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Biological activity of *Spondias pinnata*: a review



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Dewa Ayu Agus Sri Laksemi*

ABSTRACT

Background: Herbal products are a promising alternative strategy to overcome infection in the era of antibiotic resistance that began to occur. Natural products from plants that are applied in medicine are increasingly and are often used because of the minimal side effects, less toxicity.

Review: Characteristics and plant content of the same species are different depend on ecology and geographic condition of land where the plant is cultivated. "Loloh" is a traditional drink from Bali, one of which is quite well known is loloh cemcem which is

often found mainly in the tourist village of Penglipuran Bangli. "Loloh cemcem" is made from "cemcem" leaves or "kedondong" leaves originating from other languages *Spondias pinnata*. Plants of the genus *Spondias*, consisting of 18 species, have been used as a traditional medicine to treat various diseases. This plant is widely cultivated commercially in multiple countries to be marketed locally and internationally. The present review highlights the current advances of phytochemical screening, pharmacologic effect, the molecular mechanism of action of *Spondias pinnata* in health.

Keywords: *Spondias pinnata*, phytochemical screening, ethnomedicine, molecular mechanism

Cite this Article: Laksemi, D.A.A.S. 2019. Biological activity of *Spondias pinnata*: a review. *IJBS* 13(2): 88-93. DOI:10.15562/ijbs.v13i2.218

Department of Parasitology,
Medical Faculty, Universitas
Udayana

INTRODUCTION

Herbal products are a promising alternative strategy to overcome infection in the era of antibiotic resistance that began to occur. Natural products from plants that are applied in medicine are increasingly and are often used because of the minimal side effects, less toxicity. WHO reports 65-80% of the world's population entrusts efforts to fight disease and maintain health by using ingredients prepared from plants. Plant species range from 250,000 that exist today, only 1% of those species which ability and effect of therapy and pharmacy have been studied. The treatment of drugs from synthetic materials over a long period gives rise to resistance.¹

HISTORY OF THE PLANT

The origin of *S. pinnata* itself is still unclear and confusing to ascertain due to extensive cultivation and natural tendencies. This plant species is commonly found in Malaysia, India, and Indonesia. The origins of *S. pinnata* are still being debated to this day. The full DNA analysis is not yet available. Thus it is still considered "naturally present" in Indonesia, Malaysia, including in various places in Bali. Characteristics and plant content of the same species are different depend on ecology and geographic condition of land where the plant is

cultivated.²

S. pinnata in Bali was first called 'catsjemtsjem' (pronounced: 'kecemcem') in the meaning of the Balinese condondum. The first scientific report on the existence of the species in Bali showed that it was a native plant of Bali or at least Bali was included in the natural distribution area. It was likely brought to Bali from Java by Javanese Hindus Majapahit who fled in Bali.²

"Loloh" is a traditional drink from Bali, one of which is quite well known is "loloh cemcem" which is often found mainly in the tourist village of Penglipuran Bangli. "Loloh cemcem" is made from "cemcem" leaves or "kedondong" leaves originating from other languages *S. pinnata*.

CHARACTERISTICS

S. pinnata are decidua trees, can be found in primary and secondary forests. People generally name *S. pinnata* by the name of "kedondong hutan".² Plants of the genus *Spondias*, consisting of 18 species, have been used as a traditional medicine to treat various diseases.¹⁻⁵ The characteristics are ornamental trees whose height can reach 12 to 18 m with erect growth. The surface of the tree bark is smooth, with irregular cracks, grey to pale reddish-brown, with clear, sticky and turpentine sap. The leaves are fragrant, arranged in a spiral. The leaves have a sour taste and can be used for flavouring.

*Corresponding to:

Dewa Ayu Agus Sri Laksemi;
Department of Parasitology,
Medical Faculty, Universitas
Udayana
srilaksmidps@gmail.com

Received: 2019-10-21
Accepted: 2019-12-24
Published: 2019-12-30

Its flowers are not stemmed, white and bisexual. Its fruits are yellow, fleshy, seeds are hard, jagged and have a fibrous surface with a soft edible middle part. This plant is widely cultivated commercially in various countries to be marketed locally and internationally.^{4,6} Its taxonomy is classified as⁵:

Kingdom	: <i>Plantae</i>
Subkingdom	: <i>Viridiplantae</i>
Infrakingdom	: <i>Streptophyta</i>
Division	: <i>Tracheophyta</i>
Subdivision	: <i>Spermatophytina</i>
Infradivision	: <i>Angiospermae</i>
Class	: <i>Magnoliopsida</i>
Superorder	: <i>Rosanae</i>
Order	: <i>Sapindales</i>
Family	: <i>Anacardiaceae</i>
Genus	: <i>Spondias</i>

ETHNOMEDICINE

In Ayur Vedas, it is said that *S. pinnata* destroys *Vata*, enriches the blood and heals rheumatism. Leaf buds taste sour with a fruit-like odour.⁵ In India, *S. pinnata* is traditionally used as an anthelmintic, anti-inflammatory, anti-pyretic, anti-tumour

and anti-bacterial.⁷ The *Sabara* tribes of Orissa state use the decoction of fresh barks for treating helminthiasis in children.³

Plant parts of the genus *Spondias*, as from the skin, roots, fruit, and leaves, have a variety of benefits and have been used as a traditional medicine in various countries. In terms of ethnomedicine, *S. pinnata* has anti-bacterial activity and inhibits lime impact.⁸

In traditional medicine, the skin of *S. pinnata* is used as dysentery-diarrhoea, vomiting, roots are used to regulate menstruation, plants as anti-tuberculosis, leaves as a drug for dysentery, raw fruit as aphrodisiac, while ripe fruit as constipation and anti-scorbutic drug.⁷ *Spondias pinnata* is also used as a remedy for bronchitis and skin diseases.¹ Traditionally, it is also used to treat leprosy, diabetes, diuretics, inflammation of the eye, anti-thirst, antioxidants, antimicrobials, thrombolytic agents, laxatives.⁵ Its benefits such as the root functions to regulate menstruation, fruits for the treatment of rheumatism and laryngitis, skin for the treatment of dysentery and to prevent vomiting, the plant is useful as an anti-tuberculosis, the leaves are helpful as aromatic, astringent, acidic, anti-emetic, diarrhoea, and dysentery.⁴ The flowers are used for obesity, hemorrhagic disease, anti-vomiting, dyspepsia, gonorrhoea.⁹

A description of the traditional uses of parts from various countries which have been published can be seen in Table 1. The leaves of the genus *Spondias* in several countries are used for multiple purposes including in Mexico for stomach aches and bloating, a decoction of fresh leaves is used to treat anaemia, diarrhoea, dysentery, skin infections, leaf decoction used for treating diarrhoea and dysentery in Belize, while in Nigeria, Benin and Togo are used to improve memory, whereas in southwestern Nigeria, leaves are used for diabetic patients.⁵ Ambonese people shower using boiled water with *S. pinnata* leaves when they are sick or healthy.² Other writings mention its leaves have benefits as a cure for various diseases including stomach ache, urolithiasis, and diabetes.²

The anti-diabetic effect of 'cemcem' or *S. pinnata* leaves as a herbal drink can reduce high sugar levels. "Cemcem" leaf herbal drank in the form of juice, used traditionally by Balinese for a thousand years, as written in the usada of Bali, namely since the 11th century. The earliest writing about *S. pinnata* treatment was found in an ancient Sanskrit book known as Ayurveda, while the first scientific report on the use of *S. pinnata* was in 'Hortus Malabaricus'. In the description, it was stated that *S. pinnata* could cure menstruation, dysentery, and uncontrolled gonorrhoea.²

Table 1. Administration of *S. pinnata* as Folk medicine in various countries

No	Part of plant	Country	Medicinal uses
1	Sap ⁵	India	Analgesic, bronchitis, dysentery, ulcer, diarrhoea, skin disease
2	Leaves ⁵	Nigeria	Diabetes mellitus
3	Leaves ⁵	Indonesia	Health supplement, diabetes mellitus, menstruation, dysentery, gonorrhoea
4	Bark ⁵	India	Ointment for joint pain, diarrhoea, dysentery, anti-emetic, antioxidant, free-radical scavenging, anti-mucositis
5	Root ⁵	India	Menstruation regulation, gonorrhoea
6	Fruit ²	Indonesia	Stomach health

Table 2. Benefits of *Spondias pinnata*

No	Part of Plant	Medicinal Uses
1	Sap ^{1,5}	Analgesic, bronchitis, dysentery, ulcer, diarrhoea, skin disease
2	Leaves ^{2,4,5}	Diabetes mellitus, a health supplement, diabetes mellitus, menstruation, dysentery, gonorrhoea, antiemetic, diarrhoea, dysentery
3	Flower ⁹	Obesity, hemorrhagic, antiemetic, dyspepsia
4	Stem bark ^{4,7}	Antiemetic, diarrhoea, dysentery
5	Root ⁷	Menstruation regulation
6	Fruit ^{1,5}	Aphrodisiac, constipation, anti-scorbutic, rheumatic, sore throat, Bronchitis, skin disease

Chloroform and methanol extracts of *S. pinnata* peel produce significant diuretic and laxative activity. Stem heart extract and *S. pinnata* bark show anthelmintic activity against *Pheretima posthuma* earthworms.⁴ Bark decoction is used to treat anaemia, diarrhoea, dysentery, and skin infections. In India, its bark is used as an ointment on joint pain, diarrhoea, and dysentery to prevent vomiting. The decoction of the root bark is used to regulate menstruation and treat gonorrhoea.⁵ Its bark is also used to treat dysentery, has antioxidant effects, free-radical scavenging, anti-mucolytic property.¹⁰

PHYTOCHEMICAL SCREENING

S. pinnata is an energy source of 348 kcal / 100 grams, containing phenol components, natural antioxidants and minerals. Also a source of ascorbic acid, malic acid, calcium, phosphorus. Its phytochemical screening contains alkaloids, saponins and tannins. It also contains gallic acid, salicylic acid, chlorogenic acid, ellagic acid, p-coumaric acid, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, quercetin, catechin, myricetin, rutin, vitamin E, furfural, phytosterol, campesterol and fatty acids.¹¹ Its leaves contain flavonoids, tannins, gums, alkaloids, saponins and terpenoids. High total phenolic and flavonoid content is equivalent to gallic acid and quercetin.¹

Phytochemical screening results revealed that *S. pinnata* ethanol extract containing alkaloids, carbohydrates, flavonoids, triterpenoids, steroids, tannins, resins, saponins. Essential oils from pulp contain carboxyl acid, esters, alcohol, aromatic hydrocarbons.¹² Other research mentioned its content includes tannins, flavonoids, sterols, triterpenoids, saponins, essential oils, amino acids, polysaccharides.⁴ Phytochemical analysis from different research found 24-methylene cycloartanone, lignoceric acid, sitosterol and D-glucoside has been isolated from *S. pinnata*.¹³

The pharmacological activity of *S. pinnata* varies according to phytoconstituents that exist in these plants. The content includes sterols, flavonoids, polysaccharides, gums, β -amyrin, oleanolic acid, amino acids include glycine, cysteine, serine, alanine, leucine, daucosterol, cycloartanone-24 methylene, lignoceric acid, ellagitannic acid, lelligitannin gallon, lelligitannin gallon, lelligitannin β carotene.¹² Secondary metabolites of plant products include tannins, terpenoids, alkaloids, flavonoids. Many plants are studied to get anti-bacterial and antioxidant effects. Natural ingredients can minimize free radicals induced by biomolecules such as fat, protein and amino acids. Natural antioxidants can fight oxidative stress

related to cancer, atherosclerosis, inflammation, diabetes, hair loss, ischemic heart disease, neurodegenerative disorder including Alzheimer's and Parkinson's diseases.¹

The bark content includes β -Amyrin and oleanolic acid, glycine, cysteine, serine, alanine and leucine in fruits, lignoceric acid, β -sitosterol.⁷ *Spondias pinnata* is rich in phenol and flavonoid components.⁹ The essential oil consists of carboxylic esters, alcohols, aromatic hydrocarbons. Its extract as much as 100 mg contains 91.47 mg/ml gallic acid equivalent phenolic content and 350.5 mg/ml quercetin equivalent flavonoid content.⁵

Almost 70% methanol extract of *S. pinnata* stem bark has cytotoxic activity against cancer cells of human lung adenocarcinoma with IC₅₀ 147.84 μ g/ml whereas for human breast adenocarcinoma of 149.34 μ g/ml. The bark within the extract also has a hypoglycemic effect equivalent to glibenclamide, while ethanol extract one has an analgesic effect equivalent to acetylsalicylic acid. Methanol and water extracts of *S. mangifera* also have antibacterial activity against *V.cholera*, *S. typhimurium* and *E. coli*. Other 70% methanol extract bark can also reduce liver toxicity caused by iron.⁵

Fruits contain polysaccharides namely L arabinose, D-galactose and galacturonic acid, B-amyrin and oleanolic acid, glycine, cysteine, serine, alanine and leucine. Ethanol extract of *S. pinnata* fruit has antibacterial activity against *Paeruginosa* and *S. epidermidis* at a dose of 500 μ g / disc with a disc diffusion method, potent cytotoxicity at IC₅₀ 2.12 μ g / ml.⁵

PHARMACOLOGICAL EFFECT

The pharmacological effect of *S. pinnata* in this section is a summary of various research that has been published in journals, obtained through Researchgate, Semantic Scholar, Google Scholar, NCBI. Studies show that several phytochemical bioactive components have been isolated from the genus *Spondias*.

Pharmacological effects of this genus include cytotoxic, anti-oxidant, protective ulcer, hepatoprotective, anti-inflammatory, anti-arthritis, anti-dementia, antipyretic, analgesic, thrombolytic, hypoglycemia, antifertility, anti-hypertension, antimicrobial, and anthelmintic.⁵ Bark extract of *S. pinnata* has an anthelmintic effect on *Pheretima posthuma*, chloroform extract is better than other extracts.³ Various *S.pinnata* extracts have antibacterial, hypoglycemic, anti-oxidant and free radical scavenging activities. In mice, that were made into diabetes with streptozotocin, *S.pinnata* bark extract was reported to have anti-diabetic activity with an optimum therapeutic dose of 1 g/

kg BW.¹³ Ethanol extract of *S. pinnata* bark has an antipyretic effect at doses of 200 and 400 mg/kg orally.⁷

Leaves extract of *S. pinnata* has anti-viral and anti-microbial abilities.⁵ The methanol extract of *S. pinnata* leaves contains a large number of phenolic compounds which are mainly responsible for free radical scavenging. Other studies have shown that *S. pinnata* methanol extract is useful for relieving heartburn, urolithiasis, diabetes, heartburn.²

A crude extract of *S. pinnata* has antimicrobial, anti-inflammatory, antioxidant effects.¹² Leaf extract has antibacterial activity against gram-positive bacteria including *Bacillus cereus*, *Bacillus subtilis*, *Staphylococcus aureus*, *Sarcina lutea*, and gram-negative *Salmonella paratyphi*, *Vibrio parahimolyticus*, *Escherichia coli*, *Pseudomonas aeruginosa*.⁵ Other studies have shown that it has a mild and robust antibacterial and cytotoxic effect on gram-positive and gram-negative bacteria at a concentration of 500 µg / disc, which is significant activity against *P. aeruginosa* and *S. epidermidis*, intermediate sensitivity of *S. aureus* and *S. typhi*, mild sensitivity to *V. cholera*, *S. flexneri*, and *S. pyogenes*.¹⁴

The benefits of *S. pinnata* that have been studied include ethanol extract and methanol extract of *S. pinnata* leaves affect gastrointestinal motility.⁶ Other studies also show *S. pinnata* has anti-TB activity.⁵ Ethanol and acetone extracts of *S. pinnata* stem bark as a hepatoprotector in liver damage caused by alcohol in mice.⁹ The combination of whey and *S. pinnata* has a mucoprotective effect on mice receiving etoposide chemotherapy which causes mucositis as side effects.¹⁰

DOSAGE AND INHIBITORY CONCENTRATION (IC 50) *S. pinnata*

The administration of *S. pinnata* leaf extract on Balb/ c mice with doses less than or equal to 15 g / kg body weight, is relatively safe for the liver while for the kidneys is relatively safe at doses less or equal to 15 g / kg BW. Based on acute toxicity studies, ethanol extract of *S. pinnata* is safe at doses of 2000 mg/kg BW. Side effects and deaths due to ethanol extract were observed at doses of 100, 200, 400 mg / Kg BW for six weeks, showing a range of safe treatments for *S. pinnata* is very wide.¹⁵

Inhibitory concentration (IC) 50 for *S. pinnata* as an antioxidant 49.97 µg / ml, while IC 50 as a scavenging free radical for hydroxyl, superoxide and nitric oxide 112.18 µg / ml, 13.46 µg / ml and 24.48 µg / ml, while as iron chelator 66.54. As for peroxy nitrite activity, singlet oxygen and hypochloric acid, IC values as follows 761.32, 58.07, and 127.99 µg / ml, respectively.⁵ The ethanol

extract of *S. pinnata* stems bark had IC₅₀ 44.34 µg / ml, while the chloroform extract was 61.9 µg / ml. The LC₅₀ and LC₉₀ values of ethanol extract were 65 and 160 respectively while chloroform extracts 170 and 325.¹⁶

TOXICITY

Acute and subchronic toxicity of *S. pinnata*'s bark observed in Wistar rats found acute toxicity of skin extracts observed in the form of changes in skin, hair, eyes, mucous membranes, respiration, circulation, autonomic nerves, central nervous system, somatomotor activity, and behaviour patterns. Acute toxicity conditions that receive more attention include tremor, convulsions, salivation and diarrhoea, lethargy, sleep, and coma. At doses of 0.25, 0, 50, 0.75, 1.00, 1, 25 and 2.00 g / kg weight, after giving the dose once during the first 30 minutes, periodically for the early 24 hours, and every day for a total of 14 days, acute toxicity was not found.¹³

Administration of *S. pinnata*'s bark at doses of 0.25, 0, 50, 0.75, 1.00, 1, 25 and 2, 00 g / kg weight did not find acute toxicity, mortality or morbidity. All test animals well tolerate extracts with selected doses, thus it is safe for remote administration of the extract, and the bark extract also did not inhibit mouse growth.¹³

The administration of *S. pinnata* for a 28-day repeated dose does not affect the liver, lungs, small intestine, liver, pancreas and kidney. Its extract administration does not stimulate or suppress the appetite of mice. Research showed water extracts from the bark of *S. pinnata* were safe up to 2 g / kg weight on Wistar rats. Administration for 28 days did not cause changes in general conditions, appetite, body weight, growth, biochemical parameters, haematological values and histopathological abnormalities in body tissue.¹³

MOLECULAR MECHANISM

Spondias sp leaf extract contains quercetin, rutin, ellagic acid, and acts as an antioxidant and antimicrobial (Table 3). *Spondias pinnata* leaf extract has antituberculosis activity against *M. tuberculosis* MDR bacteria. Other studies found that the water fraction of *S. pinnata* leaves causes protein damage and changes in the morphology of *B. cereus* cells.¹⁷

Antimicrobial activity of *S. pinnata* resin has been investigated. Its resin, can eliminate the insects, fungi and inhibit excessive metabolism. Ethanol extract of *S. pinnata*'s pulp has antibacterial ability against *Staphylococcus aureus*, *E. coli*, *Pseudomonas aeruginosa* and antifungal activity against *Candida albicans* and *Aspergillus flavus*. Resins secreted

by *S. pinnata* contain flavonoids, some literature states that flavonoids act as antibacterial.¹⁸ Resins and flavonoids were found to play a role in the antibacterial activity of *S. pinnata*. However, *S. pinnata* resins are not effective against Gram (-) bacteria, *S. cerevisiae*, and fungi. Only *B. subtilis* bacteria are most susceptible to resins from *S. pinnata*.¹⁹

The bark of *S. pinnata* extract has antioxidant effects while crude extract of *S. pinnata* has antibacterial activity.^{10,18,20} In *S. pinnata* bark extract, the component which plays a role in inhibiting NO synthesis is 4-O- β glucoside. Beta-sitosterol in the bark of *S. pinnata* plays a role in the mechanism of protection by GSH through reducing cytokine levels. Administration of synthetic glutathione (GSH) maintains GSH levels in the kidneys and liver.¹⁰

Free radicals cause oxidative stress that causes damage to proteins and DNA accompanied by fat peroxidation, thus can stimulate the occurrence of cancer, atherosclerosis, cardiovascular diseases, aging. Free radicals will become stable if bound to electrons from other macromolecules such as protein, fat and DNA in healthy human cells. All cells in a healthy human body will protect themselves from free radical damage through enzyme mechanisms such as superoxide dismutase (SOD) and catalase, or through the mechanism of antioxidant components such as ascorbic

acid, tocopherol and glutathione. Antioxidant supplements are essential in dealing with oxidative damage.²⁰

The antioxidant activity of *S. pinnata* has been investigated using the ascorbic acid-induced lipid peroxidation inhibition method. *S. pinnata* leaf and bark extracts have antioxidant activity due to their high polyphenol content and flavonoids. Mechanism of action of flavonoids as antioxidants by acting as a superoxide anions scavenger.²⁰ By the time, its extract is added to the temporary solution. The radical hydroxy will be removed from the sugar and prevent further oxidative stress reactions. This process shows the extract of *S. pinnata* is a better hydroxyl radical scavenger than mannitol as a control.²⁰

Nitric oxide plays a role in the inflammatory process. The continuous production of NO causes toxicity to tissues and causes vascular collapse that associated with septic shock, while the long-term NO expression contributes to cancer and inflammatory conditions including juvenile diabetes, multiple sclerosis, arthritis and ulcerative colitis. NO toxicity increases when interacting with superoxide radicals thus will stimulate peroxynitrite anion (ONOO-) formation which is very reactive. NO results from the side reaction of sodium nitrous with oxygen to form nitrite. *S. pinnata* extract inhibits the nitrite formation by competing directly against oxygen in reaction with NO.²⁰

Table 3. Summary of the mechanism of action of *Spondias pinnata*

No	Part of Plant	Active Component	Mechanism of Action	Effect
1	Bark ¹⁰	4-O- β glucoside	Inhibit NO synthesis	Antioxidant
2	Bark ¹⁰	β -sitosterol	Decrease cytokine level	Antioxidant
3	Leaf ¹⁷⁻¹⁹	resin, flavonoid	Stimulate protein destruction and morphological change	Anti-bacterial (<i>B. cereus</i> , <i>B. subtilis</i> , <i>Staphylococcus aureus</i> , <i>E. coli</i> <i>Pseudo-monas aeruginosa</i>)
4	Pulp ¹⁸	Resin	Stimulate protein destruction and inhibit excessive metabolism	Anti-fungus (<i>C. albicans</i> , <i>A. flavus</i>)
5	Leaf, stem bark ²⁰	Flavonoid Glutathione	Superoxide anions scavenger Prevent formation of nitrite, hydroxyl radical scavenger	Antioxidant
6	Bark ²¹	Flavonoid, phenol	Prevention of chain initiation, decomposition of peroxides, reducing capacity and radical scavenging	Antioxidant
7	Bark ²¹	not mentioned	Induce apoptosis through the intrinsic pathway thus increase Bax/ Bcl-2 ratio and activate caspases cascade that stimulates polyadeno ribose polymerase cleavage	Anti-cancer
8	Bark ¹⁹	not mentioned	not mentioned	Hepatoprotector, thrombolytic, ulcer protective, anti-diarrhoea, anti-hypertension, hypoglycemic

Antioxidant activities through various mechanisms include prevention of chain initiation, decomposition of peroxides, reducing capacity and radical scavenging.²¹ The mechanism of flavonoids as antioxidants through the process of scavenging or chelation. Phenols within the bark of *S. pinnata* have scavenging ability because of their hydroxyl groups. That bark containing flavonoids and phenols has antioxidant activity, and free radical scavenging also chelates iron and has reduced power.²¹ Extract of *S. pinnata* induces apoptosis in both malignant cell lines and induces DNA fragmentation in A549 and MCF-7 cells. The methanol extract of *S. pinnata*'s bark induces apoptosis through an intrinsic pathway by producing an increase in the Bax / Bcl-2 ratio which will cause activation of the cascade caspase which stimulates the breakdown of Poly adeno ribose polymerase.²¹

S. pinnata have hepatoprotective, thrombolytic, protective ulcer, anti-diarrhoea, anti-hypertension, hypoglycemic, antioxidant, anthelmintic, anti-bacterial effects.¹⁹ It has been widely studied, the benefits, content in the health sector, but research on the mechanism of action, especially molecular and cellular mechanisms seem still limited.

CONCLUSION

Every part of *S. pinnata* has numerous benefit. Phytochemistry screening has found it contains alkaloids, saponins and tannins, flavonoids, terpenoids, phenolic and flavonoid. It affects as antioxidant, antibacterial, anti-TBC, antifungus, anti-cancer, hepatoprotector, thrombolytic, ulcer protective, anti-diarrhoea, anti-hypertension, antidiabetic. However, the mechanism of action of those effects remains unclear. Further investigation regarding the mechanism of action of *S. pinnata* is necessary.

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