

A Brief Review On Pharmacological Potential Of *Annona reticulata*

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ABSTRACT

Annona reticulata Linn is a versatile tree and its parts are used as a source of medicine, commonly known as custard apple or bullock's heart, while it is primarily cultivated for its delicious fruit, various parts of the *Annona reticulata* plant have also been traditionally used in herbal medicine for their potential pharmacological properties. The genus *Annona* is a Latin-derived word "anon" which means "yearly produce" which signifies the production of fruits to the plants of this family. It is widely distributed with phytoconstituents like tannins, phenols, glycosides, flavonoids, and steroids. It possesses various medicinal properties such as anthelmintic, analgesic, anti-inflammatory, antipyretic, wound healing, and cytotoxic effects. The crushed leaves are used for wounds and decoction for gastritis. The leaves and stem bark contains acetogenins that have cytotoxic activity and has potential use in cancer treatment. It is extensively found and cultivated throughout India up to an altitude of 900m, especially in the hilly tracts and waste lands. The present article is an attempt to highlight the pharmacological activities of *Annona reticulata* reported so far. It's important to note that while these studies indicate the pharmacological potential of *Annona reticulata*, further research is needed to fully understand the mechanisms of action and assess the safety and efficacy of using *Annona reticulata* for specific medicinal purposes.

Keywords: Botanical description, acetogenins, Bullock's heart, Chemical constituents, Distribution, Cytotoxic phytochemicals, Pharmacological activities, *Annona reticulata*.

I. INTRODUCTION

Annona reticulata is a medicinal plant and belongs to the Annonaceae family¹. Its common name, bullock's heart, refers to the heart shape of its fruit and its reddish brown outer peel when ripe. It is

one of the species used in traditional medicine that is apparent in the ayurvedic system of medicine for the treatment of various ailments². Annonaceae has approximately 119 species, according to one's estimate. The genus *Annona* is a Latin-derived word "anon" which means "yearly produce" which signifies the production of fruits to the plants of this family³. It is native to tropical regions of America, particularly in West Indies and South America. It is extensively found and cultivated throughout India up to an altitude of 900m, especially in the hilly tracts and waste lands^{4,5}.

The *Annona reticulata* is a semi-evergreen and tiny deciduous tree⁴. It is naturalized as a fruit consuming plant. These plants have a high level of phenolic constitution and have potentials that are therapeutic beneficial⁶. So far compounds like alkaloids, tannins, cardiac glycosides, flavanoids, diterpenoids, and acetogenins have been isolated from the bark, fruits, leaves, seeds, and pulp of Annonaceae^{2,7}. Pinene, pinene D, and germacrene D were the most abundant volatiles^{6,8}. Flower appears in the month of March-July and are bisexual. The fruiting begins in August-January⁴. When fully ripe, the fruit has a smooth exterior and turns to dull crimson colour⁶.

It is known that *Annona reticulata* are a source of medication and extracts made from different plant parts have medicinal properties. Epilepsy, dysentery, cardiac disease, parasite and worm infections, constipation, hemorrhage, bacterial infection, dysuria, fever, ulcer, and insecticide are just a few of the traditional uses for the plant⁹. *A. reticulata* has been used as a spasmolytic, anti-inflammatory, anti-anxiety, anti-stress, and anti-mutagenic drug. Unripe fruit are rich in tannins and has been used to treat diarrhoea and dysentery. In India, the crush of ripe fruit were applied to heal the surface tumors. Extracts from the leaves and stems have inotropic, chronotropic, and spasmolytic effects. The leaves are also used as styptic, anthelmintic, pesticides, and as a suppurant

externally³. The leaves and stem bark contains acetogenins that have cytotoxic activity which are unique to the Annonaceae species and has potential use in cancer treatment^{3,10}. *Annona reticulata* has been used widely due to its potential to put up reasonable health care based on traditional medicine¹¹.

VERNACULAR NAMES AND TAXONOMICAL CLASSIFICATION^{3,4,12,13}

Annona reticulata belongs to the family annonaceae with common names of bullocks heart is a plant species that belongs to Plantae (Kingdom), Tracheobionta (Sub Kingdom), Spermatophyta (Super division), Tracheophyta (Division), Magnoliopsida (Class), Magnoliidae (Sub Class), Magnoliales (Order), Annona (Genus), Reticulata (Species).

Vernacular name include Bullock's heart, netted custard apple, wild sweetsop (English), Ramachita (Tamil), Raamphala (Kannada), Manilanilam (Malayalam), Raamphal, Nona (Hindi), Raamaaphalam, Ramphala, Krishnabeejam (Sanskrit), Raama phalamu, Raamaseethaphalamu (Telugu), Raamaaphal (Marathi).

HABITAT

Annona reticulata is a semi-evergreen 6 m tall tiny deciduous tree⁴. It is a pantropic tree that requires a warm, humid, and tropical climate but can also survive in a subtropical climate. The leaves start to fall off at the onset of the winter and the tree remains dormant. When fully grown, it can withstand temperatures of 3° - 2°C without significant damage. The genus prefers to lodge at low altitudes with a much more humid atmosphere and grows better in deep and rich soil with reasonable drainage. This species is less drought tolerant unlike others and grows well in soil of pH 5-8^{6,14}. In Sri Lanka, its height is limited to 915 m but in India, it is up to an altitude of 1220 m. It spreads in the coastal savannah of Ecuador to 1500 m and in Guatemala, it is usually seen lower than 1,220 m. In the areas of Central America, the tree advances between 10-1500 m and have alternating seasons⁶.

DISTRIBUTION

Annona reticulata is widely distributed in tropical and subtropical regions³. It has long been naturalized and cultivated in Peru and Brazil and is grown mostly in the Bahamas, tropical Africa, and occasionally in southern Florida and Bermuda. It is

very common on the east coast of Malaysia and Southeast Asia⁶.

In India, it is widely cultivated up to an altitude of 900 m and naturalized as a fruit-consuming plant and deciduous tree. It is distributed in Bengal, Burma, and southern regions of India. Its abundant growth is found in the hilly areas and wastelands of several districts of Kerala, Karnataka, Tamil Nadu, Andhra Pradesh, Maharashtra, Punjab, Rajasthan, Uttar Pradesh, Madhya Pradesh, Bihar, Assam and Gujarat^{3,13}.

BOTANICAL DESCRIPTION

Annona reticulata is a short, upright tree, with a rounded or growing crown and trunk¹².

LEAVES

Leaves are found to be green, oblong, lanceolate, reticulate, membranous, acute, pellucid, and punctate with odor. The upper surface of leaves is glabrous and the lower surface contains few spreading hairs. When young it looks glabrous above and glaucous and pubescent beneath, with lateral nerves having 8-11 pairs, petiole grows up to 2 cm long^{3,13}.

Phytochemicals in leaves:

Annona reticulata was found to have a variety of chemical constituents. Phenolic compounds: gallic acid, flavonoids (quercetin, anthocyanins, etc.), tannins, betacyanin, carotenoids, and emodols were abundantly present¹⁴. Other constituents: carbohydrates, starch, quinones, cardiac glycosides, amino acids, alkaloids, saponins, steroids, volatile oils, and terpenoids were also found to be present in varying amounts^{13,14}. Dopamine, salsolinol, coclaurine, sesquiterpenes mainly spathenelol, muurolene, copaene, eudesmol, acetogenin – squamone, solamin, annomonicin, rolliniastatin 2, anoreticuin-9-one, triterpenoid – annonaretin A are also present¹³.



FIG 1 : *Annona reticulata* leaves

Pharmacological Activities:

1. Antipyretic activity

The dried leaves were pulverized and methanolic extract of *A. reticulata* leaf was tested for its efficacy at doses of 200 mg/kg and 400 mg/kg. 20% aqueous brewer's yeast was administered through subcutaneous route to induce pyrexia in Wistar rats, selected only if there is a rise in rectal temperature by at least 0.5°C-1°C after 18 hours of treatment. The outcomes of the extract were contrasted with those of the standard, paracetamol (150 mg/kg). After 4 hours, the temperature reduced to 38.45°C from 39.28°C at the dose 200 mg/kg and from 39.30°C to 38.08°C at the dose of 400 mg/ml. It was observed that *A. reticulata* leaf extract has notable antipyretic efficacy¹⁶.

2. Anthelmintic activity

Comparative study of petroleum ether, chloroform, ethyl acetate, and ethanol extract of *Annona reticulata* leaves for its anthelmintic activity, the effectiveness of these different fractions was tested using albendazole (400mg/kg) as the standard and 5% DMF in normal saline as control on adult Indian earthworms, *Pherentima Posthuma*. To screen anthelmintic activity by using *Pherentima Posthuma*, 20mg/ml of each extract is used and the time taken to paralyze is noted. Results showed that the ethanol fraction paralyzed the earthworms in the shortest amount of time, indicating that the ethanolic extract has significantly more activity than the other fractions¹⁷.

3. Anti hyperglycemic activity

The antihyperglycemic effect of methanolic extract of *A. reticulata* leaves was investigated using oral glucose tolerance tests in glucose loaded mice. For the study, male Swiss albino mice were divided into 6 groups, 6 each. Control group (1% tween-80 at 10 ml/kg), standard drug (10 mg/kg glibenclamide), other four groups 50, 100, 200 and 400 mg/kg of methanol extract were given. All mice received 2 g of glucose/kg of body weight after the first hour of administration, and blood samples were taken. At doses of 50, 100, 200 and 400 mg/kg, the serum glucose level was lowered to 34.8, 37.0, 49.6, and 56.1% respectively. Over all findings indicated that *A. reticulata* leaves have dose dependent antihyperglycemic action⁸.

4. Anti nociceptive activity

Swiss albino mice were used in an acetic acid-induced gastric pain model to test the methanolic extract of *Annona reticulata* leaves ability to reduce pain. The leaves were extracted using methanol (1:5 w/v) for 48 hours. The animals were divided into 6 groups, 6 each. When compared to the reference drug, aspirin (200 mg/kg and 400 mg/kg), the extract (50 mg/kg, 100 mg/kg, 200 mg/kg, 400mg/kg) revealed significant dose-dependent decrease in writhing (47.0, 55.1, 67.3, and 69.4% respectively) indicating anti nociceptive activity¹⁸.

5. Anti ulcer activity

A rat model of ulceration by ethanol and indomethacin was used to examine the antiulcer potential of an aqueous extract of *A. reticulata* leaves. Soxhlet extraction were used which was then vacuum-concentrated. Four groups of 6 rats, each were given a vehicle, a reference drug famotidine (3 mg/kg), and two extract of dose 100 mg/kg and 200 mg/kg, respectively on the rats and after 30 min ulcer was induced using 50% alcohol. Indomethacin (10 mg/kg, p.o.) was used to induce ulcer in another group. Significant dose dependent reduction in ulcer index and increase in glutathione levels and pH levels was observed in rats treated with extract and reference drug. The considerable antiulcer activity of *A. reticulata* leaves may be attributed to the phytoconstituent's cytoprotective, antisecretory, and antioxidant potential¹⁹.

6. In vitro cytotoxic and recombinant caspase inhibitory activity

Cell lines were used to test the in-vitro cytotoxic potential of methanol extract of *Annona*

reticulata leaves. Caspase inhibitory assay was performed using Caspase-9 and executioner caspases (Caspase-3 and 6). Human colorectal adenocarcinoma Caco-2, human hepatocellular carcinoma Hep G2, and human renal carcinoma HEK cell lines were used in the investigation of cytotoxic properties. Doxorubicin (10 μ M) is used as standard and as control, maintenance media treatment was taken. The extract showed 56.02% and 66.64% inhibition against caspase-6 and 76.3% and 87% against caspase-9 at 5 μ g/ml and 10 μ g/ml respectively. The study also suggested that the extract may be useful to treat colon cancer, liver cancer and degenerative disorders²⁰.

7. Antioxidant activity

Nitric oxide, superoxide, hydroxy radical, and lipid peroxidation models, 1, 1, 1-diphenyl-2-picryl hydrazyl (DPPH) and 2, 2-azinobis-(3-ethylbenzothiazoline-6-sulphonate) (ABTS) models were employed in this work for the comparative study of antioxidant potential of *Annona squamosa*, *Annona reticulata* and *Annona muricata*. The ethanolic extract of the leaves (500 μ g/ml) were prepared using 95% ethanol. After the test, *Annona reticulata* leaf extract showed 68.03, 79.79, 77.21, 50.83, 88.77 and 88.06 % inhibition in nitric oxide, hydroxyl radical, superoxide radical, lipid peroxidation, DPPH and ABTS models respectively and demonstrated greater activity in quenching DPPH and superoxide radicals, proving the plant's antioxidant potential²¹.

8. Anti Inflammatory activity (In-vitro study)

The methanolic extract was prepared by macerating powdered *Annona reticulata* leaves in methanol for 24 hours. It is then concentrated and suspended in water (1 L) and partitioned with n-hexane, ethyl acetate, n-butanol, and water solubles in order. After removing the corresponding solvent, the remaining components were obtained. By evaluating the nitrite levels in the cultured media and serum, NO production was indirectly evaluated using a colorimetric method based on the Griess reaction. The concentration of nitrite was determined using sodium nitrite as a standard curve at 540 nm absorbance and the majority of them showed considerable NO inhibition, with IC₅₀ values between 48.6 1.2 and 99.8 0.4 M. The findings showed significant explanation for the usage of *Annona reticulata* leaves to treat inflammatory illnesses²².

9. Wound healing

Ethanolic extract were prepared by maceration (30g of powdered leaves in 32% ethanol). In in-vitro study, western blot and gelatin zymography were used to assess the expression of various proteins and growth factors. The extract increased the production of transforming growth factor beta, connective tissue growth factor, vascular endothelial growth factor, alpha smooth muscle actin, matrix metalloproteinases, collagen-1, collagen-3, and focal adhesion kinase in a dose-dependent manner²³.

For the in vivo wound healing experiment, diabetic wound model of 3 groups, six each (Swiss Albino male mice) were used. 10% iodine-povidone ointment (standard) and 150 mg/kg extract as topical solution were used. The extract treated animals showed significant faster wound closure. According to mass spectrometric analysis, quercetin and beta-sitosterol were found to be the two primary components in the extract for the activity²³.

10. Immunomodulatory activity

The present study screened the immunomodulatory activity of *Annona reticulata* leaves in cultured immune cells and Swiss Albino mice. In the in-vitro assay, the effect of leaves on human peripheral blood mononuclear cells, monocytes and human macrophage cell lines were investigated. Cell proliferation assay using MTT assay, Western blot assay, activation of macrophage and NO production were also analyzed. The extract increased human PBMC proliferation, activated macrophages with rise in NO generation. Western blot revealed increase of TGF β . In the in vivo study, extract were prepared by maceration using 32% ethanol and 2 dose (150 mg/kg and 300 mg/kg) were prepared.

6 groups of 5 animals were used for the study using cyclophosphamide as an immunosuppressant. Data exhibited a significant increase in antibody titer as well as a strong delayed type hypersensitivity reaction. It also suggests that the compounds like sitosterol and quercetin can release variety of immune response-inducing mediators and could be an alternative treatment for a number of immune system-related diseases²⁴.

11. Anti-Diabetic and Anti-Hyperlipidemic Activity

The current work used Nicotinamide + Streptozotocin (60 mg/kg, i.p.) generated diabetic rats to assess the anti-diabetic and anti-hyperlipidemic potential of methanolic extract of

Annona reticulata leaves. The effect on serum glucose was noted for up to 21 days after the extracts (200 mg/kg, oral) were given and found to have considerable anti-diabetic effect similar to glibenclamide. Intriguingly, it was discovered that the treated animals had a substantial impact on repairing the lipid and hepatic enzyme profile in streptozotocin challenge rats. Quercetin and gallic acid may be the primary constituent responsible for the activity and this information supplied the rationale for the traditional usage of *A. reticulata* as a remedy for diabetes and obesity².

12. Anti-epileptic activity

The anti epileptic activity of ethanolic and aqueous extracts of *Annona reticulata* leaves was assessed by chemical and electro convulsive methods, i.e. PTZ(80mg/kg) and MES methods. This study used 5 groups of 6 each Swiss Albino rats to explore the anti epileptic effects at the dose of 100 mg/kg, 200 mg/kg, and 400 mg/kg and found dose- dependent increase in the percentage of protection. At 400mg/kg in both extracts, the majority of the animals exhibited no symptoms of convulsions. The study's data also indicated that the latency of the seizures was delayed and their duration was reduced²⁵.

13. Anti-fatigue activity

A weight-loaded forced swimming test was used to clarify the anti-fatigue efficacy of leaf extracts (75 and 150 mg/kg), and the probable mechanism was investigated by determining biochemical markers such as blood lactate and serum urea nitrogen in mice. The extract were prepared by maceration using 95 % ethanol for 3 days which was then heated for 3 hours and filtered. The study showed that leaf extracts could clearly improve the amount of time that mice could swim exhaustively, stop blood lactic acid from rising, and reduce the amount of urea and nitrogen in their blood after swimming. Taking into account all of these, the leaf extracts had a notable ability to reduce tiredness²⁶.

BARK

The bark is rough, thin, and grey in colour⁴. The inner bark is pale yellow in color and are slightly bitter in taste. It is also powerful astringent and the decoction is taken as a tonic. Decoction of the bark is used for the treatment of dysentery and diarrhea²⁷.

Phytochemicals in bark

Bark mainly constitutes monotetrahydrofuron acetogenins, reticulatacin, diterpenes, and alkaloids like liriodenine, copaene, patchoulane, bistetrahydrofuron acetogenin, bullatacin, etc whereas stem bark constitutes dopamine, salsolinol, coclaurine, diterpenes, 16- α -hydroxy-(e)-kauran-19-oic acid,(e)-kaur-16-en-19-oic acid, methyl-17-hydroxy-16- β -(e)-kauran-19-oate, reticullacinone, rolliniastatin-2, molvizarin^{4, 17, 13, 28}. Phytochemicals like saponins, glycosides, flavonoids, fats and oils, phenols, steroids, lignin, tannins, and triterpenes were also present in varying concentration²⁹.



Fig 2. *Annona reticulata* bark

Pharmacological Activities:

1. CNS depressant and analgesic activity

Bark from *A. reticulata* exhibited notable analgesic efficacy when extracted with petroleum ether, ethyl acetate, and methanol using multiple solvent extraction steps. The hot-plate method (analgesic activity) and locomotor activity (as well as pentobarbitone sleeping time test (CNS depressant activity) in Swiss albino mice were performed using 100 mg/kg of extract. For analgesic activity, pentazocin lactate injection (20 mg/kg) and for locomotor activity diazepam (2 mg/kg) were used as the standard. Pentobarbitone (40 mg/kg) was used to induce sleep. The reaction time increased in the mice treated with petroleum ether extract, and the locomotor activity decreased. It also increased the amount of sleep time caused. The extracts used in the hot plate method displayed mild to moderate CNS depressive effects²⁸.

2. Analgesic and anti-inflammatory activity

The sesquiterpene fraction of *A. reticulata* bark were investigated in both the central and peripheral nervous systems using Eddy's hot plate test and the acetic acid-induced writhing method (analgesic activity), carrageenan-induced paw oedema (anti-inflammatory activity). Sesquiterpene fraction at doses of 12.5 and 25 mg/kg and unsaponified petroleum ether extract at a dose of 50 mg/kg were used. Aspirin (200mg/kg) and pentazocine (20 mg/kg) served as the reference drug for anti-inflammatory and analgesic activity. The results showed a significant dose-dependent increase in analgesic and anti-inflammatory activity³⁰.

3. Anti-epileptic activity

The methanolic extract of *Annona reticulata* bark was screened for anti-epileptic activity by Pentylene tetrazol (PTZ)-induced seizures by monitoring various seizure behaviours like the time of onset and duration of seizure. The GABA level in mice brains was also assessed in order to examine the antiepileptic activity. Swiss albino mice were divided into 4 group, 6 each. The groups who received extract treatment (200 mg/kg) had later-onset seizures and shorter seizure durations. The total findings demonstrated that bark of *Annona reticulata* extract's considerable antiepileptic activity. Increased GABA levels in the brain may be the cause of the antiepileptic effect demonstrated by the hydroalcoholic extract of *Annona reticulata* bark³¹.

4. Anti-diarrheal and anti-motility activity

The methanolic bark was extracted by cold maceration method and different fractions were prepared a dose of 200 mg/kg, tested on mice induced by diarrhoea by castor oil. The bark's aqueous soluble fractions showed the highest percentage of diarrheal inhibition (64.9%), whereas the soluble fractions in methanol, n-hexane, chloroform, and ethyl acetate showed 26.99 %, 34.85 %, 52.71 %, and 45.45 % of diarrheal inhibition respectively. The reference standard, loperamide (5 mg/kg), demonstrated a 73.21 % inhibition of diarrhoea. The 200 mg/kg aqueous soluble fraction of the charcoal plug method's GI motility test demonstrated the strongest anti motility activity (68.71 %) ³².

ROOT

The roots are cylindrical in shape with rootlets. They have a pleasant aromatic odour³³.

Phytochemicals in root

Root is rich in phytochemicals such as glycosides, saponins, fixed oils and fats alkaloids, acetogenins, carbohydrate, tannins, proteins and flavonoids. Aporphine alkaloids like Liriodenine, Norushinsunine, Reticuline, Acetogenin neoannonin, and Sesquiterpenes mainly Spathenelol, Muurolene, Copaene, Eudesmol are concentrated in roots whereas root bark contains Anonaine, Michelalbine, Oxoushinsunine, Reticuline and other unknown phenolic compound^{13, 33, 34}.



FIG 3. *Annona reticulata* root

1. Anti proliferative activity

By using the MTT assay, the antiproliferative ability of the aporphine alkaloids liriodenine, norushinsunine, reticuline, and acetogenin neoannonin isolated from the roots of *A. reticulata* was examined against the cancer cell lines and normal cell line. 100 ml of isolated compounds, each at a concentration of 5, 10, and 20 mg, were used for the activity. As a proliferative control, untreated micro titre plates of cell lines with DMSO (0.3% v/v in water) were used. Neoannonin demonstrated strong cytotoxicity (IC₅₀ values 5.8-6.9 mg/ml) against all cancer cell lines, whereas norushinsunine shown moderate cytotoxicity (IC₅₀ values 7.4-8.8 mg/ml). When compared to cancer cell lines, the test substance was less cytotoxic (IC₅₀ values 13.8-26.0 mg/ml) on normal cell lines (Vero cells). The study came to the conclusion that the isoquinoline moiety, the presence of the hydroxyl group, and the capacity of these isolated compounds to induce apoptosis in cancer cell lines are the main causes of the isolated aporphine alkaloids' pronounced cytotoxicity³⁴.

2. Antioxidant and anti microbial activity

antioxidant screening was analyzed by DPPH free radical scavenging assay and hydrogen peroxide assay was used and for antibacterial study, agar cup method and poison plate method were used. Extract of the roots were were preaped using soxhlet equipment. At extract doses of 20, 40, 60, 80, and 100 mg/ml, antioxidant activity was assessed and the absorbance was measured at 517 nm (DPPH assay) and 230 nm (hydrogen peroxide assay). Using nutritional agar media, antibacterial activity was performed against 3 gram positive (*S. aureus*, *B.subtilis*, and *B.cereus*) and gram negative (*E coli*, *Salmonella typhi*, *Pseudomonas aeruginosa*) strains of bacteria. Penicillin was employed as the standard antibiotic while DMSO (100 ml) served as the negative control. Antibiotic scale was used to quantify zone of inhibition. The extract showed notable efficacy against all bacterial strains³⁵.

3. Anti-fungal activity

Agar cup and poison plate techniques were used in this antifungal study. By using a Soxhlet device, roots were were extracted. Using potato dextrose agar media, the extract's antifungal activity was tested against *Candida albicans*, *Fusarium moneliforme*, *Penicillium chrysogenum*, *Aspergillus flavus*, and *Aspergillus niger*. 1% griseofulvin was used as the positive control and DMSO as the negative control. Activity was assessed by looking whether fungi were growing faster or slower. It was shown that *T. viride* and *C. albicans* fungus were the targets of the antifungal action. The findings of this investigation showed that root extract of *A. reticulata* has outstanding antifungal activity³⁵.

4. Anti convulsant activity

The anti epileptic activity of root of *Annona reticulata* were assessed on seizures produced by pentylenetetrazole (PTZ; 60 mg/kg, i.p.). Swiss albino mice were divided into five groups of 6 each. Diazepam (5 mg/kg) was employed as standard. Ethanol extract (100, 200, and 400 mg/kg, p.o.) and sodium CMC (0.1%) were given before the seizures were induced. Later, the onset, duration, and course of the convulsions were noted. Straub's tail and tonic-clonic convulsions were seen in mice given PTZ whereas the extract treated delayed the start of PTZ-induced convulsion and reduced the recovery time. Important bioactives such as flavonoids, phenolics, alkaloids, and other metabolites, might be credited for anti-convulsant properties³³.

5. Skin cancer

Methanolic root extraction were prepared by maceration..Skin cancer was produced in Swiss albino mice using the technique described by Azuine and Bhide. The mice were visually examined for signs of skin cancer. The animals were subsequently given a daily dose of 20 g/kg of the topical gel filled with methanolic root extract for 4 weeks. After the therapy period, the effectiveness of curing the skin cancer was determined. In mice, both the size of the tumour and the cancerous lesion were regularly diminishing proving its potential to treat skin cancer³⁶.

SEEDS

The seeds are arillate, brownish to black, smooth or polished, glossy, and hard in nature. The number of seeds varies between 45-75 and are less than 1.25 cm in length⁴ .



FIG 4. *Annona reticulata* seeds

Phytochemicals in seeds

Seeds are rich in a series of N-fatty acyl tryptamines where acyl portion ranged from hexa decanoyl to hexa cosanoyl. Cytotoxic acetogenins such as Squamocin, cis-/trans-isomurisolenin, Annorecticuin, Annorecticuin-9-one, Bullatacin, cis-/trans-bullatacinone, cis-/transmurisalinone, Solamin, Annomonicin, Rolliniastatin-1,2 squamone and iso annonarecticin and Volatile oil constituents like α -pinene, β -pinene, Myrcene, Limonene, Terpinen-4-ol, and Germacrene D, Cycloreticulin A, Cycloreticulin B, Acetogenins mainly cis and trans iso murisolenin, Annorecticuin, Bullatacin, Squamosine, and Rolliniastatin are present. Amino acyl trimesters of Squamocin 1, and N- fatty acyl tryptamines are also present. Seeds also contain

Annonaceous acetogenins (polyketides) like Annonareticin, 2,-4-cis-isoannonareticin, 2,4-trans-isoannonareticin, Solamin, Murisolin, Reticulacinone, Anoreticuin, Annomonicin, Sitosterol, Daucosterol, Sucrose, Palmitic acid and Stearic acid^{13,37}.

Pharmacological Activities:

1. Wound healing and anti-marking activity

In conjunction with neem oil, honey, and ghee, the anti-marking and wound-healing ability of *A. reticulata*'s methanolic seed extract in male Wister Albino rats were examined. The seeds were extracted in a soxhlet extractor. To induce anaesthesia, a dose of ketamine (50 mg/kg i.p) before making wounds were administered. Rats were placed into 4 groups: control, standard, 5% w/w and 10% w/w test ointment group. From day 0-27, all received treatment and wound area were assessed to determine the % reduction in wound size. Rats given the test formulation demonstrated quicker healing with a tensile strengths than the groups treated with 5% w/w and 10% w/w ointment respectively and they were equivalent to those of the standard group³⁷.

2. Anti-diabetic, anti-hyperlipidemic, antioxidant, anti-inflammatory activity

This study evaluated the potential protective effects of ethanolic seed extract of *Annona reticulata* on experimentally generated type 2 diabetes rat model. diabetic rats treated with 50 and 100 mg/kg of seed extract (fed for 42 days); diabetic rats treated with metformin. Mice receiving extract had their body weight, fasting blood glucose, insulin levels and sensitivity, HbA1c, HOMA-IR, islet area, and insulin positive cells greatly restored and reduced the levels of triglycerides, cholesterol, and LDL, raising HDL in diabetic rats. From the current findings, it can be concluded that *A. reticulata* seed extract has anti-diabetic, anti-hyperlipidemic, antioxidant, and anti-inflammatory properties suggesting that it may be a promising treatment therapy for diabetes mellitus.

3. Anti Cancer

Acetogenins derived from Annonaceae family has potential as antineoplastic drugs. Bullatacin, cis-/trans-isomurisolenin, cis-/trans-bullatacinone, annoreticulin, annoreticulin-9-one, cis-/transmurisolinone, and squamocin are acetogenins that have been identified from *A. reticulata* seeds. Some of these substances had strong cytotoxic action against the four cancer cell lines i.e Hep.G2,

Hep.2, 3, 15, KB, and CCM2. The biological activity of annonacin was investigated and it was found that these substances killed cells in a number of cancer cell lines, including T24 bladder cancer cells and discovered that it is cytotoxic for almost all of the cancer cell lines²⁷.

II. Conclusion

The current review was an attempt to concentrate on various aspects of *A. reticulata* Linn. It was historically employed to cure several illnesses. It includes a variety of minerals and secondary metabolites that may have various therapeutic effects. One of them is acetogenins. *A. reticulata* Linn.'s phytopharmacological traits suggested that it could effectively treat a variety of illness conditions. The current study establishes the value of the *A. reticulata* Linn. plant, may be of great interest in the creation of new plant-based medications. This review also explores the complete information of *A. reticulata* Linn, might be helpful to researchers and scientists working on plant-based bioactive agents.

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