In the other hand, their leaf extract using methanol solution showed free radical scavenging activity of IC₅₀ 342.5 mg/mL. Meanwhile, their extract with an aqueous solution showed relatively little free radical scavenging activity, namely IC₅₀ 439.6 mg/mL. The extract using ascorbic acid showed the highest free radical scavenging activity, which was IC₅₀ 35.26 mg/mL.⁴

Antidiabetic activity

The antidiabetic and antioxidant properties of *A. squamosa* leaf extract may be due to the presence of these phytochemicals. The induction of streptozotocin causes specific damage to islet cells and thereby increases blood glucose concentrations. It is well known that gliclazide produces hypoglycemia and is often used as the standard drug in STZ-induced models of moderate diabetes to compare the antidiabetic properties of various compounds. Administration of *A. squamosa* leaf extract in STZ-induced diabetic rats resulted in a significant decrease in blood glucose levels.⁵⁶

Anti infertility activity

Animal subject that was administered by *A. squamosa* leaf extract showed a significant reduction of the average testicular index, this happened because of testicular weight shrinkage which indicates antifertility activity.⁵⁷ Extract of *A. squamosa* leaves affects the hormonal mechanism that regulate spermatogenesis, which decrease caudal epididymal sperm counts.⁵⁸ Administration of the ethanol extract notably showed a decrease of spermatozoa concentration and abnormalities in spermatozoa such as bent tails, spermatozoa without tails, headless spermatozoa, and spermatozoa with two heads.⁵⁷

Anti platelet activity

Anti-platelet movement: The ent-kaurane diterpenoids, which are separated from the stem of *A. squamosa*. are examined for anti-platelet action. The ent kaurane diterpenoids 'ent-Kaur- 16-en-19-oic acid' and '16alpha-hydroxy-19-entkauran- 17-oic acids' appeared total inhibitory impacts on rabbit platelet conglomeration at 200 M, detailed that *Annona* species can be misused for planning of restorative items with tall esteem.³⁷

Hepatoprotective activity

A. squamosa leaves have very high antioxidant activity, which have function to free radical capacity, while lipid peroxidation inhibitors have hepatoprotective function.³⁸ In a study conducted by Rajeskumar et al (2015)⁵⁹ which is to evaluating the hepatoprotective function of *A. squamosa* leaves, using albino rats that they were given a dose of *A. squamosa* leaf extract (1000 mg/kg body weight) could provide effective protection on liver cells by increasing protein levels, inducing a significant decreasing in serum glutamate oxaloase transaminase, and serum glutamate pyruvate transaminase levels.

Anti diarrhea activity

A. squamosa leaves contain alkaloids, tannins, steroids, flavonoids, and saponins, Tannin is the properties that have astringent to treat dysentery and diarrhea.⁶⁰ In detail, the compound leaves are alkaloids, 6, 7-dimethoxy-1-(α -hydroxy-4-methoxybenzyl)-2-methyl-1, 2, 3, 4-tetrahydroisoquinoline.⁶¹ An experiment showed that ethanolic extract of *A. squamosa* leaves was effective as an antidiarrheal.⁶²

Neuroprotective activity

A. squamosa leaf has many benefits. Based on a study conducted by Porwal et al (2015)⁶³ related to neuron protection, it was stated that sugar apple leaf extract contains anonnaine can help in treating epilepsy, mood disorders, and memory problems.

The results of the phytochemical test of *A. squamosa* leaf extract using Petroleum and Ethanolic showed that *A. squamosa* leaf contains phenols components. Phenols play an important role in preventing neurodegenerative disease conditions.⁶⁴

Cytoprotective activity

The increase in mucin levels in the pyloric ligation model and the alcohol-induced protection of the aspirin model are clear evidence of cytoprotective activity in *A. Squamosa*.⁴⁸

Hypolipidemic activity

Diabetic mice were shown to had higher total cholesterol and TGs values compared to control.⁶⁵ Therapy using aqueous and ethanolic extracts of *A. squamosa* leaves both lead to decrease in mean level of cholesterol, triglyceride, and LDL-cholesterol, while HDL-cholesterol was increased.⁶⁶ This could happen due to the initiation of lipoprotein lipase enzyme and inducement of β -cells that secrete fair amount of insulin to clear triglycerides from the plasma.^{65,67}

Immunomodulatory activity

A. squamosa leaf water extract has a possibility to be a strong immunostimulant with a nonspecific immune mechanism. The immunomodulatory movement of leaf extract watched in *A. squamosa* was showed in *Clarias batrachus* fish in hematological parameters. There was a critical increase within the concentration of extract (10ml) 50% and (15ml) 100%. At that point analyzed hematological parameters in fish blood and found an increase within the number of TEC, hemoglobin levels, TLC counts and the number of Differential Leukocytes.⁶⁸ Hematological lists such as hemoglobin, blood cell counts (RBC and WBC) revealed critical changes due to the treatment of ethanol extract of *A. squamosa* leaves and fruit. The important increase in WBC assay in treated mice observed in this study may be due to stimulation of the immune system.⁶⁹

Nephrotoxicity activity

Histopathological examination of paracetamol inebriated kidney tissue in rats was obtained at the expense of animals after 24 hours. Examination revealed intense necrosis and degeneration of the tubular epithelium. These changes suggest cell degeneration on the side of intense tubular necrosis and are most associated with histopathological changes. Insignificant swelling or direct necrosis was observed in pretreated (200 and 400mg/kg) ethanolic extract of *A. squamosa* leaves and impressively (P < 0.001) reduced BUN, creatinine, and urate corrosive levels in a urate-dependent manner. at the dose, which appears the power of renal cell regeneration.⁷⁰

CONCLUSION

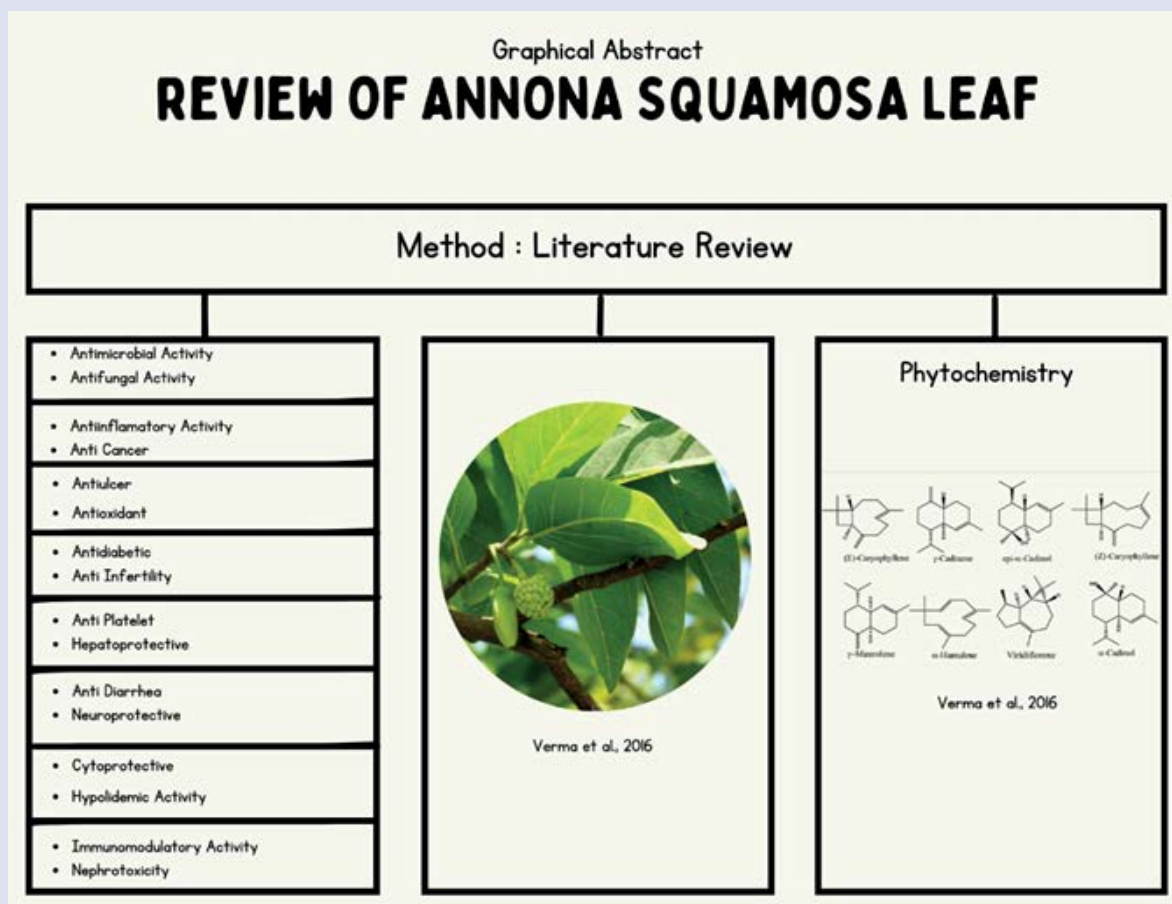
A. squamosa plant is a type of plant that was first known in Mexico and is now widely found in India. *A. squamosa* plants grow well in the lowlands and the tropics. The leaves of *A. squamosa* is a type of plant that is still rarely used. *A. squamosa* has a lot of benefits for humans such as for health functions based on the previous studies that have shown that their leaves have high nutritive value. However, research on *A. squamosa* leaves needs to be further developed to be able to convince and increase the information that *A. squamosa* leaves have many benefits, especially in the prevention and treatment of disease.

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GRAPHICAL ABSTRACT



ABOUT AUTHORS



Arifia Safira is currently pursuing a bachelor's degree in Veterinary Medicine at Airlangga University. She is part of Veterinary Anatomy Division as an Assistant Lecturer.



Prasita Widayani is currently studying bachelor of veterinary medicine of Universitas Airlangga. Besides that she is also active in the assistant lecturer of histology, and was awarded 1st place in the animal science paper competition 2020 by faculty of veterinary medicine universitas airlangga.



Dhiya' An-Najaaty is a veterinarian student of Veterinary faculty of Airlangga university. As a student, the author joined some organizations in Student Representative Council of Airlangga University in 2020, and joined as a member in Student Executive Board in 2021.



Cinta Atsa Mahesa Rani is an undergraduate student at the Faculty of Veterinary Medicine at Airlangga University, Indonesia. She is part of Veterinary Anatomy Division as an Assistant Lecturer. The author was also awarded a scholarship to study in University of Padua, Italy.



Mela Septiani is a fifth semester student at the Faculty of Veterinary Medicine at Airlangga University, Surabaya, Indonesia. She is interested in veterinary clinical science, medical plants and pharmacology.



Yan Arengga Syah Putra is a student of Veterinary Medicine, at Airlangga University, Surabaya, Indonesia.



Tridiganita Intan Solikhah is a lecturer at the Faculty of Veterinary Medicine, Universitas Airlangga, Indonesia. She has been a jury for a national essay competition for students throughout Indonesia. She research projects related to veterinary clinical sciences, medicinal plants and antidiabetic. The author also has several international journal publications.



Aswin Rafif Khairullah is a veterinarian and researcher from Faculty of Veterinary Medicine, Universitas Airlangga, Indonesia. He do some projects related to his studies, such as research in microbiology and antibiotic resistance.



Hartanto Mulyo Raharjo is a veterinarian and research assistant at the Center of Excellence for Fish Infectious Diseases, Chulalongkorn University, Thailand. Now he takes his Ph.D. in Veterinary Science and Technology from Chulalongkorn University, Thailand, and do some projects related to his studies, such as research in microbiology, fish diseases, antibiotic resistance, and bioinformatics.

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