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Rubia Cordifolia: A comprehensive review of its phytoconstituents and pharmacological profile

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Abstract
Herbal medicines are increased favored due to their powerful curative efficacy, acceptable safety profile, and less apart from having significant therapeutic to their availability and efficacy. The increasing viability of herbal remedies for treatment along with their minimal side-effects has led to a renewed interest in extraction and formulation technologies. The plant has been reported to exhibit numerous pharmacological properties, such as antioxidant, anticancer, astringent, anti-acne, antiinflammatory, antimicrobial, anti-dysenteric action, antiseptic nature as well as kidney-protective, anti-rheumatic and liver-supporting effects. Originating from the diverse Ayurvedic medicine, *Rubia cordifolia* also known as *R. cordifolia,* the plant which is commonly known as 'Indian Madder'. This plant's scientific name is *R. cordifolia* Linn, known as vasantikarma could be illustrated from different other classical texts nighantus including Acharya Charaka, Acharya Sushruta, Acharya Vagbhata. Some nighantus also mention the therapeutic applications of various establishment of juice extracts from different parts of *R. cordifolia.* This review paper presents comprehensive data on synonyms, morphological and micromorphological, phytochemical constituents, medicinal applications and various pharmacological activities.

Keywords: Manjishta, *Rubia cordifolia*, anti- cancer, Indian madder, pharmacological activity, anti-acne

Introduction
The natural world provides solutions to countless health concerns, and Ayurveda medical tradition, enriched with a vast assortment of therapeutic plants suitable for internal and external applications has been practiced since the Indus Valley Civilization and are increasingly favored today because they support skin health and contribute to aesthetic improvement [1, 2]. *R. cordifolia* often grows woods 3750 meters. It is a climbing herb which can be prickly or scabrous. Petioles are quadrangular, glabrous, shiny, and occasionally thorny on the angles. The leaves show considerable variation, typically arranged in groups of four around the stem. Their shape ranges from heart-shaped ovate forms to longer ovate lanceolate types, often displaying a slightly hearted base [3]. Stipules are absent. The stems are thin and rough to the touch, distinctly four-angled, and bear backward-curving prickles along their ridges. These stems can extend for several meters and gradually develop a woody texture near the base. The plant produces greenish-white blossoms that appear in cymose clusters. Once mature, the fruits become smooth, glossy, and purplish-black, usually appearing as round or twin-lobed structures [4]. All of our issues can be solved by nature, and the oldest medical system, Ayurveda, is strengthened by a vast range of medicinal herbs that can be applied topically or internally to treat a variety of ailments. For a long time, cosmetics have been an important part of women's lives. They help women look beautiful, which in turn supports their mental well-being and self-confidence [5].

Plant Profile
Rubia cordifolia, known as Indian Madder or Manjistha, is a perennial climbing herb in the Rubiaceae family, famous for its reddish roots used for dyes and significant Ayurvedic medicine, featuring heart-shaped leaves in whorls, small greenish flowers, and red berries, acting as a detoxifier, blood purifier, and skin healer for issues like acne, eczema, and inflammation.

It's a rough, quadrangular-stemmed climber with tiny hooks, growing across Asia, Africa, and Europe, valued for its anti-inflammatory, antioxidant, and potential anti-cancer properties, making it crucial in traditional medicine systems.

Table 1: Taxonomic Classification [6, 7]

Category	Description
Kingdom	The plant is part of the Kingdom Plantae.
Class	It belongs to the group of flowering plants categorized as Dicotyledoneae.
Subclass	It falls under the Sympetalae subclass, which includes species with fused petals.
Family	The plant which is Rubiaceae family, many medicinal species.
Genus	It is classified under the genus Rubia.
Species	The botanical species name is *Rubia cordifolia*.
Common Name	Widely recognized by the name Manjishta in traditional medicine.

Geographical Distribution

The plant grows widely in the Himalayan regions, beginning from the north-west frontier and extending eastward toward Sri Lanka and the Malay territories. It is also native to tropical Africa, China, Japan, and the island of Java. Additionally, it is reported from many regions. Reproduction occurs through seed formation as well as stem cuttings. Four distinct forms of *R. cordifolia* have been identified.

Morphological description

The plant which leaf-shedding characterized by thin stems about one-quarter inch wide. These stems are soft, pliable, and can grow as long as ten feet. The basal part is generally tender but becomes woody and remains intact for extended periods. The branchlets may be smooth or distinctly four-angled. Its flowers are small, under an inch in size, arranged in terminal cymose inflorescences that arise on leafy panicles. The blossoms exhibit shades of dark red or pinkish brown. The fruit is spherical, fleshy, and succulent, changing from deep purple to black when ripe, and contains bright scarlet juice [8].

Macroscopic

Root-The root is rounded and thin, usually showing a knot-like crown where the rootstock starts. Its size ranges from 2-9 cm long and 0.2-0.6 cm thick. The surface is smooth with delicate longitudinal lines, sometimes slightly grooved, and frequently marked with scars from lateral roots. It shows a dark reddish-brown coloration inside and outside. On breaking, the fracture is short, the taste is somewhat sweet but acrid and unpleasant, and it emits a pleasant aroma.

Microscopic

The phloem consists of parenchymatous parts, companion cells, and sieve tubes in eight to twelve concentric layers. Vessels, fibers, tracheids, and xylem parenchyma are all present in the xylem; the vessels get bigger as they approach the outside xylem region. They are between 18-90 µm wide and between 30-270 µm long. The cortical and phloem parenchyma cells of the medullary rays, which can be found in one or more layers, contain spherical to oval starch grains (Figure 1).

Powder

The material includes pieces of cork tissue, lignified xylem vessels, tracheidal elements, fibers, needle-like raphides, aggregated crystals, granular oxalate deposits, parenchyma cells with red-colored contents, and abundant starch granules [9].

Fig 1: *Rubia Cordifolia* Plant [9].

Cultivation and harvesting

R. cordifolia prefers moist, fertile loam soils in regions with heavy rainfall and must be supported as it grows as a climber. Propagation can be done using seeds or two-node root segments, with seeds being more economical and offering superior germination performance. Nursery development typically, using either seeds or root parts that have been treated. Although certain plant parts exhibit up to 90% success in establishment, seed propagation remains the more economical method, achieving 80-85% germination within approximately 20 days. For raising nursery beds to cover one hectare, about 350 g of seed is required, whereas direct field sowing necessitates a substantially larger seed quantity [10].

Chemical Constituents

The major bioactive components of *R. cordifolia* comprise quinones, iridoids, oleanane triterpenoids, bicyclic hexapeptides, and several anthraquinone molecules.

As per previous studies to characterize a bicyclic peptide belonging to the RA-series. RA-III through RA-VII were obtained from the benzene-soluble portion of the methanol extract. Structural analysis allowed the identification of anticancer, RA-VII, and RA-X. RA-VII was found to suppress protein synthesis. Additionally, a RA-X methyl ester derivative, modified at the second amino acid position with alanine, was synthesized to evaluate its cytotoxic effects against P388 leukemia cells and KB cell lines in vitro [11-17].

Conformational studies of N-Dem ethyl-Tyr (OCH_3)-3 indicated that RA-VII assumes a constrained structural arrangement after undergoing hepatic microsomal metabolism [18]. The antitumor potential has also been documented for its glucoside derivatives and for related compounds such as RA-XI, RA-XII, RA-XIII, RA-IV, 2-aminobutyric acid[1]-deoxybouvardin, and several other analogues [19-21]. In contrast, RA-XVII showed only minimal alterations in its molecular conformation [22]. Root extracts were used to identify the structures, a dimeric anticancer bicyclic hexapeptide [23-24]. O-seco-RA-V, a cyclic hexapeptide, researchers reported the discovery of two novel bicyclic six peptides [25].

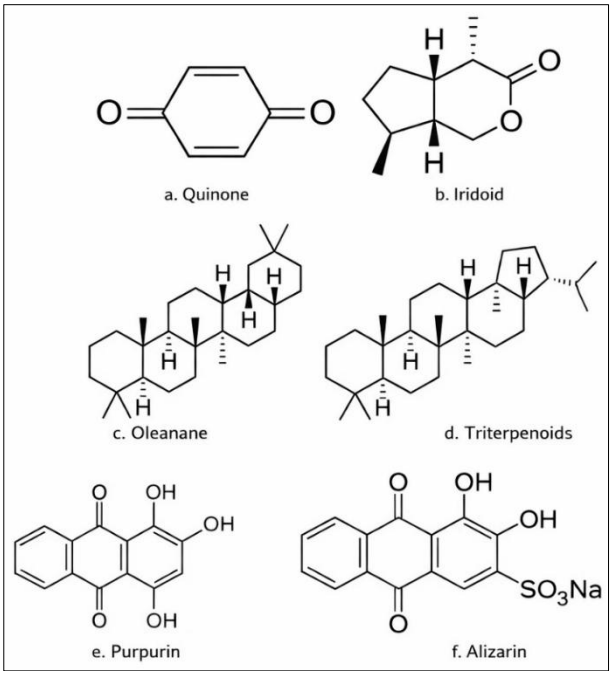

Fig 2: Chemical constituents in *R. Cordifolia*

Traditional therapeutic uses

In Ayurvedic practice, *R. cordifolia* is regarded as a highly important medicinal plant with uses:

The dried and powdered roots and fruits of the plant are traditionally used internally for the treatment of various skin conditions and spleen-related disorders. It is also applied externally in the management of major burns, ulcers, and bone fractures. The herb acts as a general tonic, helps in relieving cough, and is beneficial in cases of prolonged low-grade fever. Internally, the roots are employed in the treatment of abnormal uterine bleeding, hemorrhages, bronchitis, rheumatism, kidney and bladder disorders, gallstones, and dysentery, and are also considered useful in managing blood-related ailments. Overall, the roots exhibit a wide range of medicinal properties, including alterative, analgesic, anti-inflammatory, astringent, diuretic, expectorant, styptic, and wound-healing activities [26-29].

Pharmacological Activity

Antibacterial Activity

As per previous studies investigating the antibacterial effects of plant extracts have tested the stembark of ventilago madraspatana, the roots of *R. cordifolia*, and root-bark of *Lantana camara*, using solvents with varying polarity and agar-well diffusion method. In these experiments, twelve bacterial strains were used, contains six gram-positive and six gram-negative organisms. The findings revealed that exhibited stronger effect against gram-positive bacteria. Moreover, methanol extracts of both plants were effective against the gram-negative strain Pseudomonas aeruginosa, with inhibition levels rising in proportion to the concentration. Among the tested extracts, *R. cordifolia* demonstrated significant antibacterial activity, comparable the other effects [30-33].

It is reported that the results from an in-vitro study on 12 bacterial strains six gram +ve and six gram-ve indicated that *R. cordifolia* chloroform and methanol extracts effectively suppressed all gram-positive species. Furthermore, the methanol extract showed dose-dependent inhibition of the gram-negative bacterium *P. aeruginosa* [34].

Wound Healing Activity

This activity potential of an herbal composition containing *R. cordifolia* has been evaluated in the earlier reports. A cream that has been made from the mixture of herbal substances. *In vivo*, in animal experiments wound healing was followed every day for 20 days where in the observations were made on wound contraction, epithelization time and histopathological examination. The ointment remarkably promoted wound contraction and expedited epithelization in excision wound studies [35].

In Ayurveda, a number of plant, animal and mineral derived substances are used in the treatment of skin disorders. Additionally, research has been shown that *R. cordifolia* possesses significant wound-healing properties [36].

The fraction was shown to stimulate terminal differentiation and suppress keratinocyte proliferation in cultured human keratinocytes, suggesting potential antipsoriatic properties. A Cornified Envelope (CE) creation assay was used to assess the effect; EA fraction considerably increased CE formation [37]. In addition to causing histopathological changes, reported promote wound healing and enhance functional recovery [38].

Antioxidant Activity

R. cordifolia contains several antioxidants, including alizarin, hydroxylated anthraquinones, [39] and rubiadin, which have been utilized in various medicinal applications. The presence of hydroxyl groups on the anthraquinone nucleus is essential for the biological activity of hydroxylated anthraquinones. Glycosylation tended to reduce their potency, whereas an ortho-dihydroxy arrangement substantially enhanced their effectiveness [40].

In previous investigation evaluating in *vivo* antioxidant effects and the modulation of ethanol-induced immunosuppression, simultaneous daily administration of madder was shown to prevent the decline in humoral and cell-mediated immunity. It also preserved the phagocytic index, total leukocyte count, glutathione count producing results comparable to combined supplementation with vitamins E and C [41]. The exhibited the strongest capacity, primarily their glycosidic derivatives. Extracts of *R. cordifolia* also demonstrated the ability to inhibit and reduce homogenates, showing activity comparable to that of vitamin E and p-benzoquinone [42].

As per research done the free radical-neutralizing potential of *R. cordifolia* extracts was evaluated using the DPPH assay, while their ability to inhibit lipid peroxidation was analyzed through the TBARS procedure. Several researches the extract also showed notable antibacterial action against Propionibacterium acnes, exhibiting MIC of 600 mcg/ml as established by broth dilution method. The methanolic extract demonstrated strong inhibition of lipid peroxidation, with an IC_{50} of 138 µg/mL and a high correlation coefficient (R^2=0.9921). In comparison, curcumin exhibited greater potency, with an IC_{50} of 50 µg/mL and an R^2 of 0.9469. These findings indicate that *R. cordifolia* has significant anti-acne potential by suppressing the proliferation of P. acnes, thereby helping to prevent related skin complications [43].

Anticancer Activity

Cancer remains a major health problem worldwide, which is why natural products with selective antitumor effects are of interest for further work. Methanolic extract of *R. cordifolia*

has been reported effectively inhibit the proliferation of human cervical and laryngeal carcinoma cells with lower cytotoxicity to normal kidney cells based on in vitro study. This selective action implies that *R. cordifolia* could be a valuable reservoir of anticancer compounds suitable for therapeutic development [44].

Multiple fractions derived from the roots of *R. cordifolia* have demonstrated anticancer potential in both in vitro studies and animal-based bioassays [45]. Significant antitumor effects were also observed with quinones and the compound RC-18 [46, 47], several various leukemic models. These hexapeptides exert their action by binding to the eukaryotic 80S ribosomal subunit, thereby blocking aminoacyl-tRNA attachment and peptidyl-tRNA translocation, ultimately suppressing protein synthesis [48]. According to studies, cyclic hexapepetide extracted from dried roots had antitumor action [49].

Anti-inflammatory and Analgesic activity

Rubimallin, a constituent, has been recorded possess anti-inflammatory properties. It has been reported that the aqueous extract exhibited a dose-dependent reduction in carrageenan-induced paw edema in rats, producing effects comparable to those of phenylbutazone [50]. Notable nitric oxide scavenging action was demonstrated by a few *R. cordifolia* preparations [51]. It has also been discovered that a formulation including purpurin and munjistin from cell culture exhibits antiproliferative properties during the quick development of a model edema [52].

R. cordifolia has been traditionally reported to alleviate symptoms such as itching, burning, and skin exudation [53]. The extract demonstrated the ability to suppress, thereby reducing formation of aromatic hydroperoxides Since these hydroperoxides are involved in generating key inflammatory mediators such as leukotrienes, its inhibition suggests inflammatory conditions, like asthma, arthritis, other related disorders [54].

Hepatoprotective Activity

As per previous research using animal models has shown that the methanolic extract provides protective effects against liver damage caused by thioacetamide-induced hepatotoxicity [55]. In addition, the aqueous-methanol extract has demonstrated significant hepatoprotective activity in rats exposed to acetaminophen and CCl_4-induced liver injury [56]. Additionally, it has been discovered to stop CCl4 from prolonging pentobarbital-induced sleep duration, supporting the extract's hepatoprotective qualities. Rats' liver damage from CCl4 has been shown to return to normal after 14 days of oral rubiadin treatment [57]. Additionally, by preventing human hepatoma cells from secreting hepatitis B surface antigen, rubiadin has been shown to be useful in treating both acute as well as chronic types of hepatitis triggered by infection with the hepatitis B virus [58].

Anti-platelet activating factor activity

R. cordifolia has long been employed in Indian medicine for its blood-purifying properties. As per previous research using rabbit platelets demonstrated that a partially purified extract of the plant prevents the clumping of platelets triggered by the platelet-activating factor molecule (PAF), whereas the thrombin-induced aggregation is unaltered. PAF, a biologically active phospholipid, is involved in thrombosis, allergic reaction and neurological disorders. These data indicate that the extract inhibits binding of radiolabeled PAF to platelets in relation to its concentration and this response may resemble ligand-binding inhibition, whereas a reduced reactivity of receptor is also plausible [59].

Anti-acne property

The development of acne is at least partly associated with an anaerobic bacterium, Propionibacterium acnes, which promotes inflammation through the generation of reactive oxygen species. Previous studies evaluated the anti-inflammatory consequences. PMNLs and monocytes were incubated with P. acnes culture filtrate in the presence or absence of *R. cordifolia*. The results demonstrated that *R. cordifolia* significantly suppressed ROS generation in PMNLs showing potential to suppress inflammatory reactions through decreasing ROS and pro-inflammatory cytokine production, which are responsible for the development of acne [60]. Supporting this traditional use, studies have also shown that *R. cordifolia demonstrates* anti-acne activity efficacy comparable to that of a standard clindamycin gel [61].

Anti-diabetic activity

As per research done as indicates that extracts from both the roots or leaves the exhibit significant in animal models. Notably, suggesting mechanisms of action that extend beyond pancreatic effects [62]. As per previous study it has been reported that the aqueous extract from the roots normalize high blood sugar, high triglyceride levels, in streptozotocin-induced diabetic rats, researchers observed elevated enzyme levels, significant weight reduced [63]. Fasting rats showed improved blood glucose levels after using the leaf extract. In hyperglycemic rats given glucose, it also had a beneficial impact on the way glucose is metabolized. According to reports, the extract was found to the treatment increased protein and high-density lipoprotein (HDL) levels while reducing serum triglycerides and cholesterol in diabetic rats [64]. As per previous study methanolic extract from the roots inhibited the formation of glycated and frustrated guanosine and the modification of these compounds by reactive oxygen species, indicating its antiglycation, antioxidant, and antidiabetic properties [65].

Diuretic activity

Numerous studies have thoroughly examined the pharmacological potential of *R. cordifolia* to support the conventional assertion the diuretic potential and yielded favorable findings [66, 67]. When compared to the reference medications, both the hydroalcoholic and ethanolic extracts it markedly enhanced urine output and promoted electrolyte excretion in a dose-dependent manner [68].

Anti-microbial activity

The antibacterial efficacy of *R. cordifolia* root extracts against several pathogenic bacteria has reportedly been analyzed. Daucosterol and sitosterol have both been reported to exhibit antimicrobial activity. The compound Rubiacordone which is derived from *R. cordifolia* has a potent antibacterial activity. [69] Silver nanoparticles synthesized with green pathways using *R. cordifolia* root extract showed to be highly effective against pathogens, especially Pseudomonas aeruginosa and Plesiomonas shigelloides [70]. However, when these natural dyes were

incorporated into textile fibers, the antimicrobial activity decreased, likely because the dye concentration was below the minimum inhibitory concentration (MIC). Additionally, root extracts of *R. cordifolia* prepared have been using solvents of increasing polarity. [71, 72].

Discussion

The effects of social media on mental health have been a subject of heated controversy for quite some time now. On one hand, social media supporters say it helps people be in touch with another, get support, express themselves, etc. They demonstrate how social media brings attention to serious topics and energies social movements. In contrast, critics blame social media for causing more loneliness, anxiety and depression as another effect.

The notices are hardly convincing about the addictiveness of social media platforms or the ill effects cyberbullying and more have on mental health. Finding a balance, of the good and the not-so-good, serves as an essential foundation for maintaining a positive and constructive relationship with technology in the age of social media.

Pharmacological findings the pharmacological reports have evidenced the traditional claims that *R. cordifolia* may be effective in inflammatory disorders, skin diseases and microbial infections related to these ailments. When tested, the antimicrobial tests indicate a good activity against P. acnes and could be proposed for anti-acne preparations.

Its antioxidant activity, as evidenced by the inhibition of lipid peroxidation and scavenging of DPPH radicals, suggests that it could prevent disorders related to oxidative stress. Similarly, its anti-inflammatory activity has been also linked with the modulation of mediators like COX, iNOS and TNF-α. Although these results are encouraging, heterogeneity in extraction solvents, plant parts.

Future Prospects

Limitations of the review though there have been a good amount of study carried out on *R. cordifolia*, certain areas are still unexplored giving us scope for further research. Furthermore, advanced phytochemical profiling with innovative analytical methods (LC-MS/MS and NMR) may be useful to reveal new bioactive compounds other than the known anthraquinones and bicyclic peptides. These findings might broaden the therapeutic application of *R. cordifolia* in pharmacology.

Its pharmacological activities (free radical scavenging, anti-inflammatory, Antimicrobial and anticancer) have not been explained sufficiently; moreover its medicinal property through reference to the pharmacodynamics is also scarce. In-depth molecular studies including expression of genes and effector cytokines, pathway discovery and receptor binding.

Sustainable farming methods should also be considered. Steady supply without depletion of wild population also demands the development of agro-technology, genetic studies on diversity along with conservation approaches.

In future prospects, adoption of new scientific approaches over traditional knowledge can lead to position *R. cordifolia* as a maximally standardized and internationally recognized source of phytotherapeutics in the near future.

Conclusion

R. cordifolia, commonly known as Manjistha or Indian madder, is rich in anthraquinones and has long been valued in traditional systems of medicine for its diverse phytochemical composition and wide range of pharmacological activities. Almost all parts of the plant are used in traditional and complementary medicine, serving as sources of bioactive compounds that exhibit significant therapeutic potential, including antioxidant, free radical-scavenging, and anticancer properties. Studies suggest that these compounds may act prophylactically, helping to prevent the development of various malignancies. However, conventional methods for isolating these bioactive constituents are often time-consuming and inefficient, highlighting the need for advanced and sustainable extraction techniques to enhance yield within limited time and resources. At the same time, just as scientific progress seeks balance between innovation and efficiency, modern society faces a similar challenge in balancing the benefits and drawbacks of social media. While social media plays a vital role in spreading awareness, fostering connection, and supporting social causes, critics argue that its excessive use contributes to anxiety, depression, and social isolation. Therefore, ensuring that the benefits of technological and scientific advancements outweigh their negative impacts remains essential for promoting overall well-being in the modern era.

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