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Review Paper

Rubia cordifolia Overview: A New Approach to Treat Cardiac Disorders

Pankaj Bhatt*, A. S. Kushwah
Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, BELA, Ropar (Punjab), 140111, India

Abstract
Ethno-botanical and ethno-pharmacological studies of *Rubia cordifolia* continue to attract investigators for research work globally. *Rubia cordifolia* commonly known as Manjistha or Indian madder is an important medicinal plant growing up to 3500 meters height. Rubiae Radix (dried roots of *Rubia cordifolia,* Rubiaceae) is a rich source of anthraquinones responsible for its traditional, phytochemical and pharmacological activities. Today clinical investigations of herbal formulations and their market preparations, both are on demanding because of better safety and efficacy without or minimal side effects. This review summarizes the concept of finding new approach to treat cardiac disorders on the basis of previous reports of this plant.

*Corresponding author, Mailing address:
Pankaj Bhatt*
M. Pharm (Student)
Department of Pharmacology
ASBASJSM College of Pharmacy,
BELA, Ropar (Punjab), 140111, India
E. mail: pankaj.bhatt001@gmail.com

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INTRODUCTION:

Ayurvedic materia medica mentioned Manjistha as detoxifying herb removing "ama/toxin" from the blood. *Rubia* denotes 'red' as their internal use imparts red color to breast milk and urine[1]. Roots of this plant having high medicinal value and are recognized as official[2]. In the ethnobotanical claims, roots of *Rubia cordifolia* mentioned for the treatment of jaundice used by the folk tribes of West Bengal and Uttaranchal. Manjistha stem describes as cure for snake bite and scorpion sting. It is also effective on non healing diabetic foot ulcer[3]. Manjistha having cooling effect in the body and therefore, traditionally used for chronic pyrexia and puerperal fever. It is a popular remedy for the relief

of heat and itching in eczema, psoriasis, herpes, scabies and also reported successful in treatment of vitiligo when given with honey[4]. Manjistha has been reported for the presence of glycosides, saponins, anthraquinones, tannins, hexapeptides, quinones, triterpenoids[5].

Table 1: Taxonomical and morphological classification of *Rubia cordifolia* Linn.

Taxonomical classification		Morphological classification	
Kingdom	Plantae	Plant	Perennial herbaceous climber
Division	Magnoliophyta	Roots	Long, cylindrical, flexuous with a thin red bark
Class	Magnoliopsida	Stems	Very long, rough, grooved and woody base
Order	Gentianales	Branches	Scandent, quadrangular, glabrous and shining
Family	Rubiaceae	Leaves	Arranged in four whorls, ovate
Genus	Rubia L.	Fruits	4-6 mm in diameter, globose, purplish black when ripe
Species	Rubia cordifolia L.	Flowers	Small, greenish, terminal panicle-cymes

Literature describes the beneficial effects of *Rubia cordifolia* in treatment of number of ailments including alzheimer, diabetes, cancer, acne, inflammation, allergy, enterocolitis, bacterial and viral infection. Other reported activities are immunomodulator, analgesic, diuretic, gastroprotective, hepatoprotective and nephroprotective. *Rubia cordifolia* show potent antioxidant activity against lead nitrate and radiation induced toxicity[6, 7]. *Rubia cordifolia* has been evaluated for its wound healing activity[8]. The leaves of this plant also studied for its antiviral and *in-vitro* free radical scavenging activity[9]. Apart from its medicinal value, Manjistha has also been used as natural food colorants and natural dyes. The coloring pigments present in the roots are purpurin and munjistin in major amounts. Madder root extract has investigated for its dying characteristics and yielded beautiful orange red to scarlet shades when applied onto the woolen yarn[10].

TRADITIONAL USES:

Manjistha is an ayurvedic herb that is mentioned in Charaka and Sushruta. Charaka has categorized it as *varnya*, *jvarahara*, *vishaghna*. Sushruta has mentioned it *pittasamsamana*.

Traditional uses of manjistha mentioned in ayurvedic materia medica are following:

Table 2: Traditional activity of *Rubia cordifolia* Linn.

S. No.	Sanskrit Term	Medical Term
1.	*Varnya*	Improves complexion
2.	*Jvarahara*	Anti-pyretic
3.	*Vishaghna*	Remove toxins
4.	*Mutravirecana*	Diuretic
5.	*Raktasodhana*	Blood purifier
6.	*Rasayana*	Rejuvenative
7.	*Vranaropaka*	Wound healing
8.	*Kushthaghna*	Treat skin diseases
9.	*Sonitasthapana*	Haemostatic
10.	*Pittasamsamana*	Pacifier the pitta doshas
11.	*Asmaribhedana*	Lithagogue
12.	*Krmighna*	Antibacterial and anthelmentic
13.	*Sothahara*	Antiinflammatory
14.	*Vedanasthapana*	Analgesic
15.	*Caksusya*	Improves vision

Ayurvedic pharmacopoeia of India therapeutically indicate it for *Yoni roga* (menstrual disorder), *Kustha* (skin disease), *Sarpavisa* (snake bite), *Visarpa* (herpes virus), *Aksi roga* (eye disease), *Arsa* (haemorrhoids), *Bhagna* (Fracture)[11].

According to the ancient ayurvedic text, Bhava Prakash, Manjistha is able to bind with *amavisha* (free radicals) and *garavisha* (xenobiotics) toxins which cause inflammation, skin disease, ulcers, among other problems. Manjistha in Sanskrit also termed as *Jingi* (vibrational energy) which helps to reestablish the intelligence of the tissues. A balanced combination of *soma* (cooling) and *agni* (heat) found

in Manjistha. *Agni* allows the herb to penetrate into the cellular level of tissues and *Soma* helps to soak up the toxins and neutralize them.

Ayurvedic preparations:

Manjistha is an important ingredient of many ayurvedic formulations and preparations; Mahamanjisthadi kvatha, Manjisthadi taila, Manjistha arka, Manjistha malahara, Manjistha phanta, Septilin syrup etc.

Mahamanjisthadi kvatha: The herbal supplement used as blood purifier, immunomodulator, promotes skin health and complexion.

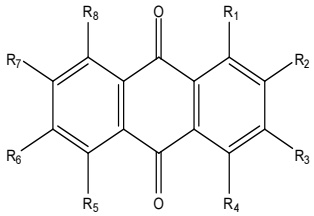
Septilin syrup: A polyherbal preparation containing *Rubia cordifolia* as one of the ingredient, tried in 40 children suffering from various upper respiratory tract infections. Very good response was seen in 34 (85%) children. Incidence of recurrences was minimal[12].

Body Revival: It is an Indian herbal formulation having suspension of *Aegle marmelos, Acorus calamus,* ***Rubia cordifolia****, Saussurea lappa, Blumea lacera, Rumex vasicarius, Curcumas melo, Symplocos racemosa* and honey. Investigation showed that Body Revival potentiates cardioprotection against isoproterenol induced myocardial ischemia and ADP or collagen induced human platelet aggregation[13].

PHYTOCHEMICAL STUDIES:

Rubia cordifolia (Manjistha) basically known for its anthraquinones and naphthohydroquinones phytochemical constituents[14]. The major phytoconstituents of *Rubia cordifolia* reported include Rubiadin[15], Rubicordone A[16], Rubiasins A-C[17], Rubiatriol (triterpenoid)[18], 6-methoxygeniposidic acid an iridoid glycoside[19] and two pentacyclic triterpenoid- Rubicoumaric acid and Rubifolic acid[20]. Mollugin, furomollugin, dehydro-alpha-lapchone are isolated from chloroform fraction[21].

The primary chromophores present in *Rubia cordifolia* are alizarin, purpurin, pseudopurpurin, xanthopurpurin, munjistin, rubiadin. All of the chromophores share the base 9,10-anthraquinone structure but with different functional groups at carbons 1-4 (Fig. A)[22].



Alizarin	R_1=R_2=OH, R_3=R_4=H
Purpurin	R_1=R_2=R_4=OH, R_3=H
Pseudopurpurin	R_1= R_2=R4=OH, R_3=COOH
Xanthopurpurin	R_1= R_3=OH, R_2=R_4=H
Munjistin	R_1= R_3=OH, R_2=COOH, R_4=H
Rubiadin	R_1= R_3=OH, R_2=CH_3, R_4=H

Figure A: Structure of primary chromophores found in Indian Madder.

Four naphthoic acid esters namely rubilactone, 3'-carbomethoxy-4'-hydroxy-naphtho[1',2'-2,3]furan, dihydromollugin and 3-carbomethoxy-2(3'-hydroxy)isopentyl-1,4-naphthohydroquinone-1-O-beta-D-glucoside were isolated from the roots of *Rubia cordifolia*[23].

Identification of aroma compounds in Rubiae Radix (dried roots of *Rubia cordifolia*) done by gas chromatography. As a result of 43 components, accounting for 91.5% of total oil detected, in which mollugin (19.6%), furomollugin (17.4%), eugenol (12.7%), (*E*)-anethole (10.6%), 4-*tert*-butyl-2-phenyl phenol (9.9%), menthol (2.7%) are the main components[24].

Biomarkers:

Table 3: Biomarkers of *Rubia cordifolia* responsible for therapeutical activities.

S. No.	Biomarker	Activity
1.	Rubiadin	- Hepatoprotective - Antioxidant
2.	Alizarin[25]	- Antigenotoxic
3.	Mollugin[26, 27]	- Antiadipogenesis - Antiplatelet
4.	Alizarin, mollugin, lucidin[28]	- Potent COX-2 inhibitor
5.	RA-700[29] RA-XI, XII, XII, XIV[30]	- Antitumor
6.	1-hydroxytectoquinone[31]	- Anti-inflammatory - Anticancer

PHARMACOLOGICAL ACTIONS:

Table 4: Reported pharmacological activities of *Rubia cordifolia* Linn.

S. No.	Activity	Plant Part	Extract/ Dose (mg/kg)	Model	Results/Findings	Refer-ence
1.	Antialzheimer	Root	Ethanol (200, 400)	β-amyloid peptide induced Alzheimer	- Improvement in memory retention activity	32
2.	Antidiabetic	Leaf	Alcohol (200, 400)	Alloxan induced Diabetes	- Antihyperglycemic - Antihyperlipidemic	33
3.	Anticancer	Root	Methanol (---) Pet-ether (---)	*In vitro* cytotoxicity assay	- cytotoxic activity against HEp-2, HeLa cell lines	34
4.	Gastroprotective	Root	Methanol (100, 200, 400) Chloroform (50, 100, 200)	Swimming stress induced ulcer	- Decrease in ulcer index - Chloroform fraction is more potent than parent methanol extract	35
5.	Immunomodulator	Root	Ethanol (50, 100, 200)	Pyrogallol and ethanol induced immunosuppression	- Stimulate humoral and Cell mediated immunity - Phagocytosis	36, 37
6.	Nephroprotective	Root	Hydroalcoholic (286, 667)	Ethylene glycol induced urolithiasis	- Inhibit urinary stones formation	38
			Hydroalcoholic (250, 500)	Cisplatin induced nephrotoxicity	- Potent antioxidant	39
7.	Diuretic	Root	Hydroalcoholic (286, 667)	Comparative study of extract with normal saline and furosemide induced diuresis	- Significant increase in diuresis, natriuresis, kaliuresis and glomerular filteration rate (GFR)	40
8.	Antiinflammatory	Stem	Ethanol (20, 40)	Carrageenan induced paw oedema	- Reduce paw oedema	41
9.	Antistress and nootropic	Root		Cold restraint test Elevated plus maze	- Reduce ulcer index - Increase brain GABA level - Increase time spent in open arm	42
10.	Antiacne	Root/stem	Methanol (---)	*Propionibacterium acnes* culture	- Inhibit proliferation of *P. acnes*	43
11.	Antienterocolitis	Root	Hydroalcoholic (300, 600)	Indomethacin induced enterocolitis	- Decrease elevated lactate dehydrogenase - Antiinflammatory	44
12.	Antibacterial	Root	Chloroform (---) Methanol (---) Aqueous (---)	*In vitro* study	- Significant activity against; *B. subtilis*, *S. aureus* and *P. aeruginosa*	45
13.	Antiviral	Root	Chloroform (---)	Human hepatoma Hep3B cell culture	- Inhibition of Hepatitis B surface antigen secretion	46
14.	Antiallergic	Root	Methanol (30, 100, 300)	Compound 48/80 induced mast cell degranulation	- Inhibit mast cell degranulation	47
15.	Antiplatelet	---	---	PAF induced platelet aggregation	- Anti-PAF (Platelet activating factor)	48

---- indicates not known.

RECENT ACTIVITIES:

1. Antibacterial activity of ethanolic extract of *Rubia cordifolia* evaluated against ESBL (Extended Spectrum Beta-Lactamase) producing urinary *E.coli* infection. Isolation of different *E.coli* strains done from urine samples of patients and all the isolates tested for different antibiotics and screened for their ESBL production. Total 7 different ESBL producing *E.coli* obtained and tested against the ethanolic extract of *Rubia cordifolia* using Kirby Bauer method and found to be inhibited variably by the extract. The plant can be a potential candidate as alternative antibacterial agent to combat drug resistant organisms[49].
2. Methanolic extract of *Rubia cordifolia* showing ameliorative effect in N-nitrosodiethylamine-induced hepatocellular carcinoma in rats. Mitochondrial enzymes and respiratory chain enzymes, which decreased in N-nitrosodiethylamine treated rats, increased significantly in *Rubia cordifolia* treated rats.

The levels of hydroxyl radicals and lipid peroxidation also decreased. Histological analysis of liver confirmed the prevention of pathological changes caused by N-nitrosodiethylamine, which suggest that *Rubia cordifolia* may be developed as an effective chemotherapeutic agent[50].

3. Psoriasis is skin disorder characterized by hyperproliferation and aberrant differentiation of epidermal keratinocytes. Ethyl acetate (EA) fraction of Radix Rubiae inhibits cell growth and promotes terminal differentiation in cultured human keratinocytes which strongly suggest its antipsoriatic activity. Evaluation is done by cornified envelope (CE) formation assay showed that EA fraction of Radix Rubiae significantly accentuated the CE formation, a well-recognized marker of terminal differentiation, in cultured HEK and HaCaT cells in a dose and time dependent manner[51].
4. Methanolic extract of *Rubia cordifolia* induced typical apoptosis in HEp-2 (Human laryngeal carcinoma) cell line through the elevation of reactive oxygen species generation. Inhibition of cell proliferation and lactate dehydrogenase release increased in a time and dose-dependent manner. Apoptotic effect of *Rubia cordifolia* extract (30 mg/ml) on HEp-2 cells confirmed by fluorescent and transmission electron microscopy based on morphological and ultrastructural changes[52].
5. Alizarin, a natural hydroxyanthraquinone derived from root of *Rubia cordifolia* evaluated as an osteotropic drug for treatment of bone tumors because of its high affinity to bone. Antitumor activity of alizarin investigated on human cell lines representative for bone metastases from prostate cancer, breast cancer and for three human osteosarcoma cell lines. Alizarin induced a dose-dependent inhibition of cell growth over time in osteosarcoma and breast cancer cell lines, whereas in prostate cancer cell line, it appeared to be cytotoxic only at higher concentration. Studies found that alizarin acted through the inhibition of ERK phosphorylation and cell cycle arrest in the S-phase[53].

CARDIOPROTECTIVE APPROACH:

Rubia cordifolia role in supporting heart health is evidenced by traditional and reported activities which show that it act as potent blood purifier, antioxidant, diuretic, calcium channel blocker, antiplatelet, antidiabetic, antiinflammatory, antistress, immunomodulator etc. *Rubia cordifolia* known for its antioxidant, antiinflammatory and potent blood purifier activities can play an important role to detoxify ischemia induced free radical generation. Diuretic activity of *Rubia cordifolia* could be an alternative therapy in the management of congestive heart failure (CHF) for rapid mobilization of edema fluid. Antistress, diuretic and vasodilating properties of Manjistha can play an important role in the management of hypertension. *Rubia cordifolia* inhibits platelet aggregation induced by PAF (Platelet Activating Factor) potentiate its therapeutic role in coronary artery disease. Antihyperglycemic and antihyperlipidemic effects of Manjistha direct its medicinal role in diabetic cardiomyopathy and diabetic macrovascular disease. *Rubia cordifolia* exhibits spasmolytic activity similar to that of verapamil suggestive of presence of calcium channel blocker(s) like constituents in this plant[54] and therefore, indicates its possibility to treat arrhythmias result from calcium overload in ischemia-reperfusion condition.

CONCLUSION:

Today prescription of combination therapy (hypolipidemic, diuretic, calcium channel blocker, vasodilator, antiplatelet) are common in patients with cardiac dysfunction. Chances of drug interaction and adverse effect arise with combination therapy. *Rubia cordifolia* an individual plant with multiple

activities that is essential to support heart health could become a new approach in the management of cardiac disorders and therefore, need research work to isolate cardiac biomarkers from this plant.

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