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A COMPREHENSIVE REVIEW ON *ANNONA RETICULATA*

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ABSTRACT: Indian literatures like Ayurveda and various ancient literatures have stated herbal remedies for a number of human ailments. *Annona reticulata* which is commonly known as bullock's-heart in English and Ramphal in Hindi and Marathi is having various pharmacological activities such as antioxidant, anticancer, analgesic and CNS depressant, antimalarial, anthelmintic, in syphilis and few more. Some compounds have been isolated and reported from the extract of various parts of the plant possessing good pharmacological activity. The studies performed on the seed and root extract also evidenced that the same compounds causes cell death in various cancer cell lines. This review article is a sincere effort to put forward the medicinal importance and botanical, phytochemical, pharmacological details of the plant.

INTRODUCTION: The medicinal plants are rich in secondary metabolites and essential oils of therapeutic importance. The important advantages claimed for therapeutic uses of medicinal plants in various ailments are their safety besides being economical, effective and their easy availability. Because of these advantages the medicinal plants have been widely used by the traditional medical practitioners in their day to day practice. From various plants which are known for their medicinal value, the plants belonging to genus *Annona* are rich in phenolic compounds and are very useful for their therapeutic potentials. The *Annona* genus (Annonaceae) consists of about 119 species¹. *Annona reticulata* is a semi-evergreen and small deciduous tree from the plant family Annonaceae².

It is well known for its fruit, commonly called custard apple having flavor sweet and pleasant, which is a very common name, shared with fruits of various other species belonging to same genus: *A. cherimola*³, *A. chrysophylla*⁴ and *A. squamosa*¹³ or sometimes it is called bullock's-heart, wild-sweetsop, or ox-heart.

ECOLOGY AND DISTRIBUTION:

History of cultivation: Plant is native of Caribbean region and has also been spread across Central and South America, Africa and Asia. *Annona* species is cultivated all over India for its edible fruit belonging to custard apple family. All parts of annona are used in natural medicine in the tropics. It is considered to be good source of natural antioxidants for various diseases. Therefore, attention in recent times has been focused on the isolation, characterization and utilization of natural antioxidants². In India the tree grows wild in many areas but is cultivated, especially around Calcutta⁵. It was found in tropical Africa in the 17th century and is grown there as a dooryard fruit tree.

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It has long been naturalized and cultivated as far south as Peru and Brazil and is grown mostly in the Bahamas and occasionally in southern Florida and Bermuda. It is very common on the east coast of Malaysia, and throughout Southeast Asia and the Philippines⁶.

Geographic Distribution:

Exotic: Mexico Bahamas, Bermuda, United States of America, Guam, Philippines, Malaysia, Peru, Brazil, South Africa, India.

Native: Guatemala, Belize.

Natural Habitat: *Annona reticulata* is a pantropic tree which needs a tropical climate and it grows in the coastal lowlands of Ecuador to 1500 m. In Guatemala, it is nearly always found below 1,220 m. The custard apple tree grows between 0-1500 m in the areas of Central America that has alternating seasons and has spread to South America. In Sri Lanka, it cannot be grown above 915 m but in India, its better from the plains up to an elevation of 1220 m while. Also it is common below 800 m around the Luzon in the Philippines. Leaves of *Annona reticulata* are shed at the first onset of cold weather and the tree is dormant throughout winter. It has survived temperatures of 3° - 2°C without serious harm when fully grown. The species prefers a more humid atmosphere⁶. The custard apple grows better in deep, low-lying, rich soil with good drainage and sufficient moisture. It grows wild in light sand, also in southern Florida it grows to full size on oolitic limestone and various other types of soils.

PROPAGATION AND MANAGEMENT⁶:

Propagation Methods: *Annona reticulata* is generally propagated by seed, the germination rate of which ranges from low to medium. The tree can be multiplied by inarching, grafting or budding onto its own seedlings or onto other annona spp. Rootstocks.

Germplasm Management: Seeds remain viable for more than 12 months in air-dry storage at 5°C.

Tree Management: *Annona reticulata* grows and responds faster to organic fertilizers, mulching, and frequent irrigation if there is dry weather during the growing period. Bullock's-heart is having

advantage of cropping in spring and also late winter when the other members of the genus are not in this season. Form of the tree can be improved by judicious pruning. With ample care, a mature tree can produce 34-45 kg of fruits per year.

Taxonomic Classification⁷:

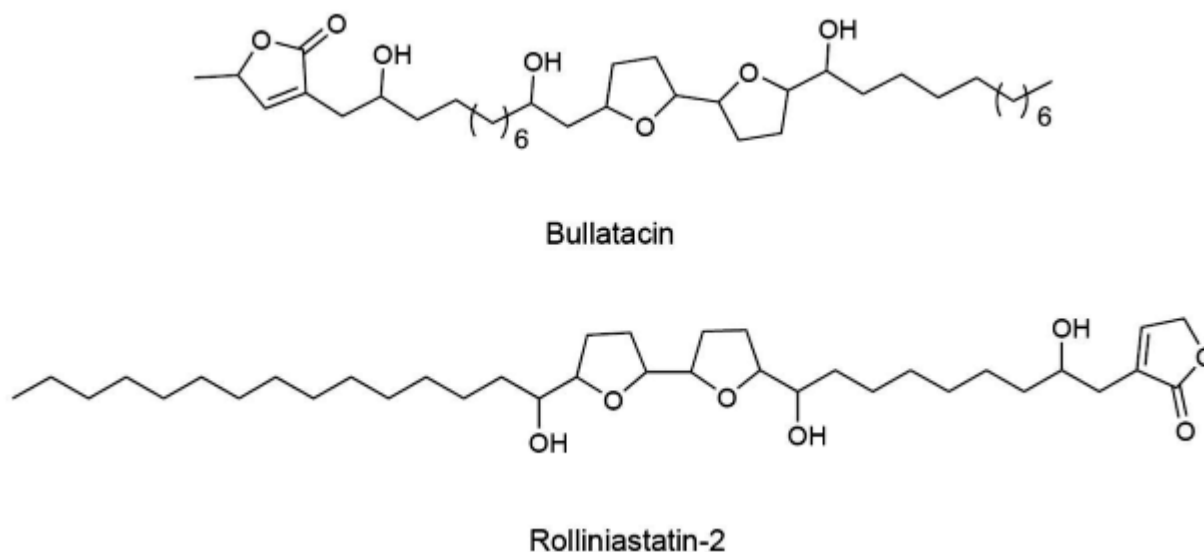
Kingdom	: Plantae
(Unranked)	: Angiosperms
(Unranked)	: Magnoliids
Order	: Magnoliales
Family	: Annonaceae
Genus	: <i>Annona</i>
Species	: <i>A. reticulata</i>

Binomial Name: *Annona reticulata* L.

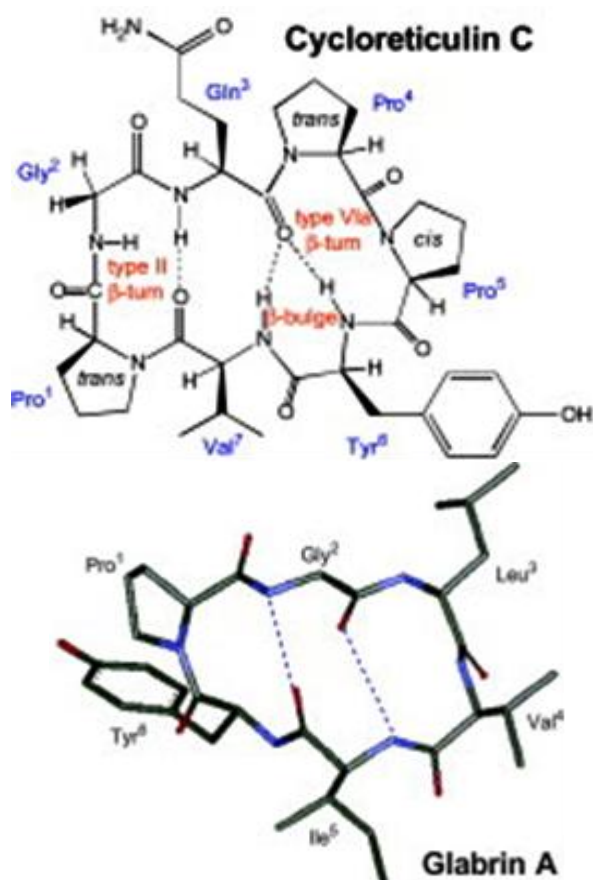
Description of plant:

Vernaculars: *Annona reticulata* is known by different names in different languages around the world including the Indian sub-continent. In English, it is known as Custard apple, Jamaican apple, Sugar apple, Netted custard apple, Bullock's heart, Sweetsop, In Malaysia it is known as Lonang, Nona kapri, while in Thailand as Noi nong. In Spanish as Anona colorada, Anona de seso Anona de redecilla, Anona roja, Corazón, Anona rosada, Mamon in French known as Corossol sauvage, Bois Cachiman, Coeur de boeuf, cachiman, while in Hindi it is called as Luvun, Ramphal, Nonai⁸.

Botanical description of the plant: *Annona reticulata* L. belonging to family Annonaceae is a low, erect tree with spreading or rounded crown and the trunk measures to about 25-35cm in diameter. It grows up to 10m high. The leaves are narrow-lanceolate, alternating, oblong and deciduous measuring to about 10-20 cm long and 2-5cm wide with conspicuous veins and bad smell. The flowers are, fragrant in drooping clusters, slender, with 3 outer narrow, fleshy petals 2-3cm long which are never fully opened. The fruit is measuring about 8-16 cm in diameter, they may be irregular, symmetrically heart-shaped, nearly round, or lopsided and are having a depression at

FIG. 3: BULLATACIN AND ROLLINIASTATIN-2²⁵

Two cyclopeptides, the cycloheptapeptide cycloreticuliculin C, *cyclo*(Pro¹-Gly²-Gln³-Pro⁴-Pro⁵-Tyr⁶-Val⁷) and the cyclohexapeptide glabrin A, *cyclo*(Pro¹-Gly²-Leu³-Val⁴-Ile⁵-Tyr⁶) have been isolated from the methanol extract of the seeds of *Annona reticulata* and Sequence and three-dimensional structure of cycloreticuliculins A and B, new cyclooctapeptides was identified^{13, 14}. It is as shown below in **figure 4**.

FIG. 4: CYCLORETICULIN C AND GLABRIN A^{13, 14}

N-fatty acyl tryptamines were also obtained from *Annona reticulata*¹⁴. Ogunwande and Ekundayo has obtained hydrodistilled oil from the leaves of *Annona reticulata* L., grown in Nigeria. Thirty nine compounds were characterized. These consisted of 18 monoterpenes amounting to 29.0%, 20 sesquiterpenes totaling 52.9% and one aromatic esters making upto 10.9%, the oil contained (E, E) farnesyl acetate (19.0%), ar-turmerone (12.0%), benzyl benzoate (10.9%) and gamma-terpinene (7.4%) as the major constituents¹⁹.

PHARMACOLOGICAL STUDIES:

Antioxidant Activity: A study was carried out on three well known species of *Annona* for the antioxidant activity. Different in vitro models were used for this study like 1, 1-diphenyl-2-picryl hydrazyl (DPPH) model, 2, 2-azinobis-(3-ethylbenzothiazoline-6-sulphonate) (ABTS) model, nitric oxide, superoxide, hydroxy radical and lipid peroxidation models. Study was found to be helpful in proving that the leaves extracts of *A. reticulata* showed better activities in quenching DPPH and superoxide radicals hence antioxidant potential of plant².

Anti-Cancer Activity: Annonaceous acetogenins are a group of constituents obtained from plants belonging to Annonaceae, having potentials of anti-neoplastic agents. Acetogenins are potent cytotoxic inhibitors of the mitochondrial NADH:ubiquinone oxidoreductase (complex I of the respiratory chain). A study shows that main five annonaceous acetogenins which are solamin, annoreticuliculin-9-

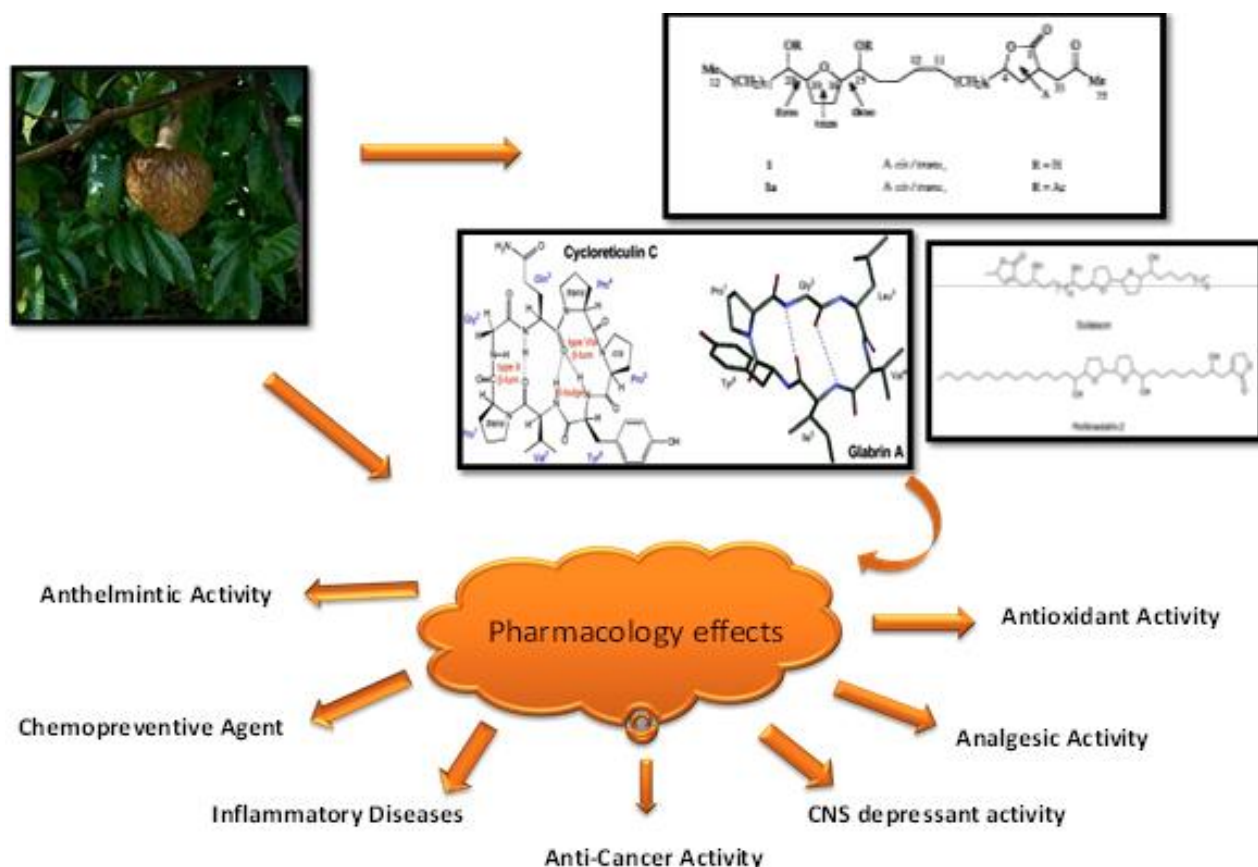
one, annomonicin, squamone, and rolliniastatin are having cytotoxic activities. Acetogenins isolated from the seeds of *A. reticulata* are bullatacin, cis-/trans-isomurisolenin, cis-/trans-bullatacinone, annoreticulin, annoreticulin-9-one, cis-/trans-murisolinone and squamocin.

Potent cytotoxic activity was shown by some of these compounds against Hep.G2, Hep.2, 3, 15, KB and CCM2, four cancer cell-lines. After further purifying annonacin it was studied for its biological activity and found that these compounds caused cell death in various cancer cell lines including T24 bladder cancer cells.

Squamocin isolated from the seeds of *A. reticulata* was also analysed for its biological effects and proved that squamocin is a cytotoxic constituent for nearly all the cancer cell lines tested^{3, 4, 20, 21}. The ethanol extract exhibited a significant *in vitro* and *in vivo* inhibitory activity against melanoma tumor cells. Alkaloids are also known to possess cytotoxic properties.

Ethanol and aqueous extract of roots of *Annona reticulata*, are evaluated for the *in vivo*, against melanoma cells in mice for anticancer activity and also *in vitro* for inhibitory activity on MDA- MB-435 human melanoma cells by the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] colorimetric assay and it was found that the ethanol extract significantly reduces growth of tumor as compared with positive control and shows a promising inhibitory activity against human melanoma cell lines at a very less concentration ranging between 10 and 40 μg however the aqueous extract was found to exhibit lesser activity at the same concentration.

Simultaneously, ethanol extracts *in vitro* inhibition towards the *vero* cell line proliferation was found to be lower in comparison with cancer cell lines²². Also *Annona reticulata* leaves shows *in vitro* cytotoxic and human recombinant caspase inhibitory effect which was studied by Susanta *et al*²³. Hence, *Annona reticulata* gets qualified as a chemopreventive agent in cancer therapy.



GRAPH 1: ANNONA RETICULATA WITH DIVERSE PHARMACOLOGICAL SPECTRUM

Anthelmintic Activity: The aqueous leaf extract has also been reported to have anthelmintic activity²⁴.

Inflammatory Diseases: Nine compounds were characterized from the leaves of *A. reticulata* L, by Thang et al., 2013 and their inhibitory activity on NO production was examined. The results provide a potential explanation for the use of the leaves of *A. reticulata* as an herbal medicine in the treatment of inflammatory diseases, and they may be potentially useful in developing new anti-inflammatory agents¹.

Analgesic and CNS depressant activity: Bhalke and Chavan [2011] investigated that Analgesic and CNS depressant activity potency increases from ethyl acetate, methanol and petroleum ether extracts. All the extracts exhibited significant central analgesic activity in the hot plate method in mice. All the extract showed statistically significant mild to moderate central nervous system depressant activity assessed by locomotor activity assay and pentobarbitone sleeping time test²⁵.

CONCLUSION: The Mother Nature has provided us with a huge count of flora and fauna. Some of the natural medicinal plants are so common that we use them in daily life without knowing their medicinal importance. *Annaona reticulata* is the best example of it. The extensive survey literature reviewed that *Annona reticulata*, is an important medicinal plant with diverse pharmacological spectrum.

Few novel chemical constituent isolated from the *Annona reticulata* showed anti-cancer, properties for bladder cancer and various cancer cell lines too. It's found to be a chemopreventive agent in cancer therapy. Further evaluation is needed to be carried out on *A. reticulata* in order to explore concealed areas and their practical clinical application, which can be used for the welfare of the mankind.

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