Review article

**Annona reticulata** Linn. (Bullock's heart): Plant profile, phytochemistry and pharmacological properties

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**A B S T R A C T**

From the beginning of human civilization plants and plant based chemicals are the most important sources of medicines. Phytochemical and different products obtained from plant are used as medicines, pharmaceuticals, cosmetics and food supplements. *Annona reticulata* Linn. (*牛心果*牛心果; Bullock’s heart) is a versatile tree and its fruits are edible. Parts of *A. reticulata* are used as source of medicine and also for industrial products. It possesses several medicinal properties such as anthelmintic, analgesic, anti-inflammatory, antipyretic, wound healing and cytotoxic effects. It is widely distributed with phytochemicals like tannins, alkaloids, phenols, glycosides, flavonoids and steroids. Present article is an attempt to highlight over taxonomy, morphology, geographical distribution, phytoconstituents and pharmacological activities of *A. reticulata* reported so far.

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1. Introduction

Plants are recognized as aromatic as well as source of medicine. The extracts obtained from various plant parts possess medicinal properties and are used as colouring agent, preservative, sweetening agent and as additive in many medicinal formulations. Plants restrain abundant amount of secondary metabolites, they are considered to be principal source of therapeutically active compounds. Along with medicinal formulations plants have been successfully utilised for the development of cosmetics and toiletry preparations. Herbal medicines cause lesser side effects. The regular consumption of synthetic drugs may lead to addiction but such effects are not observed for plant based medicines and are relatively safer than synthetic compounds. Also in pharmaceutical companies commercially plants are used as a source for the synthesis of synthetic compounds.

Most of population of developing countries utilize plant based traditional medicine for their primary health care needs. Indian traditional system of medicine; Ayurveda is also based on plant. Medicines derived from plants act as first line defence of body and help to restore the health. Extracts from different plant parts hold wide range of medicinal properties and also utilized as raw materials in herbal industry. Exploration of chemical constituents obtained from plants may provide new leads for the development of novel drug.

*Annona reticulata* Linn. (*牛心果*牛心果; Bullock’s heart) is one of the traditionally important plant used for the treatment of various ailments. It belongs to family Annonaceae. The synonyms (Table 1) of plant are Ramphal, Bullock's heart and Custard apple. Near about 119 different species of the *Annona* genus (Annonaceae) are identified among which most of them are shrubs and trees. Traditionally the plant extract is used for the treatment of diarrhoea and pediculosis.

1.1. Geographical distribution

*A. reticulata* (Table 1) is widely distributed in tropical and subtropical regions. The plant is indigenous to the West Indies. In India it is widely cultivated and naturalized as a fruit consuming plant and deciduous tree. It is distributed in Bengal, Burma and Southern regions of India. It is native to tropical regions of America,

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particularly in West Indies and South America. The plant is widely cultivated in Bangladesh and Pakistan.6,12,13

1.2. Morphology

The height of *A. reticulata* is near about 6.0–7.5 m. It contains numerous lateral branches. The stems are cylindrical having lenticels and very short coffee coloured hairs.9 Leaves are oblong, lanceolate, membranous, acute, and rounded or curate at the base. The upper surface of leaves is glabrous and on lower surface it contains few spreading hairs. Two to four flowers may present on lateral pedicel. Fruits are edible, somewhat heart shaped, rough and yellow in colour which change to yellowish red on ripening.8 Fruits are sweet, astringent and useful in blood complaints.14 Seeds are smooth and blackish in colour.8

1.3. Traditional uses

Traditionally the plant has been employed for the treatment of epilepsy, dysentery, cardiac problem, parasite and worm infestations, constipation, haemorrhage, bacterial infection, dysuria, fever, ulcer and as insecticide. Bark is a powerful astringent and

| Scientific classification | Synonyms | Botanical, common and vernacular names | Local names |
|---------------------------|----------|---------------------------------------|-------------|
| Kingdom: Plantae          | Annona excelsa Kunth. | Botanical name: Annona reticulata Linn. | Tamil: Ramachita |
| Order: Magnoliids         | Annona laevis Kunth. | Common name: Netted Custard apple | Telegu: Ramasitapalam |
| Family: Annonaceae        | Annona longifolia Moc. Annona longifolia Sesse. | English: Bullock’s heart, Corazon | Malayalan: Manilanilam |
| Genus: Annona             | Annona riparia kunth. | Portuguese: Frutoda-Condessa | Kannada: Ramaphala |
| Species: Annona reticulata | | Indonesian: Buah nona | |

| Whole plant | Leaves | Stem |
|-------------|--------|------|
| Unripe fruit | Ripened fruit | Seeds |
| Flowers | Stem bark |

Fig. 1. Parts of *Annona reticulata* Linn. plant.
used as a tonic whereas leaves used for helminthiases treatment.\textsuperscript{3,8,15}

2. Phytoconstituents

Several phytoconstituents have been identified from different parts of A. reticulata (Tables 2 and 3). Stem bark contains tannins, alkaloid and phenolic compounds. Leaves contain wide range of chemicals like alkaloids, amino acids, carbohydrates, steroids, flavonoids, proteins, tannins, glycosides and phenolics. Root has been identified for the content of acetogenin, alkaloid, carbohydrates, proteins, flavonoids, tannins. The plant also found to be rich in minerals such as Ca, P, K, Mg, Na, Cl, S, Mn, Zn, Fe, Cu, Se, Co, Ni and Cr.\textsuperscript{5,28,29}

3. Pharmacological properties

Several parts of A. reticulata (牛心果 niú xiū guǒ; Bullock’s heart) were assessed for their biological potential (Table 4). The extracts and phytoconstituents such as cytotoxic acetogenins isolated from various parts showed diverse pharmacological properties.

3.1. Antipyretic activity\textsuperscript{30}

Crude aqueous extract of leaves of A. reticulata has been screened for analgesic activity at dose of 200 mg/kg and 400 mg/kg. Hyperpyrexia was induced by injecting 20% aqueous suspension of Brewer’s yeast subcutaneously in rats. Rats showing 0.5 °C–1 °C rise or more in rectal temperature after 18 h of injection were separated and selected for the study. The results produced by the extract were compared to the standard drug, paracetamol at a dose 3.2. Anthelmintic activity\textsuperscript{8}

The anthelmintic activity of leaves of A. reticulata was screened using Indian earthworm, Pheretima posthuma. Leaves were powdered and extracted with methanol (1:5 W/v). Male swiss albino mice of weight 18–22 g were used. Mice were divided into different groups each containing six mice. Control group was treated with 1% tween-80 at 10 ml/kg body weight in water whereas standard drug, glibenclamide at 10 mg/kg body weight was used for standard treated group. Other four groups were orally treated with 50, 100, 200 and 400 mg per kg body weight of methanol extract. After one hour of administration all mice were treated with 2 g glucose/kg of body weight and blood samples were collected. The dose-dependent and statistically significant anthelmintic activity was observed. Serum glucose level was reduced to 34.8, 37.0, 49.6 and 56.1% at the dose 50, 100, 200 and 400 mg/kg body weight. Glucose oxidase method was used to estimate serum glucose levels. Overall results showed that extract of leaves of A. reticulata has significant antipyretic activity.

3.2. Anthelmintic activity\textsuperscript{8}

The anthelmintic activity of leaves of A. reticulata was screened using Indian earthworm, Pheretima posthuma. Leaves were powdered and extracted with methanol and cold maceration. Vacuum distillation was used to concentrate extract and 15.83 g yield was obtained. The total ethanolic extract was fractionated using petroleum ether, chloroform, ethyl acetate and ethanol in separating funnel. Fractions were concentrated. 3.39 g, 0.15 g, 0.13 g and 1.51 g yield was obtained for ether, chloroform, ethyl acetate and ethanol respectively. Pheretima posthuma of size 3–5 cm in length and 0.1–0.2 cm in width were considered for the study. Albendazole was used as standard. Ethanol fraction showed less time to produce paralysis which indicates ethanol fraction has more pronounced activity than other fractions.

3.3. Antihyperglycemic activity\textsuperscript{12}

The antihyperglycemic effect of methanolic extract of A. reticulata L. leaves were investigated using oral glucose tolerance tests in glucose loaded mice. Leaves were powdered and extracted with methanol (1:5 W/v). Male swiss albino mice of weight 18–22 g were used. Mice were divided into different groups each containing six mice. Control group was treated with 1% tween-80 at 10 ml/kg body weight in water whereas standard drug, glibenclamide at 10 mg/kg body weight was used for standard treated group. Other four groups were orally treated with 50, 100, 200 and 400 mg per kg body weight of methanol extract. After one hour of administration all mice were treated with 2 g glucose/kg of body weight and blood samples were collected. The dose-dependent and statistically significant antihyperglycemic activity was observed. Serum glucose level was reduced to 34.8, 37.0, 49.6 and 56.1% at the dose 50, 100, 200 and 400 mg/kg body weight. Glucose oxidase method was used to estimate serum glucose levels. Overall results showed that leaves of A. reticulata possess significant and potent antihyperglycemic activity.

3.4. Antiulcer activity\textsuperscript{27}

Antiulcer potential of aqueous extract of A. reticulata leaves was investigated using ethanol and indomethacin induced ulcer model in rats. Extract was prepared by Soxhlet extraction method and concentrated in vacuum. Rats were divided into four groups each containing six rats as vehicle treated group, famotidine (3 mg/kg) as reference drug treated group, and two extract (100 mg/kg and 200 mg/kg) treated groups respectively. Extract was administered to fasted 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. All treated rats were sacrificed after 1 h and ulcer index, acid volume, pH\textsuperscript{24} and total acidity were determined. Significant dose dependent reduction in ulcer index was observed in rats treated with extract and reference standard drug, famotidine. The extract

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|}
\hline
Plant part & Phytochemicals & References \\
\hline
Leaf & Dopamine, Salsolinol, Cochlaurine, Sesquiterpenes mainly Spathenelone, Muurolene, Copaene, Eudesmol, Acetogenin – Squamone, Solam, Annonomycin, Rollinastatin 2, Annonareticin, 9-one. Triterpenoid – annonaretin A & 8,13,16–18 \\
Bark & Monoterohydrofuron acetogenin, Reticulacatin, Diterpenes: (–)-kau-M-en-19-iacid acid and methyl 1β, 17-dihydro- (–)-kauran-19-oate, Alkaloids: Liriodenine, Copaene, Patchoulane and 1H-cycloprop (e) azulene, (-)Kau-16-en-19-oic acid, Bistreterohydrofuron acetogenin, Bullatcin. & 7,19,20 \\
Stem bark & Dopamine, Salsolinol, Cochlaurine, (–)-kau-16-en-19-oic acid, 16-α-hydroxy- (–)-kauran-19-oic acid, Methyl-17-hydroxy-16β-(–)-kuran-19-oate, Reticulacinone, Rollinastatin-2 (β-bulactin – annonin-VI), Molvizarin. & 8,13,21 \\
Root & Aporphine alkaloids Liriodenine, Norushinsunine, Reticuline, Acetogenin neouanonin, Sesquiterpenes mainly Spathenelol, Muurolene, Copaene, Eudesmol. & 13,22 \\
Root bark & Anonaine, Michellalbine, Oxoushinsunine, Reticuline, Unknown phenolic comp. & 8 \\
Seed & Series of N-fatty acyl tryptamine where acyl portion ranged from hexadecanoyl to hexacosanoyl. Cytotoxic acetogenins as Squamone, cis-trans-isomurisoolenin, Annonoreticin, Annonareticin-9-one, Bullatcin, cis-trans-bullactacine, cis-trans-murisolinone, Solam, Annonomycin, Rollinastatin-1, 2 squamone and isoannomaronetine. Volatile oil constituents like α-pinene, β-pinene, Myrcene, Limonene, Terpinen-4-ol, and Germacrene D. Cycloreticulin A, Cycloreticulin B, Acetogenins mainly cis and transisomurisoolenin, Annonoreticin, Bullatacin, Squamomine and Rollinastatin. Anonacyclol triesters of Squamocin 1, N-fatty acyl tryptamines. Annonaceous acetogenins (polykaides): Annonareticin, 2, 4-cis-isoannomaronetine, 2, 4-trans-isoannomaronetine, Solam, Murisolin, Reticulacinone, Annonoreticin, Annonomycin, Sitosterol, Daucosterol, Sucrose, Palmitic acid and Stearic acid. Annonaceae acetogenin: 2, 4-cis-isoannomaronetine. & 8,13,15,23–25 \\
Fruit & Pinene, Myrcene, Limonene, Terpinen-4-ol, Germacrene D & 12 \\
\hline
\end{tabular}
\caption{Phytochemicals of Annona reticulata Linn. plant.}
\end{table}
Table 3
Phytochemical structures of *Annona reticulata* Linn.

| Name of phytochemical | Structure | References |
|-----------------------|-----------|------------|
| Dopamine              | ![Dopamine Structure](image) | 26         |
| Salsolinol            | ![Salsolinol Structure](image) | 26         |
| Coclaurine            | ![Coclaurine Structure](image) |            |
| Acetogenin            | ![Acetogenin Structure](image) | 27         |
| Diterpenes (−)-kau-16-en-19-oic acid | ![Diterpenes Structure](image) |            |

(continued on next page)
| Name of phytochemical | Structure | References |
|-----------------------|-----------|------------|
| Acetogenin neoannonin | ![Structure](image1.png) | 22         |
| Liriodenine           | ![Structure](image2.png) | 22         |
| Reticuline            | ![Structure](image3.png) | 22         |
| Norushinsunine        | ![Structure](image4.png) | 22         |
Table 3 (continued)

| Name of phytochemical | Structure | References |
|-----------------------|-----------|------------|
| Cycloreticulin-A      | ![Cycloreticulin-A Structure](image) | 15         |
| Cycloreticulin-B      | ![Cycloreticulin-B Structure](image) | 15         |
| Reticulatacin         | ![Reticulatacin Structure](image) | 7          |
| Bullatacin            | ![Bullatacin Structure](image)     |            |

(continued on next page)
and famotidine also showed significant decrease in acid volume and contents. The extract showed significant improvement in glutathione and pH level as compared to vehicle treated rats. The study suggested that the significant antiulcer activity of aqueous extract of *A. reticulata* leaves may be due to cytoprotective, anti-secretory and antioxidant potential of phytoconstituents present in the extract.

### 3.5. In vitro cytotoxic and recombinant caspase inhibitory activity

Cell lines were used to investigate in vitro cytotoxic activity of methanol extract of *A. reticulata* leaves. Caspase inhibitory assay was performed using recombinant caspase inhibitory initiator capase (Caspase-9) and executioner capase (Caspase-3 and 6). Leaves were powdered by using mechanical grinder and dried under shade. Petroleum ether (60–80 °C), methanol and chloroform extract was obtained by Soxhlet extraction process. Cytotoxic property of extract was examined against Caco-2 (human colorectal adenocarcinoma), Hep G2 (human hepatocellular carcinoma) and HEK (human kidney carcinoma) cell lines. Doxorubicin 10 μM was used as a standard and maintenance media treatment was considered as a control. The extract showed dose dependent cytotoxic activity against Caco-2 and Hep G2. At concentration 5 μg/ml and 10 μg/ml extract showed 56.02 and 66.64% inhibition against caspase-6 and 76.35 and 87.03% inhibition against caspase-9 respectively. Such effects were not observed against caspase-3. The study concluded that the extract is effective against colon and liver cancer and might be effective in the treatment of degenerative disorders.

### 3.6. Antinociceptive activity

Acetic acid induced gastric pain model was used to screen antinociceptive potential of methanolic extract of *A. reticulata* leaves using in Swiss albino mice. The air-dried leaves were powdered and extracted with methanol (1:5 w/v) for 48 h. Swiss albino male mice of 20–25 g weight were selected and divided into different groups each containing six mice. Control group was treated with vehicle whereas standard drug treated group received aspirin at doses of 200 and 400 mg per kg body weight. Mice of remaining groups were treated with extract at the doses 50, 100, 200 and 400 mg per kg body weight. After 60 min of extract treatment the mice were intraperitoneally injected with 1% acetic acid at a dose of 10 ml per kg body weight to induce writhings. Number of writhings induced by acetic acid was counted for 10 min. The extract treated mice at 50, 100, 200 and 400 mg per kg body weight showed 33.2%, 47.0%, 58.7%, and 69.5% inhibition respectively as compared to standard aspirin at doses of 200 and 400 mg per kg body weight.

### Table 3 (continued)

| Plant part | Extraction procedure | Activity | Screening method/model | Results | References |
|------------|----------------------|----------|------------------------|---------|------------|
| Leaves     | Cold maceration      | Antipyretic | Injecting aqueous suspension of Brewer’s yeast. | Proved | 30         |
|            | Soxhlet              | Antihyperglycemic | Oral glucose tolerance tests in glucose loaded mice. | Proved | 12         |
| Bark       | Soxhlet              | Antinociceptive | Analgesic activity by Hot plate method. | Proved | 16         |
| Seed       | Soxhlet              | Wound healing and antimarking activity | Creating wounds in paravertebral area | Proved | 36         |
weight showed reduced number of writhings by 47.0, 55.1, 67.3 and 69.4% respectively. The extract exhibited significant dose-dependent effect which indicates presence of phytoconstituents in the leaves having potent antinociceptive activity.

3.7. Analgesic and CNS depressant

Petroleum ether, ethyl acetate and methanol extracts of *A. reticulata* bark showed significant analgesic activity. Extracts were prepared by successive solvent extraction process. The percentage yields of extracts obtained were petroleum ether 2.3% w/w, ethyl acetate 5.58% w/w and methanolic 13.13% w/w. Analgesic activity was carried out by the hot-plate method whereas central nervous system depressant activity was assessed using locomotor activity assay and pentobarbitone sleeping time test. For both the studies Swiss albino mice of either sex weighing 20–25 g were selected. Extract at a dose of 100 mg/kg was used for both studies. Pentazocin lactate injection 20 mg/kg intraperitoneally used as standard for analgesic activity. Locomotor activity was evaluated using actophotometer where diazepam 2 mg/kg intraperitoneally was used as standard. Sleep was induced by pentobarbitone sodium at 40 mg/kg in the mice and the time interval between losing and regaining of righting reflex was measured. The phytochemical study showed presence of terpenes and steroids in petroleum ether extract, alkaldoids and flavonoids in ethyl acetate extract while tannins, flavonoids and glycosides were observed in methanol extract. The petroleum ether extract treated mice showed highest increase in reaction time and significant reduction in the locomotor activity. Also petroleum ether extract potentiated pentobarbitone sodium induced sleeping time. Significant central analgesic activity was exhibited by the extracts in hot plate method. All extracts exhibited mild to moderate central nervous system depressant activity which might be due to increased concentration of GABA in brain.

3.8. Analgesic and anti-inflammatory

The sesquiterpene fraction of *A. reticulata* bark was screened for central as well as peripheral analgesic and anti-inflammatory activities. Study was carried out using sesquiterpene fraction obtained from unsaponified petroleum ether extract which contains mixture of three major sesquiterpenes. The percentage of sesquiterpene present in the fraction was 71.66%. Sesquiterpene fraction was studied by GC/MS which showed presence of copaene (35.40%), patchoulan (13.49%) and 1H-cycloprop(e)azulene (22.77%). Eddy’s hot plate test and acetic acid-induced writhing method was used to screen central as well as peripheral analgesic activity whereas carrageenan-induced paw oedema method was used to evaluate anti-inflammatory activities. Significant central as well as peripheral analgesic activity was observed for sesquiterpene fraction at doses 12.5 and 25 mg/kg and for unsaponified petroleum ether extract at a dose of 50 mg/kg. Pentazocin and aspirin were used as standard for analgesic activity. The significant dose-dependent inhibition of carrageenan-induced paw oedema was found in the groups treated with unsaponified petroleum ether extract and sesquiterpene fraction. The effects shown by extract and fraction were comparable with that of standard drug, aspirin.

3.9. Antiproliferative activity

Antiproliferative potential of aporphine alkaloids liriodenine, norushinsunine, reticuline and one acetonogen neoanthonin isolated from the roots of *A. reticulata* has been investigated against A-549, HeLa, MDA-MB cancer cell lines and normal cell line (Vero cells) by MTT assay. The compounds were structurally identified by 

3.10. Wound healing and antimarking activity

Ethanolic seed extract of *A. reticulata* was investigated for antimarking and wound healing potential in combination with neem oil, honey and ghee. Seeds were dried, powdered and extracted in soxhlet extractor using methanol as a solvent. Ointment was formulated containing *A. reticulata* seed extract (10 g), grape seed extract (3 g), ghee (4 g), honey (2 g) and neem oil (2 g). For the study 24 male Wister Albino rats weighing 150–200 gm were used. Rats were anesthetized by intraperitoneal injection of ketamine (50 mg/kg) and back surface was shaved to create wounds. Para vertebral area was selected and wounds of thickness 500 mm² were created in the rats. Rats were divided into control group treated with simple ointment B.P, standard drug treated group, 5% w/w test ointment treated group and 10% w/w test ointment treated group. All rats were treated from day 0 to day 27 once in a day. Wound area was observed for the progress in the wound healing and percentage reduction in original wound size was determined by measuring the wound area on graph paper.

Also one incision of thickness 6 cm was made on para vertebral area and stitched with nylon thread. No antimicrobial drugs were used during this period. Rats were treated with test formulation (5% w/w and 10% w/w ointment), standard drug (nitrofurazone ointment) and simple ointment B.P. for twice daily, until complete recovery is obtained. On day 8 sutures were removed. The complete healing strength or tensile strength of healing of incision wound was measured on day 10. The test formulation treated rats showed faster wound closure and wound contraction as compared to other rats. Significant increase in tensile strength was observed in formulation treated rats. The tensile strengths for 5% w/w ointment treated group and 10% w/w ointment treated group were 579 ± 22.7 and 673 ± 15.9 respectively which were comparable with that of Standard ointment treated group (659 ± 271). Study suggested that the test formulation is equally effective as that of standard drug formulation.

3.11. Antioxidant and antimicrobial activity

The root extract of *A. reticulata* was investigated for antioxidant and antimicrobial potential. DPPH free radical scavenging and hydrogen peroxide assay were employed for antioxidant screening. Antibacterial and antifungal study was performed using agar cup method and poison plate method. Roots were dried, powdered and extracted by Soxhlet apparatus. Antioxidant activity was determined by DPPH free radical scavenging assay and hydrogen...
peroxide (H$_2$O$_2$) assay at 20, 40, 60, 80 and 100 µg/ml concentrations of extract and absorbance was measured at 517 nm and 230 nm respectively. Antibacterial activity was carried out against three gram negative (Escherichia coli, Salmonella typhi, Pseudomonas aeruginosa) and gram positive (Staphylococcus aureus, Bacillus subtilis, Bacillus cereus) strains of bacteria using nutrient agar media. The antifungal activity of the extract was carried out against Aspergillus niger, Penicillium chrysogenum, Fusarium moniliforme, Aspergillus flavus, Trichoderma viride, and Candida albicans using potato dextrose agar media. For antibacterial study 100 ml of DMSO was used as negative control and antibiotic disk, penicillin as standard reference antibiotic (positive control). Zone of inhibition of extract sample was measured by antibiotic scale and compared with standard. Similarly for antifungal study DMSO was employed as negative control and 1% griseofulvin as positive control. Increase or decrease in growth of fungi was considered to evaluate antifungal activity. Extract exhibited dose dependent scavenging as that of standard, ascorbic acid. Extract was found to have pronounced ability to inhibit $B$. cereus and also exhibited significant activity against all strains of bacteria. Predominant antifungal activity was showed against $T$. viride, and $C$. albicans fungi. The results obtained from this study revealed that root extract of $A$. reticulata has remarkable antimicrobial activity.

4. Conclusion

Over the last several years plants have been recognized as an imperative source of medicines. Exploration of phytochemicals derived from different plant parts as potential bioactive agent has imperative sources of medicines. Exploration of phytochemicals has remarkable antimicrobial activity. This review also explores attempts to focus multiple aspects of $A$. reticulata Linn. (牛心果) which might be helpful to researchers and scientists working on plant based bioactive agents.

Conflict of interest statement

The authors declare no conflict of interest.

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