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RUBIA CORDIFOLIA – A REVIEW ON PHARMACONOSY AND PHYTOCHEMISTRY

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ABSTRACT: Herbs & its formulations have a long history of use in the treatment of human diseases. Herbal extracts have long been regarded as a source of new and useful pharmaceuticals. According to Cragg's investigation, approximately 62% of commercially available drugs have natural product origins. Manjistha, or *Rubia Cordifolia* to give it its scientific name, is a branched climber with small, greenish white flowers that are arranged in a cluster of round, fleshy, purple fruits. Its roots have a brownish red bark from which a red dye is obtained. This plant grows well in hilly districts, and the root has medicinal values. Manjistha is considered to be one of the most valuable herbs in Ayurveda, the world's oldest health care system that originated in India. The ancient physician and sage, Charaka has categorized the herb as varnya or that which improves the complexion, jvarahara, or that which reduces fever, and visaghna or that which detoxifies. It is also a well known rasayana – a rejuvenative. Another great sage, Sushruta has mentioned Manjistha as pittasamsamana or that which pacifies the pitta doshas. Acccording to Ayurveda, it is only when the three life energies or doshas, that make up every individual's constitution, are perfectly balanced can a person enjoy good health. These doshas are Vata, Pitta and Kapha, and any imbalance results in ill health. It is imbalances of the Pitta dosha that can be effectively countered by Manjistha.This review is a attempt to unite available information regarding its phytochemistry, traditional uses and biological activities.

INTRODUCTION: The practice of Pharmaconosy is devoted to the discovery and development of new Traditional agents for treating disease. The process of establishing a new drug entity is a complex process and it involves variety of disciplines. In the ancient times, the Indian sages believed that Ayurvedic herbs are one-stop solutions to cure a number of health related problems and diseases. Most of the Ayurvedic herbs, thus formulated, are free of side effects or reactions.

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This is the reason why Ayurveda is growing in popularity across the globe.

Rubia cordifolia, often known as Common Madder or Indian Madder, is a species of flowering plant in the coffee family, Rubiaceae. It has been cultivated for a red pigment derived from roots. Genus *Rubia* fell into about 70 species distributed widely around the world, a total of 36 species and 2 varieties were reported from China. The extracts and phytochemicals of *Rubia* plants had drawn considerable attention due to their potent bioactivities. [1]

Today there is growing interest in chemical composition of plant based medicines. Several bioactive constituents have been isolated and studied for pharmacological activity. *R. cordifolia* is an important medicinal plant commonly used in

the traditional and Ayurvedic 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.

Description of plant:

It is a perennial, prickly climber with a stem, growing up to 12 m long. Leaves are highly variable, ovate lanceolate, 5-7 nerved, 2-10 cm long and 2-5 cm broad, occurring in whorls of 4-6. Flowers are fragrant, minute, whitish or greenish yellow. Fruit is minute, glabrous, 1-2 seeded, dark purplish or blackish when mature. During August-October plant carries flower and fruit. Roots are perennial, long, cylindrical, and rusty brown in colour. [2]

Scientific Classification of Rubia:

Kingdom	:	Plantae
Class	:	Dicotyledoneae
Subclass	:	Sympetalae
Order	:	Rubiales
Family	:	Rubiaceae
Genus	:	Rubia
Species	:	*cordifolia*

Distribution:

It is found throughout India, ascending to an altitude of 3750 m from North- West Himalayas eastwards.

The roots of *Rubia cordifolia* are also the source of a medicine used in Ayurveda. Manjistha" *Rubia cordifolia*, L. (family-*Rubiaceae*), is an important herbal drug used in Indian system of medicine. The root of the plant is commonly known as Manjistha and sold in the market under the commercial name Manjith. Plant drug has number of vernacular names like Aruna, Bhandi, Bhandiralatik in Sanskrit, Mandar, Majathi in Assamme, Manjith, Manjistha in Bengali, Indian Madder in English, Manjithi in Malayalum, Manjestha in Marathi and Majit, Manjit in Hindi. [3]

Rubia species being one of the earliest plant resources possessed important commercial and medicinal values. Commercially, they were used as natural dye-stuffs in old days and improved commodity circulation; medically, these species being used as drugs were first recorded in the world famous pharmacy book of China, *Divine Famer's Materia Medica*, which has over 2000 years history[4]. According to many medical books, the roots of *Rubia* plants being reputed for their satisfactory efficacy were wildly used for the treatment of cancers, tuberculosis, rheumatism, hematemesis, metrorrhagia, epistaxis, contusion and menoxenia in the Chinese traditional medicine [5, 6]. Besides, Indian folk medicine also comprised numerous prescriptions involved in Genus *Rubia* for healing wounds, inflammation, skin infections, and so on [7].

Rubia cordifolia is highly valuable plant in Ayurvedic system of medicine used for treatment of various skin diseases [8, 9]. The root of this plant is used internally in the treatment of abnormal uterine bleeding, internal and external haemorrhage, bronchitis, rheumatism, stones in the kidney and gall bladder, diuretic, dysentery etc. The roots are used to lower the blood pressure [10-15].

It has many other traditional medicinal values. The roots contain quinones like glycosides includind rubiadin,1-hydroxy,2-methoxy anthraquinone,3-dimethoxy 2 carboxy anthraquinone, rubiprasin A,B,C, ruiearbonls, aborane triterpenoids,

mangistin, alizarin, garancin, mollugin, furomollugin. [16-19]

The detail of phytoconstituents identified in *Rubia cordifolia* were- anthraquinone constituents are munjistin, purpurin, and pseudopurpurin. New anthraquinones namely 1-hydroxy-2,7-dimethyl anthraquinone, 2-hydroxy -6-methyl anthraquinone, 2,6-dihydroxy anthraquinone, 1-hydroxy 2-methyl anthraquinone, nordamnacanthal, physcion, 1,4-dihydroxy 6-methyl-anthraquinone, 1,4-dihydroxy 2-methyl anthraquinone, 1,5-dihydroxy 2-methyl anthraquinone, 3-prenyl methoxy 1,4-naphthoquinone, 1-hydroxy 2-methoxy anthraquinone, 1,4-dihydroxy 2-methyl 5-methoxy anthraquinone or 1,4-dihydroxy 2-methyl 8-methoxy anthraquinone, 1,3-dimethoxy 2-carboxy anthraquinone and rubiadin have been isolated from *Rubia cordifolia* roots [20-23]. Three new anthracene derivatives, rubiasins A–C, were isolated from the combined roots and stems of *Rubia cordifolia***.** [24]

The roots of the plant are sweet, bitter, acrid and used as anti-inflammatory [25] haemostatic [26], antidysentric, antipyretic, analgesic, anthelmentic, improves the voice, the complexion and cures the Kapha, the inflammation diseases of the uterus, the vagina, the eye, the ear and the blood. It is also used in the cure of leucoderma, ulcers, urinary discharges, jaundice and piles. [27]

Traditional Therapeutic Uses:

It is highly valuable plant in Ayurvedic system of medicine used for,

1. Powdered dried roots and fruits are taken internally for the treatment of skin diseases and disorder of spleen. [8, 9]
2. It is used for the treatment of major burns, ulcers and bone fractures. [9]
3. It is considered tonic, antitussive, and useful in chronic low fevers. [9]
4. The roots are used internally in the treatment of abnormal uterine bleeding, internal and external haemorrhage, bronchitis, rheumatism, stones in the kidney, bladder and gall, dysentery etc. The plant is used in the treatment of blood disorders. [10]
5. The roots are alterative, anodyne, antiphlogistic, astringent, diuretic, expectorant, styptic and vulnerary.[15]

Phytochemical Studies:

Two pigments were isolated from the root of Prismatomerismalayana, rubiadin-1-methyl ether and rubiadin respectively [28]. Later on by using the unambiguous approach, a number of substance having the proposed structures show well-defined characteristics, mainly in the ^{1}H-NMR and ^{13}c-NMR spectra of their peracetates.[29]

In later stages it was found that triterpenes isolated from Rubia shows anticonvulsant and behavioral action. This effect was studied on convulsions induced by maximum electro shock (MES), electrical kindling and various chemoconvulsants in rat and mice. The effect was also investigated on behavior and gamma-aminobutyric acid(GABA) and serotonin (5-HT) content in mouse brain.triterpene inhibited seizures induced by MES, electrical kindling, pentylenetetrazol(PTZ), and lithium-pilocarpine. [30]

Two new anthraquinones, named cordifoliol and cordifodiol, have been isolated from the roots of Rubia cordifolia. Their structures have been established as 1-hydroxy-3-ethyl-9, 10-anthraquinone (1) and 1,8-dihydroxy-11,20 (15-pentyl-naphthaquinonyl) phenanthrene (2) on the basis of spectral data analyses and chemical reactions. [31]

A new anthraquinone, Rubiacordone A(1) (6-acetoxy-1-hydroxy-2-methylanthraquinone-3-O-alpha-L-rhamnopyranoside), was isolated together with the known anthraquinone, 1-acetoxy-6-hydroxy-2-methylanthraquinone-3-O-[alpha – L -rhamnopyranosyl-(1-2)-beta-D glucopyra noside] (2), from the dried roots of Rubia cordifolia. Their structures were elucidated on the basis of extensive 1D and 2D-NMR, as well as HRESI-MS spectroscopic analysis. Metabolites 1 and 2 showed

considerable antimicrobial activity against Gram-positive bacteria. [32]

Purpurin is the major anthraquinone present in *Rubia cordifolia*. It has an antigenotoxic activity. A sensitive, selective, precise, and robust high-performance thin-layer chromatographic (HPTLC) method of analysis of purpurin from the parts of *Rubia cordifolia* and pharmaceutical dosage forms has been developed and validated. The method employs aluminum foil HPTLC plates coated with silica gel $60F_{254.}$ Densitometric analysis of purpurin was carried out in the absorbance mode at 255 nm. The method was validated for linearity (100–600 ng per band), precision (intra-day variation 0.28 to 1.39%, inter-day variation 0.72 to 2.21%), recovery (96.54 to 98.53%), robustness, and stability of purpurin. [33]

Alizarin (1,2-dihydroxyanthraquinone) was isolated and characterized from *R. cordifolia* L. and evaluated for its antigenotoxic potential against a battery of mutagens viz. 4-nitro-o-phenylenediamine (NPD) and 2-aminofluorene (2-AF) in Ames assay using TA98 tester strain of Salmonella typhimurium; hydrogen peroxide (H2O2) and 4-nitroquinoline-1-oxide (4NQO) in SOS chromotest using PQ37 strain of Escherichia coli and in Comet assay using human blood lymphocytes. Our results showed that alizarin possessed significant modulatory role against the genotoxicity of mutagens.[34]

The hepatoprotective effects of rubiadin, a major constituent isolated from *Rubia cordifolia* Linn., were evaluated against carbon tetrachloride(CCl4)-induced hepatic damage in rats. Rubiadin at a dose of 50, 100 and 200 mg/kgwas administered orally once daily for 14 days. The substantially elevated serum enzymatic activities of serum glutamic oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), serum alkaline phosphatase (SALP) and glutmyl transferase (-GT) due to carbontetrachloride treatment were dose dependently restored towards normalization. The results of this study strongly indicate that rubiadin has a potent hepatoprotective action against carbon tetrachloride induced hepatic damage in rats. [35]
Anti-adipogenic activity of 2-carbomethoxy-2, 3-epoxy-3-prenyl-1, 4-naphthoquinone (CMEP-NQ) isolated from the roots of Rubia cordifolia L., its effects on cell viability, apoptosis, and adipogenesis in 3T3-L1 preadipocytes were investigated. [36]

One of the components in *Rubia cordifolia* L., the anthraquinone precursor 1,4-dihydroxy-2-naphthoic acid (DHNA), induces HaCaT keratinocytes apoptosis through G0/G1 cell cycle arrest. We have also demonstrated that DHNA acts through both caspase-dependent and caspase-independent pathways. Besides, cytotoxicity and IL-1α release assays indicate that DHNA causes less irritation problems than dithranol, which is commonly employed to treat psoriasis in many countries. Since DHNA possesses similar apoptotic effects on keratinocytes as dithranol but causes less irritation, DHNA therefore constitutes a promising alternative agent for treating psoriasis. [37]

In a study, *Rubia cordifolia, Curcuma longa*, *Hemidesmus indicus*, and *Azadirachta indica* extracts caused significant suppression of reactive oxygen species from polymorphonuclear leukocytes and proinflammatory cytokine induced monocytes. [38]

Rubicoumaric acid and rubifolic acid isolated from *Rubia cordifolia* have been shown to be 30-hydroxy-3β-*p*-hydroxycoumaryloxy-urs-12-ene-28-oic acid and 3β,30-dihydroxy-urs-12-ene-28-oic acid(30-hydroxyursolic acid) respectively on the basis of ^{1}H NMR, ^{13}C NMR and mass spectral and chemical evidence. [39]

Two antitumor cyclic componds hexapeptides, named RA-V & RA-VII have been isolated as active principles from R.cordifolia & R. akane,& Their structure is elucidated by various instrumental & chemical analysis. [40]

A novel antitumor bicyclic hexapeptide dimer, RA-dimer A (**3**), was isolated from the roots of *Rubia cordifolia* L. The structure of **3** was determined by analysis of spectroscopic data and chemical correlations. Peptide **3** is the first example of the RA congeners having a dimeric structure. [41]

A novel antitumor bicyclic hexapeptide RA-XVII was isolated from the roots of *Rubia cordifolia*. By

spectral studies and synthetic approach, its structure was determined to be [D-2-aminobutyric acid-1]deoxybouvardin. Studies on the effect of side chain at residue 1 on cytotoxic activity and conformation showed that although it had little effect on the conformation of the molecule, it decreased the activity as it grew longer. [42]

Rubiaceae-type cyclopeptides (RAs), cyclic hexapeptides from *Rubia* plants, have shown potential antitumor activity *in vitro* and *in vivo*. Based on the review about plant cyclopeptides (*Chem. Rev*., 2006, *106*: 840), this mini-review will highlight new progress on the discovery, synthesis, and mechanism of RAs isolated during 2005 to 2011, covering recent work in our group. [43]

Three new anthracene derivatives, rubiasins A–C (**1**–**3**), were isolated from the combined roots and stems of *Rubia cordifolia*, and their structures were elucidated by spectroscopic analysis. Their absolute configurations were determined by Mosher ester methodology. A known compound, mollugin (**4**), was obtained as an active antiproliferative principle by bioassay-monitored fractionation using a human colon cancer (Col2) cell line. [44]

O-Seco-RA-XXIV, a new cyclic peptide, cyclo-(d-alanyl-l-glutaminyl-*N*,*O*-dimethyl-l- tyrosyl - l-alanyl-*N*-methyl-l-tyrosyl-*N*-methyl-l-tyrosyl), was isolated from the roots of *Rubia cordifolia* L. along with RA-XXIV. Its structure and relative stereochemistry were determined by interpretation of the spectroscopic data and X-ray crystallography, and its absolute stereochemistry by the Marfey's amino acid analysis of its acid hydrolysate. Isolation of the two peptides from the same plant source may indicate that *O*-seco-RA-XXIV is a possible precursor of RA-XXIV and that the formation of the diphenyl ether linkage in the cycloisodityrosine moiety is to be formed after the formation of the cyclohexapeptide chain in this series of peptides. [45]

The extracts and phytochemicals of the genus *Rubia* have drawn much attention due to their potent effects; among them, naphthoquinone and cyclopeptide derivatives, with significant biological activities, have great potential to be developed to new drugs. This review updates and compiles a total of 142 quinone derivatives including anthraquinone and naphthoquinone derivatives, occuring in twelve *Rubia* species. These compounds were listed together with their sources, melting points, bioactivities, as well as 112 corresponding references. Furthermore, the structure—activity relationships of these quinone derivatives were discussed. [46]

Rubicoumaric acid and rubifolic acid isolated from *Rubia cordifolia* have been shown to be 30-hydroxy-3β-*p*-hydroxycoumaryloxy-urs-12-ene-28-oic acid and 3β,30-dihydroxy-urs-12-ene-28-oic acid(30-hydroxyursolic acid) respectively on the basis of ^{1}H NMR, ^{13}C NMR and mass spectral and chemical evidence. [47]

An immunoassay system was established for the estimation of the quantity of an antitumor cyclic hexapeptide RA-VII (1) from *Rubia cordifolia* L. and R. akane Nakai (Rubiaceae). First, 1 was converted into its hapten, which was then conjugated with a carrier protein to be used as an effective antigen to obtain its monoclonal antibody (MAb). In the resulting conjugate, the molecular ratio between 1 and the carrier protein as assayed by matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) was about 5:1. Then, the splenocytes from the mouse immunized with the conjugate were fused with mouse myeloma cells to produce hybridoma, secreting MAb against 1. Two clones were isolated, one producing MAb IgG(1) and the other IgM, both having a κ light chain. The sensitivity and cross-reactivity of the thus obtained MAb were also assayed. [48]

The phenolic constituents in the roots of *Rheum officinale* and *Rubia cordifolia* were identified with the aid of high-performance liquid chromatography and liquid chromatography-mass spectrometry and by comparison with authentic standards. A total of 17 hydroxyanthraquinones, gallic acid, and tannins were separated, and 14 of them were identified, being the main phenolic constituents present. Their antioxidant activity (Trolox equivalent antioxidant capacity) was evaluated using the improved 2,2-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt method. Hydroxyanthraquinones were the predominant antioxidant phenolic

constituents in the roots of *R. cordifolia*. The structure-radical scavenging activity relationships of the tested hydroxyanthraquinones were systematically demonstrated as follows: Hydroxy groups on one benzene ring of the anthraquinone structure were essential for hydroxyanthraquinones to show activity, the ortho-dihydroxy structure in the hydroxyanthraquinone molecules could greatly enhance their radical scavenging effect, and glycosylation of the hydroxyanthraquinones reduced activity. [49]

The alpha-glucosidase inhibitors were isolated by the column chromatographic techniques and the bioassay-guided method in vitro from *Rubia cordifolia.* A combination of MS and NMR spectroscopy was used to identify the chemical structures. The chloroform extract showed high inhibitory activity, and three active compounds were isolated and identified as 1,3-dihydroxy-2-methylanthraquinone(1),1-hydroxy-2-methylanthra quinone(2) and 1,2dihydroxyanthraquinone (3). The IC5o values of compound 1-3 were all lower than that of acarbose. Compound 1 and 2 shown competitive type manner on alpha-glucosidase, whereas compound 3 shown noncompetitive type model. [50]

Purpurin is the major anthraquinone present in *Rubia cordifolia*. It has an antigenotoxic activity. A sensitive, selective, precise, and robust high-performance thin-layer chromatographic (HPTLC) method of analysis of purpurin from the parts of *Rubia cordifolia* and pharmaceutical dosage forms has been developed and validated. The method employs aluminum foil HPTLC plates coated with silica gel 60F $_{254.}$ Densitometric analysis of purpurin was carried out in the absorbance mode at 255 nm. The method was validated for linearity (100–600 ng per band), precision (intra-day variation 0.28 to 1.39%, inter-day variation 0.72 to 2.21%), recovery (96.54 to 98.53%), robustness, and stability of purpurin. [51]

Mollugin is the active compound of *Rubia cordifolia,* which has been used as a traditional Chinese medicine for the treatment of various inflammatory diseases including arthritis and uteritis. [52]

Pharmacological actions:

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. [53]

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 their *in-vivo* anti-inflammatory effect. 1-Hydroxytectoquinone and oleanonic acid exhibited promising cytotoxicity against A375 cells. [54]

Neuroprotective Properties:

R. cordifolia has been shown to exert cell/neuroprotective properties via preventing the depletion and increasing GSH (glutathione) levels by inducing GCLC (c-glutamylcysteine ligase) expression, reducing oxidant levels by direct scavenging, and decreasing iNOS expression. The protective ability may be attributed to the GSH and vitamin C content of the herb. [55]

Neuroprotective effect of *Rubia cordifolia* Linn. was studied on β-amyloid Induced cognitive dysfunction in Mice. Ethanolic extract of *Rubia cordifolia* administration significantly ($P<0.01$) reduced the β-amyloid induced cognitive and memory dysfunction. The extract decreases the neurodegeneration and helps in memory retention activity. The extract showed significant effects ($P<0.05$) in short term retention and increases long term retention of memory in step-down inhibitory avoidance task and an increase ($P<0.05$) in number of head dippings, line crossings and rearings in the open field, and the water-maze test. The neuroprotective activity of the plant on alzheimer's type dementia may be due to inhibition of AChE, MAO, free radical scavenging activity. [56]

Antibacterial Activity:

The antibacterial activity of the extracts of *Ventilago madraspatana* stem-bark, *Rubia cordifolia* root and *Lantana camara* root-bark, prepared with solvents of different polarity, was evaluated by the agar-well diffusion method. Twelve bacteria, six each of gram-positive and gram-negative strains, were used in this study. Chloroform and methanol extracts of *R. cordifolia* and *L. camara* was found to be more specific towards the gram-positive strains, although gram-negative *P. aeruginosa* was also inhibited by the methanol extracts of both these plants in a dose dependent manner. *R. cordifolia* was significantly active against *B. subtilis* and *S. aureus* compared with streptomycin and penicillin G used as standards. [57]

Comparative studies of *Rubia cordifolia* and its Commercial Samples were done. It was carried out by comparing the authentic sample from its commercial samples keeping in mind the pharmacopoeial standards of Ayurveda. The quantitative phytochemical studies of the drug samples were carried out by studying the percentage of ash, extractive values and qualitative screening was carried out by Thin Layer Chromatography and different biochemical tests. [58]

Hepatoprotective Activity:

The hepatoprotective activity of an aqueous-methanol extract of *Rubia cordifolia* (Rubiaceae) was investigated against acetaminophen and CCl_4induced 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.[59]

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. [60]

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 ½ 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. [61]

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 (600µg/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 treatment.[62]

Radioprotective Property:

Radioprotective potential of alcoholic extract of root of Manjistha showed a significant radiation protection (67%) as assessed by increased animal survival when *R. cordifolia* extract was administered intraperitoneally before radiation exposure. Results suggest the alcoholic root extract provides protection against radiation-induced lipid peroxidation, hemopoietic injury and genotoxicity.[63]

Nephrotoxicity:

The hydro-alcoholic extract of *Rubia cordifolia* could decrease the intensity of cisplatin induced nephrotoxicity in Swiss albino mice. The extract could significantly decrease the cisplatin induced nephrotoxicity as inferred from the tissue antioxidant status in the drug administered animals. Remarkable change was observed in serum creatinine and urea levels. Lipid peroxidation in the kidney and liver tissues was also considerably reduced in *Rubia cordifolia* extract treated animals.[64] An effective column-switching counter-current chromatography (CCC) protocol combining stepwise elution mode was successfully developed for simultaneous and preparative separation of anti-oxidative components from ethyl acetate extract of traditional Chinese herbal medicine *Rubia cordifolia*. [65]

Anti-proliferating Property:

Ethyl acetate fraction of the root of *Rubia cordifolia* L. inhibits keratinocyte proliferation in vitro and promotes keratinocyte differentiation in vivo. Ethanolic extract of Radix Rubiae was fractioned sequentially with hexane, ethyl acetate (EA), n-butanol and water. EA fraction was found to possess most potent antiproliferative action on HaCaT cells (IC (50) 0.9 microg/ml). The standardized EA fraction was formulated into topical gel and its keratinocyte-modulating action was tested on mouse tail model. EA fraction dose-dependently increased the number and thickness of granular layer and epidermal thickness on mouse tail skin, indicative of the keratinocyte differentiation-inducing activity. Taking the in vitro and in vivo findings together, the present preclinical study confirms that EA fraction is a promising antipsoriatic agent warranting further development for psoriasis treatment. [66]

Protective effect:

Protective effect of the hydro-alcoholic extract of roots of *Rubia cordifolia* Linn. (HARC) against ethylene glycol induced urolithiasis and its possible underlying mechanisms using male wistar albino rats. Ethylene glycol feeding resulted in hyperoxaluria, hypocalciuria as well as increased renal excretion of phosphate. The increased calcium and oxalate levels and number of calcium oxalate crystals deposits in the kidney tissue of calculogenic rats was significantly reverted by HARC treatment. The HARC supplementation also prevents the impairment of renal functions. The results indicate that the HARC can protect against ethylene glycol induced urolithiasis as it reduced and prevented the growth of urinary stones. Therefore, HARC is helpful to prevent the recurrence of the disease as it showed its effect on early stages of stone development. The mechanism underlying this effect is mediated possibly through an antioxidant, nephroprotection and its effect on the urinary concentration of stone-forming constituents and risk factors. [67]

The protective effect of *Rubia cordifolia* against lead nitrate-induced immune response impairment and kidney oxidative damage was studied. Seventy-two adult male Swiss albino mice were used for biochemical and immunological studies and were divided into six groups of six mice each. Mice were treated with lead nitrate (40 mg/kg, orally) either alone and or in combination with RC (50 and 100 mg/kg body weight) daily for 40 days. Lead nitrate administration induced a significant (P<0.001) increase in LPO, whereas a significant (P<0.001) depletion of CAT and GSH in renal tissues.

In addition, it also showed a significant (P<0.001) reduction in macrophage yield, viability of macrophage, phagocyte index, serum immunoglobulin level, and PFC in kidney. However, combination treatment with RC observed a significant (P<0.001) reversal of lead nitrate-induced toxicity on oxidative stress and immunological parameters. The lead nitrate-induced immunosuppression is due to oxidative stress and RC can prevent the same by virtue of its *in vivo* antioxidant property. [68]

Antioxidant effect:

R. cordifolia extracts were also evaluated for antioxidant and lipid peroxidation inhibitory activity by 1, 1-diphenyl-2-picryl-hydrazyl and TBARs Thiobarbituric acid reactive substances method respectively. Extract of *R. cordifolia* showed a significant inhibitory activity against Propioni bacterium acnes standardized culture. The evaluation was carried out by broth dilution method; suggested MIC of *R. cordifolia* extract was 600µg/ml. The methanolic extract of *R. cordifolia* showed significant lipid peroxidation inhibitory activity. The IC50 value of 138µg/ml and R2 was 0.9921.The result was compared with curcumin as standard (IC50 50µg/ml, R2 0.9469). These investigations have revealed *R.cordifolia* as a promising anti-acne agent because it inhibits the proliferation of *Propioni bacterium acnes* and hence prevents its consequences. [69]

The *in vitro* antioxidant status of methanolic extract of roots and rhizomes of *R. cordifolia* (M-RC) was determined. The effect of M-RC on tacrine-induced tremulous jaw movements in rats and sodium nitrite-induced hypoxia in mice was studied. IC50 value for lipid peroxidation of a linoleic acid emulsion was found to be 120 µg/ml. IC50 value for free radical and hydroxyl radical scavenging activity were found to be 130 ppm and 135 ppm, respectively. In M-RC, 1.8679 ± 0.29 µg/g gallic acid phenol equivalents were detected. M RC significantly inhibited tacrine-induced vacuous chewing movements (VCM), tongue protrusions (TP) and orofacial bursts (OB). M-RC also significantly potentiates sodium nitrite-induced hypoxia and decreased the latency for death after sodium nitrite administration. The study concludes that *R. cordifolia* has an anticholinergic activity which may be attributed to antioxidant activity and presence of phenolic compounds. [70]

Anti Ulcer Effect:

The effect of *Rubia cordifolia* (Rubiaceae) against experimentally induced gastric ulcer and compare activity with its fractions by employing aspirin plus pylorus-ligated ulcer screening model in wistar rats. The study confirmed that chloroform fraction showed the significant activity at lower doses compared to parent extract. The mechanism can be attributed to decrease in gastric acid secretary activity along with strengthening of mucosal defensive mechanism by prostaglandin synthesis and antioxidant potential. [71]

Anti-Adipogenic Activity:

Anti-adipogenic activity of 2-carbomethoxy-2, 3-epoxy-3-prenyl-1, 4-naphthoquinone (CMEP-NQ) isolated from the roots of *Rubia cordifolia* L., its effects on cell viability, apoptosis, and adipogenesis in 3T3-L1 preadipocytes were investigated [72]

Anti-HIV Activity:

Assessment of anti-HIV activity of various extracts prepared from Indian medicinal plants. The plants were chosen on the basis of similarity of chemical constituents with reported anti-HIV compounds or on the basis of their traditional usage as immunomodulators. Different extracts were prepared by Soxhlet extraction and liquid-liquid partitioning. Ninety-two extracts were prepared from 23 plants. Anti-HIV activity was measured in a human CD4+ T-cell line, CEM-GFP cells infected with HIV-1NL4.3. Nine extracts of 8 different plants significantly reduced viral

production in CEM-GFP cells infected with HIV-1NL4.3. *Aegle marmelos, Argemone mexicana, Asparagus racemosus, Coleus forskohlii,* and *Rubia cordifolia* demonstrated promising anti-HIV potential. [73]

Wound Healing Effect:

Assessment of Wound Healing of a polyherbal formulation containing *Rubia cordifolia* was done. Cream formulation of the herbal drug combination of *R.cordifolia, C.asiatica, T.belerica, P.zeylanica*, and *W.somnifera* was formulated. Animals were inspected daily up to 20th days and healing was assessed based on physical parameter namely, wound contraction, period of epithelization and histological study. It promotes contraction and epithelization of excision wound. [74]

Anti-tumour activity:

Anti-tumour activity of RC-18, a pure isolate from *Rubia cordifolia* was repeatedly tested in different sets of experiments on a spectrum of experimental murine tumours, viz. P388, L1210, L5178Y, B16 melanoma, Lewis lung carcinoma and sarcoma-180. RC-18 exhibited significant increase in life span of ascites leukaemia P388, L1210, L5178Y and a solid tumour B16 melanoma. However, it failed to show any inhibitory effect on solid tumours, Lewis lung carcinoma and sarcoma 180. Promising results against a spectrum of experimental tumours suggest that RC-18 may lead to the development of a potential anti-cancer agent.[75]

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