



A Complete Review on Rubia Cordifolia

Dr. Siva Rami Reddy E

Research Scholar, Faculty of Homoeopathy, Tania University,
Sri Ganganagar, Rajasthan, India

ABSTRACT

Medicinal herbs are significant source of synthetic and herbal drugs. In the commercial market, medicinal herbs are used as raw drugs, extracts or tinctures. Isolated active constituents are used for applied research. For the last few decades, phytochemistry has been making rapid progress and herbal products are becoming popular. The formulations incorporate single herb or more than two herbs (polyherbal formulations). Medicinal herb contains multitude of chemical compounds like alkaloids, glycosides, saponins, resins, oleoresins, sesquiterpene, lactones and oils. Today there is growing interest in chemical composition of plant based medicines. Several bioactive constituents have been isolated and studied for pharmacological activity. *Rubia cordifolia* is an important medicinal plant commonly used in the traditional and AYUSH system of medicine for treatment of different ailments. This review illustrates its major constituents, pharmacological actions substantiating the claims made about this plant in the traditional system of medicine and its clinical applications.

Keywords: *Rubia cordifolia*, *Phytochemical*, *pharmacological study*

I. Introduction

In India, medicines based on herbal origin have been the basis of treatment and cure for various diseases¹. Moreover, Indian folk medicine comprises numerous prescriptions for therapeutic purposes such as healing of wounds, inflammation, skin infections, leprosy,

diarrhoea, scabies, venereal disease, ulcers, snake bite, etc². More than 80% of the world's population still depends upon traditional medicines for various skin diseases³. Herbal medicines in wound management involve disinfection, debridement and providing a moist environment to encourage the establishment of the suitable environment for natural healing process^{3,4}.

Rubia cordifolia (Rubiaceae) is also known as, Manjishtha, Indian madder which is distributed throughout India⁵. It is found throughout the hilly districts of India from northwest Himalayas eastwards, ascending to 8000 ft and southwards to Ceylon. The roots of this plant are of high medicinal value and are recognized as official⁶. This perennial herbaceous prickly creeper or climber is upto 10m long, found throughout the country ascending to 3750 m and grow well in light (sandy), medium (loamy) and heavy (clay) soils⁷.

The family Rubiaceae comprises about 450 genera and 6500 species and includes trees, shrubs and infrequently herbs. *Rubia cordifolia* L. (Rubiaceae), also known as 'manjistha', is a perennial, herbaceous climbing plant, with very long roots, cylindrical, flexuous, with a thin red bark. Stems often have a long, rough, grooved, woody base. Plants belonging to this family are known to contain substantial amounts of anthraquinones, especially in the roots⁸. The traditional therapeutic use of the plant has been for skin disorders and for anticancer activity. Furthermore, the anthraquinones of the Rubiaceae

family exhibit some interesting in vivo biological activities, such as antitumor⁹, anti-inflammatory¹⁰, hepatoprotective¹¹⁻¹³, antimicrobial and immunomodulatory.

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, cordateovate 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.¹⁴⁻¹⁸

Table 1: Vernacular Names

Places	Indian languages
Assam	Majathi
Bengali	Manjith
Bihar	Majith
Marathi	Madar
Kannada	Siomalate, Siragatti, Manjustha
Kashmir	Dandlu
Khasi	Ryhoi, Soh-misem

Urdu	Mañjiṣṭha
Punjab	Kukarphali, Tiuru, Manjit, Sheni, Mitu, Runang
Tamil	Shevelli, Manjitti
Telugu	Tamravalli, Chiranji, Manjestatiga
Malayalam	Poont, Manjetti
Nepal	Manjito
Oriya	Barheipani, Mañjiṣṭha
Khasi	Ryhoi, Soh-misem
Urdu	Mañjiṣṭha
Naga	Enhu, Chenhu
Manipur	Moyam
Lepecha	Vhyem

It is famous as Varnya in the traditional medicine. At present it is used mainly as natural colouring agent in the fabrics industry. It is often debated which is the useful part of *Rubia cordifolia*. In the market we come across the samples which appear as stems as well as roots. In Vaidya chintamani, *Rubia cordifolia* is enumerated among the kandasara dravyas. Therefore, it may be concluded that root is the useful part of *Rubia cordifolia*. Stem of *Rubia cordifolia* which are somewhat quadrangular and have a smooth greenish yellow outer surface is generally used as a substitute of its root. Olden landia umbellata or Hispidia indica known as chayaver in Tamil is an adulterant of *Rubia cordifolia*.^{19,20}

Figure -1: Different Stages of *Rubia cordifolia*

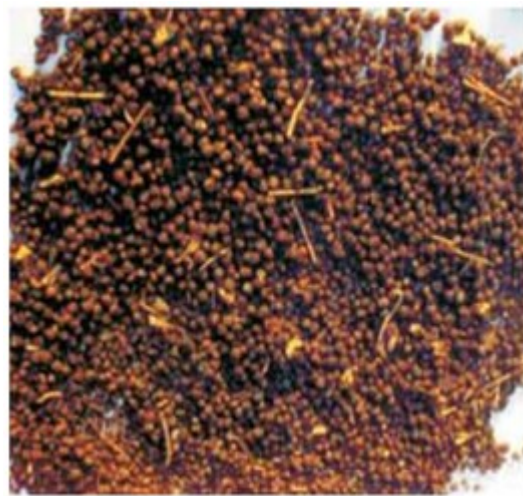


(A) Flower in Stage

(B) Fruiting Stage



(C) Mature Fruit Stage



(D) Seeds of Rubia cordifolia

II. HISTORY AND DISTRIBUTION:

It is distributed throughout the lower hills of Indian Himalayas in the North and Western Ghats in the South, and Japan, Indonesia, Ceylon, Malay Peninsula, Java and Tropical Africa in moist temperature and tropical forest, upto an altitude of 3500 m.^{21,22}

III. BOTANICAL DESCRIPTION:

Rubia cordifolia roots are Very long, cylindric, flexuose with a thin red bark, Stems are often many yards long, rough, grooved, becoming slightly woody at the base. *Rubia cordifolia* barks are White, branches scan dent by means of numerous divaricate or deflexed branches lets and petioles, quadrangular, sometimes prickly on the angles, glabrous, shining. This plant Leaves are 3.8-9 by 1.6-3.5 cm, in wholes of 4(one pair of each whorl often larger and with longer petioles than the other) ovate, acute, the lower leaves larger than the up-per, all scabrous above, on the nerves beneath, and on the margins with minute white prickles, base rounded or slightly cordate, the base of the upper leaves sometimes acute, all 5 nerved from the base, petioles triangular with many sharp recurved prickles on the edges, often deflexed. stipules 0. Flowers are In terminal paniced cymes, branches trichotomous, spreading, bracts ovate, acute, leafy. Calyx – 0.85mm long, tube globose, glabrous limb 0 and Corolla – Greenish, divided nearly to the base, tube scarcely any, lobes 5, ovate, acute, 3mm long, style 2, stigma globose. These plants Fruitts are 4-6 mm diameter, didymous or globose, smooth, shining, purplish black when ripe, dried and pieces of pericarp and other refuse separated by sifting. It occurs mostly in loamy soil rich in humus. the rainfall is high in the regions in which this plant grows. The plant is a climber and

requires support for growth. The plant is propagated through seeds and two node root cuttings. The seeds are collected during December and January. It is preferable to use seeds for large scale cultivation, considering the cost factor and high rate of germination.²³⁻²⁵

IV. PHYTOCHEMICAL STUDIES:

Rubia cordifolia (Manjistha) basically known for its anthraquinones and naphthohydroquinones phytochemical constituents²⁶. The major phytoconstituents of *Rubia cordifolia* reported include Rubiadin²⁷, Rubicordone A²⁸, Rubiasins AC²⁹, Rubiatriol (triterpenoid), 6-methoxygeniposidic acid an iridoid glycoside³⁰ and two pentacyclic triterpenoid- Rubicoumaric acid and Rubifolic acid^{31,32}. Mollugin, furomollugin, dehydro-alpha-lapchone are isolated from chloroform fraction³³. 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 (Figure B)³⁴.

Alizarin	R1=R2=OH, R3=R4=H
Purpurin	R1=R2=R4=OH, R3=H
Pseudopurpurin	R1= R2=R4=OH, R3=COOH
Xanthopurpurin	R1= R3=OH, R2=R4=H
Munjistin	R1= R3=OH, R2=COOH, R4=H
Rubiadin	R1= R3=OH, R2=CH3, R4=H

Table 2: 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-Obeta- D-glucoside were isolated from the roots of *Rubia cordifolia* ³⁵. 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%), fuomollugin (17.4%), eugenol (12.7%), (E)-anethole (10.6%), 4-tert-butyl-2-phenyl phenol (9.9%), menthol (2.7%) are the main components³⁶.

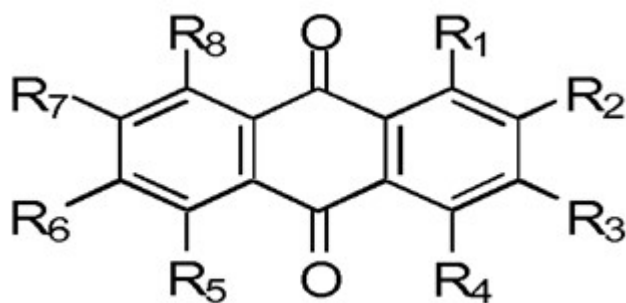


Figure 2: Rubia cordifolia Phytochemical Structure

Different classes of bioactive compounds such as anthraquinones and their glycosides, naphthoquinones and glycosides, terpenes, bicyclic hexapeptides, iridoids,³⁷ 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- anthra-quinone-3-O-(6'-Oacetyl)- α -L-rhamnosyl (1 \rightarrow 2)- β - D-glucoside, 1, 3, 6-tri hydroxy-2-methyl-9, 10- anthraqueinone-3-O- β -L-rhamnosyl (1 \rightarrow 2)- β -D-glucoside, 1, 3, 6-trihydrozy-2-methyl-9,10-anthraquinone-3-O-(6'- Oacetyl)- β -D-glucoside, 2-carbomethoxy+++3-prenyl-1, 4-naphthohydroquinone di- β -D-glucoside, rubimallin, β - sitosterol and daucosterol were also isolated from roots.³⁸ Several naphthoquinones and hydroxyl anhraquinones and their glycosides were also isolated.³⁹ 1-hydroxy 2-methyl anthraquinone, nordamnacanthal, physcion and 1, 4 dihydroxy 6-methyl-anthraquinone,⁴⁰ rubiatriol,⁴¹ 1-hydroxy 2-methoxy anthraquinone; 1, 4- dihydroxy 2- methyl 5-methoxy anthraquinone; 1, 3- dimethoxy 2-carboxy anthraquinone, rubiadin,⁴² naphthaquinones,⁴³ 1, 4-

dihydroxy 2- methylanthraquinone and 1, 5-dihydroxy 2- methylanthraquinone and 3-prenyl methoxy 1, 4-naphthoquinone⁴⁴.

V. PHARMACOLOGICAL STUDIES:

A. Anti Diabetic Property:

Effect of alcoholic extract of roots of *Rubia cordifolia* was studied on elevated blood glucose level in alloxan treated animals. The extract reduced the blood sugar level raised by alloxan. Alcoholic extract enhanced brain γ -amino-n-butyric acid (GABA) levels and decreased brain dopamine and plasma corticosterone levels. Acidity and ulcers caused due to cold restraint stress were inhibited by alcoholic extract. Animals treated with alcoholic extract spent more time in open arm in elevated plus maze model. It also antagonized scopolamine induced learning and memory impairment. Baclofen induced catatonia was potentiated by alcoholic extract.⁴⁵ The hypoglycaemic activity of the alcoholic extract of roots of *Rubia cordifolia* (RCAE, 50,100 and 200 mg/kg, p.o.) was studied in normal, glucose fed and alloxan induced diabetic rats.

The normal rats were treated with single dose of RCAE (200 mg/kg, p.o.) reduced the blood glucose by 20.4 %. The rats pre treated with RCAE (200 mg/kg, p.o.) improved oralglucose tolerance by 124.7 % at $\frac{1}{2}$ h compared to glucose fed rats, exogenously injected insulin (1 IU/kg, s.c.) with RCAE (200 mg/kg, p.o.) caused 26% potentiation of hypoglycaemic effect at 6 h as compared with alone insulin treatment.⁴⁶ The study was designed to investigate the effect of alcohol extract of leaves of *Rubia cordifolia* Linn.in normal and alloxan induced diabetic rats. *Rubia cordifolia* alcohol extract was evaluated for its acute toxicity in female mice. Two doses of *Rubia cordifolia* alcohol extract were selected and were evaluated for antidiabetic activity in alloxan induced diabetic male rats and for hypoglycemic activity in normal fasted rats. In normal treated rats both the doses of *Rubia cordifolia* alcohol extract, 200 and 400 mg/kg decrease (d) the blood glucose level by 32.15 and 39.02%, respectively compared to glibenclamide (600 μ g/kg) by 45.72% after 15 days of treatment. In addition, the extract also showed a favorable effect on glucose disposition in glucose fed hyperglycemic rats after 90 min of glucose administration. In alloxan induced diabetic rats both the doses of *Rubia cordifolia* alcohol extract decreases the blood glucose level by 48.46 and

51.56%, respectively compared to the glibenclamide by 57.28% after 15 days treatment⁴⁷.

B. Anti Inflammatory Effect:

Rubia cordifolia, Linn. (Indian Manjishtha), was studied for the antiinflammatory effect in rats with carrageenan paw oedema. The plant showed significant anti inflammatory activity at a dose of 10 and 20 ml/kg of the water extracts. The activity was comparable to that of phenylbutazone (100 mg/kg). The *in vivo* antioxidant activity of alcoholic extract of the roots of *Rubia cordifolia* Linn. (RC) and to study its influence on ethanol induced impairment of immune responses. Chronic administration of ethanol decreased the humoral and cell mediated immune response, phagocytosis, phagocytosis index, TLC, GSH, CAT and SOD activities and increased the LPO. These influences of ethanol were prevented by concurrent daily administration of RC and the effect was comparable with that of the combination of vitamin E and C.⁴⁸

Anti inflammatory and anticancer compounds from three medicinal plants, viz. *Ventilago madraspatana* Gaertn. *Rubia cordifolia* Linn. and *Lantana camara* Linn were investigated. The NO* scavenging potential of selected plant extracts was determined on LPS/IFN gamma activated murine peritoneal macrophage cultures, and iNOS and COX-2 expression was evaluated by Western blot analysis. Bio assay guided fractionation yielded four compounds: physcion and emodin from *V. madraspatana*, 1-hydroxytectoquinone from *R. cordifolia*. The anti inflammatory activity of these compounds was tested through the carrageenan induced rat paw oedema model. They were then tested against a murine tumour (Ehrlich ascites carcinoma), and three human cancer cell lines, namely A375 (malignant skin melanoma), Hep2 (epidermoid laryngeal carcinoma) and U937 (lymphoma). All four compounds dose dependently inhibited NO through suppression of iNOS protein without affecting macrophage viability. Physcion and emodin caused 65-68% reduction of oedema volume at 40 mg/kg, which validated there *in vivo* anti inflammatory effect. 1-Hydroxytectoquinone and oleanonic acid exhibited promising cytotoxicity against A375 cells.⁴⁹

C. Hepatoprotective Activity:

The hepatoprotective activity of an aqueous methanol extract of *Rubia cordifolia* (Rubiaceae) was investigated against acetaminophen and CCl₄induced

hepatic damage. Acetaminophen produced 100% mortality at a dose of 1 g/kg in mice while pretreatment of animals with plant extract (500 mg/kg) reduced the death rate to 30%. Acetaminophen at a dose of 640 mg/kg produced liver damage in rats as manifested by the rise in serum levels of GOT and GPT to 1447±182 and 899±201 IU/L (*n* =10) respectively, compared with respective control values of 97±10 and 36±11. Pretreatment of rats with plant extract (500 mg/kg) lowered significantly (*p*<0.005) the respective serum GOT and GPT levels to 161±48 and 73±29.⁵⁰

D. Anti microbial activity:

The root extract of *Rubia cordifolia* was found to have antimicrobial activity against various pathogenic bacteria. Sitosterol and daucosterol possessed antibacterial activity. The root extracts constituents such as anthraquinones and flavonoids were found to suppress the activity of phytopathogens of *Gossypium*. Aldehyde acetate, dihydromollugin and rubimallin were reported to have significant antibacterial activity against *Klebsiella pneumoniae*. Ethanolic extract of *Rubia cordifolia* was found to inhibit β -Lactamase producing uro-pathogenic *E. coli*.⁵¹ The chloroform and the methanolic extracts of *Rubia cordifolia* reported to have antibacterial activity on gram-positive strains and gram negative *Pseudomonas aeruginosa* in a dose dependent manner. The aqueous extract of *Rubia cordifolia* was found to active against *Bacillus subtilis* and *Staphylococcus aureus*. *Rubia cordifolia* was reported to have considerable antimicrobial activity against Gram positive bacteria like *Bacillus subtilis*, *Streptococcus faecalis* and *Bacillus cereus*. The green synthesized silver nano particles using *Rubia cordifolia* plant root extract were reported to have highly inhibitory activity of the bacterial pathogens like *Vibrio alginolyticus*, *Pseudomonas aeruginosa*, *Shigella* spp, *Plesiomonas higeloides* and *Vibrio parahaemolyticus*.⁵²

E. Immunomodulating activity:

The alkaloids, cardiac glycosides, tannins, flavonoids and phenols in *Rubia cordifolia* are responsible for enhanced immunomodulation. The ethanolic extract of the whole plant found to exhibit immunosuppressive activity, cell mediated and humoral immunopotentiating activity.⁵³ The extracts of *Rubia cordifolia* and *Rubiadanthus* were found to inhibit the IgE production in peanut allergic mice. In another study revealed that, the administration of

ethanolic plant extract to cyclophosphamide exposed animal was found to enhance immune responses.⁵⁴

F. Anti oxidant activity

Rubia cordifolia contains a wide variety of antioxidants like alizarin, hydroxyl anthraquinones⁵⁵ and rubiadin⁵⁶ 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 orthodihydroxy structure could greatly enhance their effect, and glycosylation reduced activity.⁵⁷ The study of *in vivo* antioxidant activity and its influence on ethanol induced immunosuppression 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.⁵⁸ Rubiadin prevented lipid peroxidation induced by FeSO₄ and butyl hydroperoxide in a dose dependent manner.^{59,60} 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.⁶¹ The alcoholic root extract has some effect on body weight due to rubiadin.

G. Anti tumour activity:

The cyclic hexapeptides and quinones of *Rubia* exhibited a significant anticancer activity against various proliferating cells. The hexapeptides showed potent antitumour activity by binding to eukaryotic 80S ribosomes resulting in inhibition of aminoacyl - tRNA binding and peptidyl - tRNA translocation, thus leading to the stoppage of protein synthesis⁶². The antitumor activity of RA-700, a cyclic hexapeptide isolated from *R. cordifolia*, was evaluated in comparison with deoxybouvardin and vincristine (VCR). The antitumor activity of RA-700 was similar to that of deoxybouvardin and VCR against P388 leukemia. As with deoxybouvardin and VCR, the therapeutic efficacy of RA-700 depends on the time schedule. RA-700 showed marginal activity against L1210 leukemia (50% ILS), similar to that of deoxybouvardin but inferior to that of VCR. RA-700 inhibited Lewis tumor growth in the early stage after tumor implantation, whereas deoxybouvardin and VCR did not. A slight reduction of peripheral WBC

counts was observed with the drug, but no reduction of RBC and platelet counts. Bilirubin, creatinine, GPT and GOT levels in plasma did not change with the administration of the drug⁶³. The anticancer as well as antiviral property had been reviewed⁶⁴. From the chloroform fraction of *R. cordifolia* roots three constituents were isolated namely mollugin, furomollugin and dehydroalapchone. Mollugin has shown inhibition of passive cutaneous anaphylaxis (PCA) and protection of mast cell degranulation in rats.

It also exhibited considerable activity against lymphoid leukemia (P338) in mice⁶⁵. The *R. cordifolia* extract had shown a mitodepressive effect on the rate of cell division in bone marrow cells of Swiss male mice. This exposure time dependent reduction was attributed to the effect of inhibiting protein synthesis, suggesting probable effect of *Rubia* extract on the biosynthesis of certain amino acids as well as RNA synthesis⁶⁶. *R. cordifolia* had shown an increase in leukocyte count in leucopenia⁶⁷. The cytotoxic action of *R. cordifolia* had been evaluated with DNA Topoisomerases I and II inhibition and cytotoxicity of constituents isolated from the roots was tested. Topoisomerases I and II inhibitory activities were measured by assessing the relaxation of supercoiled pBR 322 plasmid DNA. The tetrazolium based colorimetric assay (MTT assay) was used for the cytotoxicity towards human colon carcinoma (HT-29), human breast carcinoma (MCF-7) and human liver carcinoma (HepG2) cell lines. Seven compounds were isolated possessing cytotoxic activity⁶⁸. Antitumor activity of RC-18, a pure isolate from *R. cordifolia*, was repeatedly tested in different sets of experiments on a spectrum of experimental murine tumors, viz P388, L1210, L5178Y, B16 melanoma, Lewis lung carcinoma and sarcoma-180. RC-18 exhibited significant increase in life span of ascites leukemia P388, L1210, L5178Y and a solid tumor B16 melanoma. However, it failed to show any inhibitory effect on solid tumors, Lewis lung carcinoma and sarcoma 180. Promising results against a spectrum of experimental tumors suggested that RC-18 may lead to the development of a potential anti cancer agent⁶⁹. The anticancer activity of extracts of *R. cordifolia*, tested against the P388 tumor system in BDF1 mice, compared well with that of the positive control, 5 fluorouracil⁷⁰.

VI. CONCLUSION:

The above collected information regarding the uses and pharmacological activities of *Rubia cordifolia* is immensely useful for further studies. In the present scenario, ethnobotanical and traditional uses of natural compounds, especially of plant origin have received much attention, as they are well tested for their efficacy and are generally believed to be safe for human use. It is best classical approach in the search of new molecules for management of various diseases. Thorough screening of literature available on *Rubia cordifolia* depicted the fact that it is a popular remedy among the various ethnic groups, AYSUH and traditional practitioners for treatment of various ailments. Researchers are exploring the therapeutic potential of this plant as it has more therapeutic properties which have not been investigated. This review will be helpful in the development of polyherbal formulation as well as for conducting further research to explore the therapeutic potential of *Rubia cordifolia*.

VII. Financial Support and sponsorship

Nil

VIII. Conflicts of interest

None declared.

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