



Traditional and Modern Use of Indian Madder (*Rubia cordifolia* L.): An Overview

Devi Priya M, E.A. Siril*

Department of Botany, University of Kerala, Kariavattom, Trivandrum 695 581, India.

*Corresponding author's E-mail: easiril@yahoo.com

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ABSTRACT

Rubia cordifolia (Indian Madder) is an age old ethnic medicinal plant in India. The chiefly valuable plant part is its root stocks, which contains phytochemicals like anthraquinone, terpenes, glycosides etc... and are recognized as the active curative agents to wide and diverse forms of ailments. A comprehensive scan on available literature revealed that the medicinal property of the plant is well documented and we summarized all the available information of *R. cordifolia* to help those researchers who are interested to work on this magnificent plant in future.

Keywords: *Rubia cordifolia*, anthraquinone, root extract, anticancer.

INTRODUCTION

R*ubia cordifolia* (Indian Madder) is growing most often near streams and rivers along the upper Ghats in evergreen forests up to 3750m above sea level. It is a perennial, prickly or scabrous, climbing herb belongs to rubiaceae. Leaves variable, arranged four in a whorl, cordate-ovate to ovate-lanceolate, base slightly cordate,¹ petioles are quadrangular, sometimes prickly on the angles, glabrous and shining. Stipules are absent. Stems is slender, rough, four angled with sharp recurved prickles on the ridges, which are often many yards long, becoming slightly woody at the base. Flowers are in cymes, greenish white. Fruits are didymous or globose, smooth, shining and purplish black when ripe.²

In ancient world, manjistha is reputed as an efficient blood purifier and hence is extensively used against blood, skin and urinary diseases.³ The root is sweet, bitter, acrid, astringent, thermogenic, antidysenteric, anti-inflammatory, antipyretic, analgesic, anodyne, anthelmintic, antiseptic, constipating, diuretic, galactopurifier, febrifuge, rejuvenating and tonic. It is useful in vitiated conditions of *kapha*, the body fluid principles relates to mucus and *pitta*, an energy principle which uses bile to direct digestion. In modern pharmacopoeia, the plant has been used to treat variety of ailments.^{4,5,6} The root extract has wide range of pharmacological properties thus used against ailments such as arthralgia, arthritis, cephalalgia, cough, diabetes, discolouration of the skin, dysmenorrhoea, emmenagogue, general debility, hemorrhoids, hepatopathy, intermittent fevers, jaundice, leucorrhoea, neuralgia, pectoral diseases, pharyngitis, ophthalmopathy, otopathy, splenopathy, strangury, slow healing of broken bones, tubercular conditions of the skin and mucous tissue, tuberculosis and urethrorrhoea.⁷ Besides, the roots are used for laxative, analgesic, rheumatism, dropsy, paralysis and intestinal ulcers. The dried stem is used in blood, skin and urinogenital disorders, dysentery, piles, ulcers, inflammations,

erysipelas, skin diseases and rheumatism.⁸ The plant is also used in curing some of the heart problems.^{9,10}

The roots were used in Ayurvedic (traditional Indian system of medicine) medicine as a coloring agent in medicated oils. Root derived powder has been used in many Asian countries as a natural dye, for imparting shades of red, scarlet, brown and mauve to cotton and other fabrics.

Chemical constituents in *Rubia cordifolia*

Different classes of bioactive compounds such as anthraquinones and their glycosides, naphthoquinones and glycosides, terpenes, bicyclic hexapeptides, iridoids,¹¹ carboxylic acids (malic, citric, quinic, rosmarinic acids) and saccharides (xylose, ribose, fructose, glucose, sucrose, primverose) were isolated from various parts of *R. cordifolia*. The roots contain a mixture of purpurin, munjistin, small amounts of xanthopurpurin and pseudopurpurin. Alizarin (1, 3-dihydroxy-2-ethoxymethyl-9, 10-anthraquinone), mollugin (1-hydroxy-2-methyl-9, 10-anthraquinone), 1, 3, 6-trihydroxy-2-methyl-9, 10-anthraquinone-3-O-(6'-Oacetyl)- α -L-rhamnosyl (1 \rightarrow 2)- β -D-glucoside, 1, 3, 6-tri hydroxy-2-methyl-9, 10-anthraquinone-3-O- β -L-rhamnosyl (1 \rightarrow 2)- β -D-glucoside, 1, 3, 6-trihydroxy-2-methyl-9,10-anthraquinone-3-O-(6'-O-acetyl)- β -D-glucoside, 2-carbomethoxy+++3-prenyl-1, 4-naphthohydroquinone di- β -D-glucoside, rubimallin, β -sitosterol and daucosterol were also isolated from roots.¹² Several naphthoquinones and hydroxy anhraquinones and their glycosides were also isolated.¹³ 1-hydroxy 2-methyl anthraquinone, nordamnacanthal, physcion and 1, 4-dihydroxy 6-methyl-anthraquinone,¹⁴ rubiatrionol,¹⁵ 1-hydroxy 2-methoxy anthraquinone; 1, 4-dihydroxy 2- methyl 5-methoxy anthraquinone; 1, 3-dimethoxy 2-carboxy anthraquinone, rubiadin,¹⁶ naphthaquinones,¹⁷ 1, 4-dihydroxy 2-methylantraquinone and 1, 5-dihydroxy 2-methylantraquinone and 3-prenyl methoxy 1, 4-naphthoquinone¹⁸ and an anti-inflammatory compound

rubimallin and antibacterial agents like α -sitosterol and daucosterol,¹⁹ rubicoumaric acid and rubifolic acid were identified and their structure was elucidated spectrometrically.²⁰ Other quinones isolated were 4-dihydroxy 2-methylanthraquinone, 1, 5-dihydroxy 2-methyl anthraquinone, 3-prenyl methoxy 1, 4-naphthoquinone, lucidin primeveroside, ruberythric acid anthraquinones, 2-methyl-1, 3, 6-trihydroxy-9, 10-anthraquinone and 2-methyl-1, 3, 6-trihydroxy-9, 10-anthraquinone 3-O α -rhamnosyl (1 \rightarrow 2)- β -glucoside. 6-Methoxy geniposidic acid (iridoids) is found along with manjistin, garancin and alizarin.²¹ Oleananes such as rupiprasin A, B and C along with arborane triterpenoids including rubiarbonol A, B, C, D, E and F have been isolate.^{22,23} Naphtho hydroquinones, furomollugin, mollugin, rubilactone,²⁴ nordamnacanthal, naphthohydroquinone anhydride were isolated from root extracts.²⁵ The dried roots contain mollugin, furomollugin, eugenol and (E) anethole as chief component in the essential oil and eugenol, geraniol and geranyl acetate were the most aroma compounds.²⁶ A new anthraquinone, rubiacordone A,²⁷ naphthoic acid esters like rubilactone, dihydromollugin were identified based on the physicochemical properties and spectrometric analyses.²⁸ Cordifoliol and cordifodiol also have been isolated from the roots.^{29,30} Epoxy-mollugin,³¹ 1-hydroxy-2, 7-dimethylanthraquinone, 2-hydroxy-6-methylanthraquinone and 2, 6-methylanthraquinone, *n*-nonadecane, *n*-heptadecane, 8'-hydroxy-*n*-pentadecanyl decan-4-en-1-oate and *noctaosanyl* octa-1-oate were isolated from the roots.³² Recently, the chloroform soluble fraction of the chloroform-methanol extract of the dried roots led to isolation of one new naphtho hydroquinone dimer and 3- α -friedelinol, atraric acid, vanillic acid and D-3-*O*-methoxy-chiro-inositol.³³

Bicyclic peptide of RA-series was elucidated from spectroscopic and chemical evidences from the roots of *R. cordifolia*. The bicyclic hexapeptides RA-I and RA-II³² have been isolated from chloroform/methanol extract. RA-III to RAVII has been obtained from the benzene-soluble fraction of methanol extracts.^{34,35} The structures of antitumor bicyclic hexapeptides RA-VI, RA-VIII,³⁶ RA-VII and RA-X were identified.³⁷ RA-VII is an inhibitor of protein biosynthesis *in vitro* and *in vivo*.³⁸ Ala 2 modified RA-VII derivative had been synthesized from RA-X methyl ester and evaluated for cytotoxicity to P388 leukemia and KB cells *in vitro*.³⁹ The conformational analysis of [N-Demethyl-Tyr (OCH₃)-3] RA-VII, derived from RA-VII by hepatic microsomal biotransformation revealed a restricted conformational state.⁴⁰ The bicyclic hexapeptides glucosides RA-IX and -X,⁴¹ RAXI, RA-XII, XIII, RA-IV,⁴² RA-XV and -XVI possess antitumour activity.⁴³ RA-XVII (2-aminobutyric acid-1 deoxybouvardin) was another antitumour agent, which showed little effect on the conformation of the molecule.⁴⁴ The spectroscopic studies revealed the structure of hexapeptides like RA-XV, RA-XVI, RA-XII,⁴⁵ RA-XVII,⁴⁴ RA-XIX, -XX, -XXI and -XXII. RA-XVIII is a hydroxylated derivative of RA-VII by the semi-synthesis from deoxybouvardin, showed cytotoxicity

against P-388 cells.⁴⁶ The structure of RA-XXIII and RA-XXIV⁴⁷ and RA-dimer A, a dimeric antitumor bicyclic hexapeptides, were also identified from the root extracts.⁴⁸ Recently two new bicyclic hexapeptides, allo-RA-V and neo-RA-V, and one cyclic hexapeptide, *O*-seco-RA-V were isolated.⁴⁹

Ethno-medicinal Importance of Madder

The roots of *R. cordifolia* have been used in Indian and Chinese traditional system of medicines to treat haematemesis, haematuria, inflammations, ulcers and skin diseases. It is an important ingredient in *Chadanasava*, an Ayurvedic wine preparation which contains 5–10 % of self generated alcohol, prescribed for urinogenetal disorders. Jatyaadi Ghrita externally for chronic and septic ulcers; Phala Sarpi Ghrita and Phal Kalyaan Ghrita for amenorrhoea and are helpful in all types of gynecological problems, defects in ovary and male reproductive system; Manjisthadi Taila (oil) for headaches, ring worm and other fungal infections. Manjistadi Taila and Kadalipatra prevent formation of discoloration, eschar and contracture to the patient of burn in comparison of bactigauze.⁵⁰ The Vedic physician, Charaka has suggested powdered roots and fruits, for eczematous dermatosis and diseases of the spleen.⁸ Manjistha extracted in purified butter, was prescribed in classic Ayurvedic script Sushrutasamhita for bleeding piles. The decoction of manjistha cooked with ghee and *Moringa oleifera* is useful for bleeding piles.⁵¹ Externally, manjistha was applied on major burns, mixed with honey on freckles and blemishes. It remained a potent drug for obstinate skin diseases, erysipelas and oedema. Also used as febrifuge and against blood disorders in *Ayurveda*. Traditionally, it is used in many polyherbal formulations for various ailments and cosmetic preparations because of its inflammatory, antiseptic and galactopurifier activity.⁵² Root is used externally and internally to gain lustre and glow of the skin and aids to remove pimples, freckles, and discoloration.⁵³ Traditionally the roots are used to treat various systemic problems and pigmentation anomalies of skin, leucoderma and is an excellent aid in the promotion of complexion. Dried and crushed orange peels, powders of sandal, turmeric and manjistha makes an excellent face pack. The finely crushed root powder along with little honey applied to face for healing skin tissues damaged by injury or infection. The root powder mixed with ghee, for the medicament of acne.⁵⁴ Ethnobotanical survey done in 2010 has documented the administration of root decoction in the treatment of diabetes.⁵⁵ It is also effective on non-healing diabetic foot ulcer. Vanraji tribes of Kumaun Himalaya use the whole plant pulp rubbed with honey as a cure for acne and dark spots on face.⁵⁶ In Central Bastar of Chhattisgarh, the root paste is applied externally for eczema for 3-4 months, and its decoction is given internally for the same period.⁵⁷ It is an excellent expectorant and also used to relieve from cough and cold and respiratory problems especially in infants.⁵⁸

In India and neighbouring countries, an infusion of the root has been prescribed to women after delivery for clearing the uterine channels and also to cure blood related ailments. In traditional Korean system of medicine, the root is used to treat rheumatism, jaundice and menstrual disorders. In Philippine system, a decoction of root is drunk as a remedy for urinary disorders.⁵⁹ In traditional Chinese system of medicine, the herb is internally used for abnormal uterine bleeding, internal and external haemorrhage, bronchitis, and rheumatism.⁶⁰ The natives of the Republic of South Africa take a decoction of the leaf or root for pleurisy and other inflammatory conditions of the chest. Ethnic group of Zulu take a decoction of root to cure lack of seminal emission, and adolescent Zulu females take a preparation of the root to hasten the inception of menstruation and in the treatment of over- due menses.⁶¹ The stem is used in Tibetan system of medicine in the treatment of blood disorders and spreading fever of kidneys and intestines.⁶² Badola *et al.* reported the application of *R. cordifolia* in various diseases.⁶³ Its leaf and root juice are taken during fever, stomachache and dysentery. Fruit is to lower the body temperature; decoction of leaves and stems as vermifuge. Root paste is used externally to cure headache.⁶⁴ In northern Sikkim, India the decoction of roots is used to treat irregular menstruation and also to dye and ear diseases.⁶⁵ Several ethnic communities use root decoction to cure jaundice and associated liver troubles.^{66,67} In Tamil Nadu, the powdered/fresh roots/tender shoot paste was externally used on iron weapon injured part of the body,^{68,69} and the stem and root powder is used internally to treat diabetes.⁷⁰ In traditional phytotherapy for jaundice, seed powder with common salt in the ratio of 5:2 or 30-40 ml root decoction is administered orally till cure.⁷¹ In Tamil Nadu, the Kanikkar tribes of Tirunelveli district used the roots to treat skin diseases⁷² and the Paliyar tribes apply root paste topologically for boils.⁷³ In Mayurbhanj district of Odisha, India the root is used to treat diarrhea and dysentery.⁷⁴ In Amarkanatak region, M.P., India the roots are used to treat rheumatism, ulcers, inflammation, skin disease, leucoderma, dysentery, chronic fever and urinary problems.⁷⁵ The Konda Dora tribes of A.P., India use the paste of tuber of *R. cordifolia* and *Mirabilis jalapa* to make pills, which is orally administered on empty stomach to treat jaundice.⁷⁶ The tuber is used as a febrifuge in Sovva panchayat of A.P., India.⁷⁷ Gireesha *et al.* reported the use of the whole part of *R. cordifolia* in the treatment of bronchitis, rheumatism and renal lithiasis by the tribal people of Western Ghats.⁷⁸ Mullu Kurma and Kurichar tribes of Wayanad district, Kerala, India use root paste in conjunction with turmeric to treat skin diseases.^{79,80} The stem is used as a cure scorpion sting.^{81,82} Root paste is applied topically on heel once a day to heal cracks.⁸³ In Kollimalai hill tracts of Tamil Nadu, India, the infusion of roots and stem is regarded as an astringent bitter tonic.⁸⁴ The leaf juice is administered internally to relieve from uterine pain by tribes of Maharashtra,⁸⁵ where as it is regarded as an excellent

blood purifier by Baiga tribals in Madhya Pradesh.⁸⁶ The root powder mixed with honey is applied for healing damaged face skin tissues. 50g root powder mixed with 50g 'gur' is orally taken to cure constipation and other stomach problems.⁸⁷ A paste of root powder smeared over betel leaf is applied externally to treat rheumatic swellings. The leaves and stem is also used to cure mouth infection in babies and in the treatment of pneumonia.⁸⁸ Leaf extract is applied on scabies and ringworm.⁹ Seed taken in vinegar and honey helps the swelling and hardness of spleen. Similarly manjistha and *Glycyrrhiza glabra* are pounded with sours applied as paste to treat fracture.⁵¹ The oil extract of whole plant is used to cure eczema.⁵⁸

USES IN MODERN PHARMACOLOGY

Anti-acne property

The anti-acne activity of anthraquinone rich fraction of *R. cordifolia* in a gel formulation against *Propionibacterium acne*, *Staphylococcus epidermidis*, *Malassezia furfur* when compared with standard Clindamycin gel.⁸⁹

Anti-arthritis property:

The anthraquinones rich fraction of ethanolic extract of *R. cordifolia* has imperative anti-arthritis potential and showed paw edema inhibition in induced arthritic model, which is similar to a standard non-steroidal anti-inflammatory drug, aspirin.⁹⁰

Anti-cancer property

Anticancer activities of various fractions of *R. cordifolia* roots extracts was demonstrated through *in vitro* and/or in bioassays based on animal models. The crude aqueous extracts demonstrated growth inhibitory activity on selected cancer cell lines as well as on normal human mammary epithelial cells.⁹¹ The quinones and RC-18 exhibited significant anticancer activity against P388 leukemia, L1210, L5178Y, B16 melanoma,^{92,93} S-180 and the cyclic hexapeptides against leukemia. The hexapeptides binds to eukaryotic 80S ribosomes, resulting in inhibition of aminoacyl-tRNA binding and peptidyl-tRNA translocation, thus leading to the stoppage of protein synthesis.⁹⁴ The cyclic hexapeptide isolated from dried roots showed antitumor activity.⁹⁵ Alkyl ether and ester derivatives of RA-V showed significant effects against human nasopharynx carcinoma, P388 lymphocytic leukemia and MM2 mammary carcinoma cells.⁹⁶ RA-700 showed antitumor activity similar to that of deoxybouvardin and vincristine against P388 leukemia and L1210 leukemia.^{97,98} RA-700 were injected to neoplastic patients, showed changed blood pressure, sigma QRS, ejection fraction, and fractional shortening.⁹⁹ Mollugin showed inhibition of passive cutaneous anaphylaxis and protection of mast cell degranulation and also exhibited considerable activity against lymphoid leukemia (P338) in mice.¹⁰⁰ Inhibition of formation of hepatic DNA adducts in male C57bl6 mice after a single dose of the heterocyclic amine dietary carcinogen Trp-P-2 was observed by short-term dietary supplementation with purpurin. The



inhibition of adduct formation was dose-dependent.^{101,102} In another study, anti mutagenicity of purpurin against a number of heterocyclic amines in the Ames mutagenicity test was proven.¹⁰³ Mollugin may have potential as a chemotherapeutic agent for human oral squamous cell carcinoma cells via the upregulation of the HO-1 and Nrf2 pathways and the down regulation of NF- κ B¹⁰⁴ and an active antiproliferative principle in human colon cancer (Col2) cell line.¹⁰⁵ The extract can inhibit cell proliferation in HEp-2 cell line and induced apoptosis through the elevation of reactive oxygen species generation.¹⁰⁶ The mito-depressive effect of root extract on the rate of cell division in bone marrow cells of mice was demonstrated.¹⁰⁷ In leucopenia, it had produced an increase in leukocyte count.¹⁰⁸ The extract also showed cytotoxicity towards human colon carcinoma (HT-29), human breast carcinoma (MCF-7) and human liver carcinoma (HepG2) cell lines. The anticancer activity of extracts of *R. cordifolia*, tested against the P388 tumor system in mice, compared well with that of the positive control, 5-fluorouracil.¹⁰⁹ Numerous animal and laboratory studies revealed that rubicordifolin has been shown to have both cytotoxic and antitumor properties.¹¹⁰ Ethanol fraction exhibited potent inhibition of human cervical cancer cell line.¹¹¹ Methanol fraction of extract exhibited potent inhibition of Hep G32 cell line while found to be less cytotoxic against normal human kidney cells displaying safety for normal cells.¹¹² Dichromethane fraction of madder root extract exhibited inhibition of human leukemia cell line and human histolytic lymphoma cell line.¹¹³ The ethanol extract of root showed cytotoxic effect against human larynx carcinoma and human cervical cancer.¹¹⁴ The methanolic extract of *R. cordifolia* leaf showed nearly 50 % MCF-7 cell line (breast cancer) inhibition at 200 μ g/ml tested dose.¹¹⁵

Anti-convulsant Activity

In modern medicine, *R. cordifolia* was reported to have anticonvulsant activity. Triterpenes inhibited seizures induced by maximum electric shock, electrical kindling and various chemoconvulsants in rats. Brain GABA and serotonin (5-HT) contents were raised by the compound proves its anticonvulsant property.¹¹⁶

Anti-diabetic

Alcoholic extract of root and leaf extracts were found to have promising antidiabetic activity against animal models. The extract of roots reduced the blood sugar level in alloxan treated diabetic rats, indicates that the extract has an extra pancreatic effect.¹¹⁷ The aqueous root extracts was found to normalize hyperglycemia, hyper triglyceridemia, enhanced transaminases of liver and kidney, hypochromic microcytic anemia, and loss of body weight in streptozotocin -induced diabetic rat models.¹¹⁸ The leaf extract decreased in the blood glucose level compared to the glibenclamide n normal fasted rat and alloxan-induced diabetic rats. In addition, the extract also showed a favorable effect on glucose disposition in glucose-fed hyperglycemic rats. Serum cholesterol and

triglyceride level were decreased where as serum high-density lipoprotein and protein levels were increased in diabetic rats.¹¹⁹ Methanolic root extract inhibited glycated and fructated guanosine and ROS-modification of glycated and fructated guanosine, which proves its antiglycation, antioxidant and anti-diabetic activities.¹²⁰

Anti-inflammatory activity

Rubia cordifolia root extract has been used as anti-inflammatory agent because of the presence of rubimallin. The aqueous extract showed anti-inflammatory activity in rats with carrageenan paw oedema in a dose dependent manner, which is comparable to that of phenylbutazone.¹²¹ It also inhibited the lipoxygenase enzyme pathway, which catalyses the production of various inflammatory mediators such as leukotrienes that are involved in asthma, arthritis, and other inflammatory disorders, and the production of cumene hydroperoxides.¹²² Notable nitric oxide scavenging activity was exhibited *in vitro* by some extracts of *R. cordifolia*.¹²³ A formulation of munjistin and purpurin from cell culture manifested to have and antiproliferative action during the rapid development of a model edema.¹²⁴

Wound healing activity

The root extract of *R. cordifolia* was reported as an effective wound healing principle in experimental models as wound healer.¹²⁵ Ethanolic extract and the hydrogel formulation of roots were found to be effective in the functional recovery and healing of wounds and also lead to histo-pathological alterations.¹²⁶

Anti-microbial activity

The root extracts of *R. cordifolia* have been studied for their antimicrobial activity against various pathogenic bacteria. Sitosterol and daucosterol possess antibacterial activity. The root extracts constituents such as anthraquinones and flavonoids suppressed the activity phytopathogens of *Gossypium*.¹²⁷ Aldehyde aceate, dihydromollugin and rubimallin reported to have significant antibacterial activity against *Klebsiella pneumonia*.¹²⁸ Ethanolic extract inhibited β -Lactamase producing uro-pathogenic *E. coli*.¹²⁹ The chloroform and the methanol extracts reported to have antibacterial activity on gram-positive strains, although gram negative *Pseudomonas aeruginosa* was also inhibited by the methanol extracts in a dose dependent manner. According to Basu *et al.*, the aqueous extract is active against *Bacillus subtilis* and *Staphylococcus aureus* compared with streptomycin and penicillin G.¹³⁰ The ethanolic whole plant extract also showed same result.¹³¹ Rubiacordone A reported to have considerable antimicrobial activity against Gram +ve bacteria like *Bacillus subtilis*, *Streptococcus faecalis* and *Bacillus cereus*.²⁷ The green synthesized silver nanoparticles using *R. cordifolia* plant root extract was highly inhibiting the bacterial pathogens like *Vibrio alginolyticus*, *Pseudomonas aeruginosa*, *Shigella spp*, *Plesiomonas*



shigelloides and *Vibrio parahaemolyticus*. They had highest antimicrobial effect against *Pseudomonas aeruginosa* and *Plesiomonas shigelloides*.¹³²

Anti-oxidant activity

Rubia cordifolia contains a wide variety of antioxidants like alizarin, hydroxyl anthraquinones¹³³ and rubiadin¹³⁴ which have been using in various medicaments. Hydroxy groups on one benzene ring of the anthraquinone structure were essential for hydroxyl anthraquinones to show the activity; its ortho-dihydroxy structure could greatly enhance their effect, and glycosylation reduced activity.¹³⁵ The study of *in vivo* antioxidant activity and its influence on ethanol-induced immuno-suppression showed that the concurrent daily administration of madder prevented the decrease of humoral and cell-mediated immune response, phagocytosis index, leukocyte count, glutathione content, catalase and superoxide dismutase activities etc., which were comparable with that of the combination of vitamin E and C.¹³⁶ Rubiadin prevented lipid peroxidation induced by FeSO₄ and butyl hydroperoxide in a dose dependent manner.^{137,138} Hexane and ethyl acetate fraction of root showed maximum free radical scavenging activity due to anthraquinones and their glycosides present in it. *R. cordifolia* extracts can protect peroxidation and reduced glutathione content in rat liver homogenate compared with vitamin E and parabenzoquinone.¹³⁹ The alcoholic root extract has some effect on body weight due to rubiadin.

Anti-peroxidative activity

Solvent free alcoholic extract of *R. cordifolia* showed antiperoxidative property in rat liver homogenate. The cumene hydroperoxide induced malondialdehyde formation accompanied by the reduced glutathione level even in the presence of above toxin.¹⁴⁰

Anti-platelet activating effect

In Ayurvedic System, the plant is prescribed to cure blood related ailments. Partially purified fraction of the whole plant inhibits the action of platelet activating factor at its receptor level either by its blocking or by desensitization property.¹⁴¹

Anti-proliferative property

Aqueous, ethanolic extract of root reported to have significant anti-proliferative effect. The antiproliferative property was also tested on A-431 cells (epidermal carcinomoid cells) and 3T3 fibroblast cells and recorded that the inhibition incorporation of [3H]-thymidine, is in a dose dependent manner. It also inhibited the phorbol 12-myristate 13-acetate induced expression of c-fos genes in A-431 cells due to the inhibition of DNA synthesis.¹⁴² Mollugin found to be an active antiproliferative principle by bioassay-monitored fractionation. It did not exert cytotoxicity to human fibroblast cell line.¹⁴³

Antistress and nootropic activity

Alcoholic extract enhanced brain γ -amino-n-butyric acid levels and decreased brain dopamine and plasma corticosterone levels.¹²¹ The extract inhibited acidity and ulcers caused due to cold restraint stress. Animals treated with alcoholic extract spent more time in open arm in elevated plus maze model, which antagonized scopolamine induced learning and memory impairment.

Anti-ulcer activity

The effect of alcoholic extracts of roots of *R. cordifolia* and its antiulcer potential on alcohol, ibuprofen, cold-restraint stress and pyloric ligation-induced gastric lesions was studied along with ranitidine, a standard drug.¹⁴⁴ The extract showed substantial and significant protection against gastric ulcers in all the models compared to ranitidine. In polyherbal formulations, the ulcerogenicity effect in rats showed significantly lesser ulcer effect even at very high dosage as compared to that of aspirin.¹⁴⁵

Antiviral activity

The naphthohydroquinones are reported to have antiviral activity. 6-hydroxy group and a pyran or furan ring of fuomollugin and mollugin strongly suppressed the secretion of hepatitis B surface antigen, in human hepatoma Hep3B cells.²⁴ The methanolic extracts of leaves have minimum inhibitory concentration of different virus using HEL cell cultures and Vero cell cultures.¹⁴⁶

Diuretic activity

To substantiate the traditional claim, the hydroalcoholic root extract of *R. cordifolia* was evaluated for its diuretic property and got positive results.^{147,148} The hydroalcoholic extract as well as the ethanol extract showed significant increase in urine volume and electrolyte excretion in a dose dependent manner compared with the reference drugs.¹³⁷

Gastroprotective activity

Rubia cordifolia has both gastroprotective and ulcer healing properties.¹⁰³ Triterpenoids present in root extracts are potent antiulcer and antioxidant compound which can be clinically explored.¹⁴⁹ The methanolic extract and the chloroform fraction showed reduction in ulcer index, lipid peroxidation, and increase in the mucin content, CAT and reduced glutathione in stomach tissue.¹⁵⁰

Hepatoprotective activity

The quinone derivatives from *R. cordifolia* reported to have hepatoprotective effect on animal systems. Animal model studies proved that the methanolic extract protects the liver thioacetamide-induced hepatotoxicity.¹⁵¹ The aqueous-methanol extract is active against acetaminophen and CCl₄-induced hepatic damage in rats.¹⁵² The extract also prevented CCl₄-induced prolongation in pentobarbital sleeping time, which authenticates the hepatoprotective effects of the extract.



The oral administration of rubiadin can normalize CCl_4 induced hepatic damage in rats within 14 days¹⁵³ It has found to be effective against acute and chronic hepatitis caused by the hepatitis B virus¹³⁸ by interfering with the secretion of hepatitis B surface antigen in human hepatoma cells.

Immuno-modulating activity

The alkaloids, cardiac glycosides, tannins, flavonoids and phenols present in *R. cordifolia* are responsible for enhanced immuno-modulation. Ethanolic extracts of the whole plant were administered to rats to test immuno-suppressive activity and showed enhanced cell mediated and humoral immuno-potentiating activity.¹⁵⁴ Hence *R. cordifolia* can be utilized as a source of immunity enhancing drug. The extracts of *R. cordifolia* and *Dianthus superbus* inhibited the IgE production *in vivo* and *in vitro* in peanut-allergic mice, suggesting potentials for allergy treatments. In another study the administration of ethanolic plant extracts to cyclophosphamide exposed animals resulted in enhanced immune responses.¹⁵⁵

Neuroprotection

Rubia cordifolia has been reported to contain a wide variety of antioxidants and exhibited strong free radical scavenging properties against reactive oxygen and nitrogen species. The herb attenuate oxidative stress mediated cell injury during oxygen glucose deprivation and exert the above effects at both the cytosolic as well as at gene expression level and may be an effective therapeutic tool against ischemic brain damage.^{156,157} The alcoholic extract administration reduced the β -amyloid induced cognitive and memory dysfunction in rats. The extract decreases the neuro-degeneration and helps in memory retention activity.¹⁵⁸ Mollugin showed potent neuro-protective effects against glutamate-induced neurotoxicity and reactive oxygen species generation in mouse hippocampal HT22 cells and BV2 cells, thus can be used for the treatment of neurodegenerative diseases related to neuro-inflammation.¹⁵⁹

Radiation protection

Oxidative stress induced by oxygen derived reactive oxygen species produces several adverse effects which are highly implicated in several degenerative diseases such as cancer. The therapeutic applications of *R. cordifolia* extract provide significant protection against radiation induced lipid peroxidation, hemopoietic injury and genotoxicity when administered intra-peritoneally before the radiation exposure.¹⁶⁰ Single strand breaks induced in plasmid pBR322 DNA following ionizing radiations was effectively prevented by the aqueous extract.¹⁶¹

Other relevant uses

Apart from its medicinal value, this plant has also been used as natural colourants in food, medicated oils, syrups etc... Root derived dye also used as textile and hair dye. Madder extracts is commonly used as a colorant for

confections and soft drinks, because of its advantageous resistance to heat and light. The persuasive antioxidant activity of madder is effectively exploited in food industry as chemo-preventive agents. *R. cordifolia* can be used as a single drug to cure Chikungunya fever.¹⁶² Leaf extract is used during cataract of eyes, conjunctivitis and also to clean the eyes. In patients with eczema, the topical application of the plant caused reduction in the severity of score and oedema, exudation and itching being significantly relieved. Crude methanolic extract suppressed the spontaneous contractions of guinea-pig atria, rabbit jejunum and rat uterus in a concentration dependent manner. The indicated spasmolytic activity similar to that of verapamil, a standard Ca^{++} channel blocker, suggests the presence of calcium channel like constituents in the plant, which may be responsible for the folkloric use of this plant for disintegration of urinary stones.¹⁶³ DNA Topoisomerases I and II Inhibition by the constituents from the roots of *R. cordifolia* were established.¹⁶⁴ Psoriasis is a skin disease associated with hyper proliferation and aberrant differentiation of keratinocytes. The *in vitro* and *in vivo* findings together, the preclinical study confirms that ethanol fraction is a promising antipsoriatic agent.¹⁶⁵ It can protect indomethacin-induced enterocolitis in rats and may be beneficial in patients with inflammatory bowel diseases.¹⁴⁸ Wool dyed with extracts from madder also showed improved insect resistance for carpet beetle.¹⁶⁶

IN VITRO METHODS

In India, although *R. cordifolia* is recorded to be widespread, the plant has been regionally assessed as threatened, because of over exploitation to meet the increasing demand in medication and other health products. The plant can be propagated by seed, stem cutting and micropropagation methods. Normally seeds show poor viability, but may be germinated when sown immediately after ripening. Alternatively, multiplication through *in vitro* method was attempted.^{167,168} The nodal explants regenerated on MS basal medium supplemented with Indole-3-Butyric Acid (1 mg l^{-1}) developed roots.¹⁶⁹ Similarly 1 mg l^{-1} benzyladenine and 0.02 mg l^{-1} indole-3-acetic acid produced shoots within two weeks from nodes and split vertical halves of the node respectively.¹⁷⁰ In another study the MS basal medium supplemented with thidiazuron (1 mg l^{-1}) induced highest number of shoots than other cytokinins. Rooting of micropropagated shoots were achieved on half strength MS basal medium supplemented with 2 mg l^{-1} of naphthalene acetic acid.¹⁷¹ In culture media, combined effects of NAA concentration, glucose concentration, myo-inositol concentration, nitrogen source composition, kinetin concentration reported to independently influence the production of anthraquinones,¹⁷² surface active agents like Tween series, span series, and POE (polyethylene) series were added at the incubation time of 14 days in MS basal medium and it was found that anthraquinone formation was not influenced by the addition of the POE series.¹⁷³



The transformation of *R. cordifolia* cells by the 35SroIB and 35S- roIC genes of *Agrobacterium rhizogenes* caused a growth inhibition of the resulting cultures and an induction of the biosynthesis of phytoalexins.¹⁷⁴ Cell culture studies further revealed that the increase in anthraquinone content in *R. cordifolia* cells transformed by rol genes does not involve activation of Ca²⁺ dependent NADPH oxidase signalling pathway.¹⁷⁵ The anthraquinone content caused significant increase in rol-gene transformed transgenic cultures.¹⁷⁶ The octadecanoid signaling pathway initiated by the rol genes in normal and transformed *R. cordifolia* cell cultures, stimulated anthraquinone production in a greater extent.¹⁷⁷ In cell suspension cultures of *R. cordifolia*, lovastatin increased the yield and clomazone decreased the yield of purpurin and mollugin, where as methyl jasmonate increased the purpurin yield, and decreased the mollugin yield compared with control.¹⁷⁸

CONCLUSION

In the recent past, wide attention is being given to traditional medicines to cure various ailments. *Rubia cordifolia* is an ethnic plant that all the parts of which have been medicated. The reported phytochemicals and pharmacological studies support its traditional use and have now proven as source of several clinically important drug resources. Experimental studies confirmed madder as prophylactic agent, which offers great potential to inhibit the carcinogenic process.

The antioxidant and free radical scavenging activities of phyto-components isolated from this plant give us an impression that Indian madder might be the future drug for diversified panel of tumors and cancers. But the conventional methods to isolate the bioactive compounds are tedious and spun out. To ensure ample production of phyto-constituents with in limited space and time, new approaches must be adopted. In order to facilitate this, cell suspension techniques as well as genetic manipulations to increase the production of secondary metabolites are to be focused for the well being of the generations to come.

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