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Rubia cordifolia as a Therapeutic Agent in Various Gynaecological Disorders: Insights from Clinical and Experimental Studies

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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. Manjishtha is an herb with potential benefits in treating various gynaecological disorders, particularly for blood purification and related issues. It's commonly used in Ayurvedic formulations for conditions like abnormal uterine bleeding, striae gravidarum (stretch marks), and skin problems during pregnancy. While research on Manjishtha's specific effects on gynaecological disorders is ongoing, traditional Ayurvedic practices and some studies suggest its potential in addressing these conditions.

Key Words: Manjishtha, Gynaecological disorders,

Introduction

Rubia 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, antiinflammatory, 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-ethoxymethyl9, 10-anthraquinone), mollugin (1-hydroxy-2-methyl-9, 10-anthraquinone), 1, 3, 6-trihydroxy-2-methyl-9, 10anthra-quinone-3-O-(6'-Oacetyl)-α-L-rhamnosyl (1→2)-βD-glucoside, 1, 3, 6-tri hydroxy-2-methyl-9, 10anthraqueinone-3-O-β-L-rhamnosyl (1→2)-β-D-glucoside, 1, 3, 6-trihydrozy-2-methyl-9,10-anthraquinone-3-O-(6'O-acetyl)-β-D-glucoside, 2-carbomethyoxy+++-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 rubiatriol,15 1-hydroxy 2-methoxy anthraquinone; 1, 4dihydroxy 2-methyl 5-methoxy anthraquinone; 1, 3- dimethoxy 2-carboxy anthraquinone, rubiadin,16 naphthaquinones,17 1, 4-dihydroxy 2methylanthraquinone and 1, 5-dihydroxy 2methylanthraquinone and 3-prenyl methoxy 1, 4naphthoquinone18 and an anti-inflammatory compound rubimallin and antibacterial agents like - sitosterol and daucosterol,19 rubicoumaric acid and rubifolic acid were identified and their structure was elucidated spectrometrically.20 Other quinones isolated were 4dihydroxy 2-methylanthraquinone, 1, 5-dihydroxy 2methyl anthraquinone, 3-prenyl methoxy 1, 4naphthoquinone, lucidin primeveroside, ruberythric acid anthraquinones, 2-methyl-1, 3, 6-trihydroxy-9, 10anthraquinone and 2-methyl-1, 3, 6-trihydroxy-9,

10anthraquinone 3-O -rhamnosyl (1→2)- -glucoside. 6Methoxy geniposidic acid (iridoids) is found alongwith 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] Epoxymollugin,[31] 1-hydroxy-2, 7- dimethylanthraquinone, 2-hydroxy-6methylanthraquinone and 2, 6-methylanthraquinone, nnonadecane, n-heptadecane, 8'-hydroxy-n-pentadecanyl decan-4en-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- - 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 P[38] 8 leukemia and KB cells in vitro.[39] The conformational analysis of [NDemethyl-Tyr (OCH_3)-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] RAXVII (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, RAXVI, RA-XII,[45] RA-XVII,44 RA-XIX, -XX, -XXI and -XXII. RAXVIII is a hydroxylated derivative of RA-VII by the semisynthesis from deoxybouvardin, showed cytotoxicity against P-388 cells.[46] The structure of RA-XXIII and RAXXIV[47] and RA-dimer A, a dimeric antitumor bicyclic hexapeptides, were also identified from the root extacts.[48] Recently two new bicyclic hexapeptides, alloRA-V and neo-RA-V, and one cyclic hexapeptide, O-seco- RA-V were isolated.[49]

Ethno-medicinal Importance of Manjishtha

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 Ayrurvedic 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 administrated orally till cure.[71] In Tamil Nadu, the Kanikkar tribes of Tirunelveli

district used the roots to treat skin diseases[72] 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 administrated 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 finely crushed root powder along with little honey applied to face for healing skin tissues damaged by injury or infection. 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. 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. The oil extract of whole plant is used to cure eczema.

Clinical Uses of Manjishtha in Gynaecological Disorders

Manjishtha in Dysmenorrhea

Raktavardhaka (Blood enhancing) property of Manjishtha (Rubia Cordifolia L.) improves pain threshold by improving the Immunity. The biological investigations have shown that many of the medicinal properties claimed for Rubia Cordifolia (Manjishtha) in the historical texts have sound scientific basis (Singh et al., 2005). It has a variety of uses such as blood purifying etc. (Joharapurkar et al., 2003). Intensity and duration of pain was observed to be reduced in maximum patients. Anti-inflammatory and Analgesic activity of Rubia cordifolia is quoted by many Researchers. [89]

Rubia cordifolia L. is said to contain substantial amount of Anthraquinones, especially in the roots which is responsible for its pharmacological activities (e.g. Antiinflammatory and Analgesic). (Meena et al., 2010); (Anar Patel et al., 2010); (Yeungnam 2007), (Gonzalez, et al., 1974); (Schildknecht et al., 1976); (Itokawa et al., 1989); (Ho, et al., 1996); (Hua, et al., 1992); (Kawasaki et al., 1992); (Marec et al., 2001); (Chung et al., 1994); (Antarkar et al., 1983); (Tripathi and Sharma 1998); (Wealth of India 2002).

Psychological factors like Depression, Anxiety and Stress are quoted as the risk factors of Dysmenorrhoea (L Wang et al., 2004) and due to Anti-stress property (Patil, Jagdale et al., 2006) of Rubia cordifolia (Manjishtha) it is more likely to modify the factor like pain in Kashtartava (Dysmenorrhoea).

Prostaglandins and Prostinoids are biosynthesized from Arachidonic acid through the COX pathway after production of Arachidonic acid from hydrolysis of Phospholipids by Phospholipase. In excess or imbalanced amount of Prostinoids released from the Endometrium during menstruation induces uterus to contract frequently and dysrhythmically, with increased basal tone and increased active pressure. Uterine hyper contractility, reduced uterine blood flow and increased peripheral nerve hypersensitivity induce pain. Mollugin is one of the major 2H naphtho pyran component isolated from Rubia cordifolia is having strong inhibitory activity on arachidonic acid. Thus Rubia cordifolia L.(Manjishtha) by breaking the pathway of pain production improves the condition like Dysmenorrhoea.

Manjishtha on PCOS [90]

The present study provided a rationale for the folkloric uses of standardized ethanolic extract of *Rubia cardifolia* (SERC) in gynecological disorders. SERC significantly improved ovarian pathology with a reduction of cystic follicles and a greater number of primary, growing, and developing follicles, an indicator of improved ovulation. It reduced serum insulin levels with the improvement of insulin sensitivity that is depicted with restoration of LH/FSH ration and lower serum concentration of testosterone and a little higher concentration of estrogen. The proposed mechanism might be the restoration of normal health of the ovary and liver due to inhibition of ROS production of lipid peroxidation in these tissues which is evident with upregulation of antioxidant enzyme markers (CAT, SOD, and GSH and downregulation of lipid peroxidation marker (MDA). These effects are produced by phytoconstituents as HPLC analysis revealed the presence of chlorogenic acid, *p*-coumaric acid, gallic acid, and kaempferol in SERC. This study opens a new era for further research to affirm these findings at the molecular and genetic level.

Specific Benefits and Applications:

- **Blood Purification:**

Manjishtha is known for its blood-purifying properties, making it useful for conditions like menorrhagia (heavy menstrual bleeding) and other blood-related disorders.

- **Striae Gravidarum:**

Manjishtha Ghrita (ghee prepared with Manjishtha) has shown promising results in treating and preventing stretch marks during pregnancy.

- **Skin Problems:**

Its anti-inflammatory, antifungal, and antibacterial properties make it beneficial for skin issues like itching and infections, especially during pregnancy.

- **Menstrual Disorders:**

Ayurvedic texts and practitioners use Manjishtha to address conditions like dysmenorrhea (painful menstruation) and other menstrual irregularities.

- **Infertility:**

While not a primary treatment, Manjishtha can be part of an Ayurvedic approach to address certain aspects of infertility, particularly those related to blood imbalances or hormonal issues.

Concluion

- While traditionally used, it's crucial to consult with a qualified Ayurvedic practitioner or healthcare professional before using Manjishtha, especially during pregnancy or if you have any existing health conditions.
- Dosage and preparation methods may vary depending on the specific condition and individual needs.
- More rigorous scientific research is needed to fully understand the efficacy and safety of Manjishtha in treating specific gynaecological disorders.

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