

CORDIA DICHOTOMA G FORST: A COMPREHENSIVE REVIEW

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ABSTRACT

Cordia dichotoma, belongs to the family Boraginaceae is used in the traditional system of medicine for number of diseases viz., intestinal parasite infestation, allergy, erysipelas, fever, dropsy, anasarca, urticaria, dyspepsia, cholera, dysentery, diuretic, demulcent, ulcer, anthelmintics and snake bite. The present study is to give comprehensive review on pharmacognostical, phytoconstituents and scientifically proved pharmacological activity of *C. dichotoma*.

Key Words: *Cordia dichotoma*; comprehensive review, phytoconstituents, pharmacological activity.

INTRODUCTION

India is the richest sources of medicinal plant with activity. As per WHO 80% of the people rely on herbal drugs for alleviation of diseases. More than 3000 plant species have reported to possess beneficial effect for the treatment of diseases as per Siddha, Ayurveda, Amchi and Unani. One such plant is *Cordia dichotoma* G. Forst.

C. dichotoma is deciduous plants available all over India. *C. dichotoma* are extensively used as intestinal parasite infestation, allergy, erysipelas, fever, dropsy, anasarca, urticaria, dyspepsia, cholera, dysentery, diuretic, demulcent, ulcer, anthelmintics and snake bite.

GEOGRAPHICAL DISTRIBUTION

C. dichotoma grows in the deciduous forests of Rajasthan, Western Ghats, Myanmar and the sub-Himalayan tract at about 1500 m elevation. It is native to India, China, Japan, Pakistan, Sri Lanka, Australia. It is a tree of tropical and subtropical regions [1-3].

COMMON NAMES:

Fragrant man jack, snotty gobbles, cumming cordia, glue berry, anonang, pink pearl, bird lime tree, and Indian cherry [4].

VERNACULAR NAMES:

English: Indian cherry, Clammy cherry, Fragrant manjack

- Assamese: Goborhut, bahubara
- Bengali: Bahubara, Boch
- Hindi: Lasora
- Malayalam: Naruvari
- Marathi: Bhokar, Shelu
- Gujarati: Vad gundo
- Kannada: Challe, Haadige, Doddachallu, Kaaduchalle, Mannadike, Kendal

- Sanskrit: Bahuvarah
- Tamil: Naruvili, Citam, Naruvali
- Telugu: Bankanakkera, Chinna-Nakkeru, Botgiri

PLANT DESCRIPTION:

Taxonomy of the plant

Kingdom: Plantae
 Division: Magnoliophyta
 Class: Dicotyledons
 Subclass: Astaridae
 Order: Lamiales
 Family: Boraginaceae
 Genus: *Cordia*
 Species: *dichotoma*

MACROSCOPIC CHARACTERS:

Cordia dichotoma G. Forst. is small to medium-size deciduous tree with a short-crooked trunk, short bole and spreading crown leaves are simple, entire, and slightly dentate, elliptical-lanceolate to broad ovate with a round and cordate base. The stem bark is greyish brown smooth or longitudinally wrinkled. Flowers are short stalked, bisexual, and white to pinkish in colour and appear in loose corymbose cymes. Fruits are edible with sticky flesh mass. It is a yellow or pinkish-yellow shining globose or ovoid drupe seated in a saucer-like enlarged calyx. It turns black on ripening and the pulp gets viscid.

MICROSCOPICAL AND POWDER CHARACTERISTICS OF LEAF

Microscopy of *Cordia dichotoma* showed features like scattered vascular bundles having patches of perimedullary phloem, unicellular and multicellular covering trichomes. Xylem vessels and calcium oxalate crystals were seen too in powder microscopy [5-8].

NUTRITIONAL INFORMATION:

The chemical composition of the fruit was reported as (g/100 g on dry matter basis): protein (2); fat (2), crude fibre (2) and total available carbohydrates (92). The mineral composition was (mg/100 g on dry matter basis): Ca (552), P (275 ± 15), Zn (2), Fe (6) and Mn (2). The antinutritional factors reported were phytic acid, 355 ± 30, phytate phosphorus, 100 = 10 and oxalic acid, 250 ± 19 mg/100 g on dry matter basis [9].

Preliminary analysis of mucilage obtained from the fruit gave methoxyl content, 5.28 %; uronide content 15.7 % and acetyl ester, 4.17 %. Hydrolysis and chromatography of mucilage revealed the presence of D-galactose, L-arabinose, D-xylose and D-galacturonic acid. A structure was suggested for mucilage based on methylation, fractionation and hydrolysis studies [10].

The seeds showed presence of sugars namely D-glucose, D-xylose, D-ribose, L-rhamnose, D-glucuronic acid, D-arabinose, lactose, L-fructose and amino acids viz, glycine, leucine, glutamic acid, cystine, alanine, threonine, aspartic acid and proline [11]. The seed kernels contained 46.3 % fatty oil and 31.5 % proteins. The protein contained seventeen amino acids namely, cystine, aspartic acid, serine, glycine, glutamic acid, threonine, lysine, histidine, arginine, tyrosine, alanine, methionine, valine, phenylalanine, leucine, isoleucine and proline. The percentage composition of the fatty acids in the kernel oil was reported as palmitic acid, 15.58; stearic acid, 6.5; arachidic acid, 1.85; behenic acid, 0.95; oleic and linoleic acids (combined), 67.65 and other unidentified acids, 7.47[12]. The fatty acid composition of fixed oil was also determined by solid liquid counter current separation and spectrophotometric methods and reported as palmitic, 7.84; 8.57; stearic, 13.35; 13.15; oleic, 9.95; 59.45 and linoleic, 18.86; 18.83 %, respectively. The unsaponifiable portion yielded β-sitosterol [13, 14].

The seeds were reported to contain taxifolin-3-rhamnoside [15]; taxifolin-3. 5-0-α-L-dirhamnoside [16] and 3', 4'.5.7 tetrahydroxyflavanone-3-0-D-xylopyranoside [17]. The petroleum ether extract of seeds yielded α-amyrin, betulin, octacosanol and lupeol-3-rhamnoside. Further extraction with benzene led to isolation of β-sitosterol, β-sitosterol-3-glucoside. Hentricontanol, hentricontane and the chloroform extract yielded hesperetin-7-0-rhamnoside and earlier reported taxifolin-3. 5-rhamnoside [18].

The chemical composition of leaves collected from Palampur was reported as (% in dry matter): crude protein, 12.37; ether extract, 1.53; crude fibre, 26.76; nitrogen-free extract, 41.93; calcium, 3.55 and phosphorus, 0.25[19]. The composition of tree leaves used as fodder was earlier reported [20].

The percentage of protein nitrogen, protein, total nitrogen and extractability of leaf protein concentrate (LPC) (g/100 g dry weight) was estimated as 1.98, 12.37, 2.17 and 05.16. respectively during flowering stage. Further, the LPC was analysed for total nitrogen, protein nitrogen, protein (N x 6.25) and estimated as 3.68, 2.40 and 15.00 %, respectively. The extractability of total and protein nitrogen of LPC was also determined [21].

The composition of mature leaves obtained from forests of Doon Valley was reported as Ca, 4.93; carbon, 43.7 and nitrogen, 2.19 % [22]. The crude protein (10.21 % of dry matter) [23] and tannin (0.42-0.84 g/100 g dry matter) contents of leaves collected from Palampur were also reported [24].

The energy values of tree leaves used as fodder were reported in terms of digestible energy, 2711.0; metabolizable energy, 2299.4 and net energy for fattening, 1217.0 expressed as Kcal/kg dry matter [25].

The stem bark yielded allantoin, β -sitosterol and 3', 5-dihydroxy-4-methoxyflavanone-7 O- α -L-rhamnopyranoside [14].

The destructive distillation of hardwood yielded (expressed as % of dry wood): charcoal (35.1), tar (5.0), and pyroligneous acid (42.4). The pyroligneous acid was analysed for its acid, ester, acetone and methanol contents [26] and wood ash analysis was reported [27].

The root revealed the presence of β -sitosterol [28], flavanol glycosides 5, 7-dimethyltaxifolin-3-O- α -L-rhamnopyranoside [29], hesperetin-7-O- α -L-rhamnopyranoside [30] and triterpene glycosides lupa-20, 29-ene-3-O-8-D-maltoside [31], lupa-20(29)-ene-3-O- α -L-rhamnopyranoside [32].

CULTIVATION:

The *C. dichotoma* grows in areas where the mean annual rainfall is in the range 250 - 3,000 mm, prefers deep moist sandy loams. When the tree reaches pole stage it prefers complete overhead light, but seedlings and saplings can withstand a fair amount of shade. Young seedlings are frost tender and suffer from exposure to hot sun. They are susceptible to browsing and fire but recover appreciably from these injuries. The trees reach a height of 4 metres in 4 years and a diameter of over 20 cm in 8 - 9 years [1].

Flowers are stalk less, white or yellowish- white, about 7 mm long and borne in lax inflorescences 5 to 10 cm long. 1 in (25mm) long dull pinkish edible fruits with sticky flesh flowers are short stalked, bisexual and white in colour, appear in loose corymbose cymes follow these flowers. The calyx is ovoid. The corolla tube no longer than the calyx with spreading and relaxed lobes. Throat of the corolla and stamens are hairy.

The fruit is a yellow or pinkish-yellow shining globose or ovoid drupe in an enlarged calyx. It turns black on ripening and the pulp gets viscid. The hard stone is 1-4 seeded [33]. Flowering takes place from March to May. The old leaves are shed during winter and the trees are leafless for a short period in early summer. Fruits are formed soon after flowering, develop quickly and ripen from June to August in north India and normally before May in south India. Seed dispersal is aided by birds and monkeys which feed on the ripe fruit; Odour: Characteristic; Taste: Sweet [34].

GERMPLASM MANAGEMENT:

Ripe fruits are collected from the trees and rubbed to remove the flesh. The healthy stones are dried in the shade and kept in tin containers. The stones can be stored for 1 year in airtight containers kept in a dry place to avoid insect attack. There are 4 000-7 000 stones/kg [35].

PESTS AND MANAGEMENT

A large number of larvae of *Chrysomelidae*, *Glyphiplerygidae*, *Noctuidae*, *Lymantridae*, *Notodontidae*, *Pyalidae*, *Sphingidae* and *Yponomeutidae* are reported to defoliate the leaves. Larvae of *Gracilariidae* and *Lyonetiidae* mine the leaves and those of *Eucosmidae* roll the leaves. Larvae of some insects belonging to families *Eucosmidae*, *Curculionidae* and *Pyalidae* bore into the fruits and shoots. *Austrothrips cochinchinensis* forms galls and feeds on the sap. *Aceria gallae* and *A. pobuzii* infest and cause galls on leaves, fruits, shoots and tender stems. The weevil *Barioscapus cordiae*, adults attack the fruits and feed on the green pedicel, sepals and pollen grains inside the buds [36].

AYURVEDIC PROPERTIES:

- RASA- bark is Kashaya [astringent] tikta[bitter] fruit is Madhura[sweet]
- GUNA [qualities] – snigdha [slimy] guru [heavy]
- VIPAKA- bark - katu [undergoes pungent taste after digestion]
- VEERYA [potency] – sheeta [cold]
- KARMA [actions] – fruit is pitta vata [reduces vitiated pitta and vata dosha] bark is kapha pitta shamaka [reduces kapha and pitta dosha] [37].

PARTS USED:

- Leaf, stem bark, leaves and fruits

TRADITIONAL USE:

The parts of the tree are used in intestinal parasite infestation, allergy and erysipelas [38]; fever, dropsy, anasarca, urticaria, dyspepsia, cholera and dysentery [39]; as astringent, anthelmintic, diuretic, demulcent, expectorant, in diseases of lungs and spleen, dyspepsia, fever, ringworm, ulcers and snake bite [40,41].

PHARMACEUTICAL INDUSTRIAL USES-

- Tablet binder: The fruit of *Cordia dichotoma* is highly sticky in nature this property is used for binding of tablets. In future Cordia gum could compete favourably with gelatin as binder in tablet formulations
- Emulsifier
The Cordia gum as pharmaceutical excipient, may use as an emulsifier. The Cordia gum will be a good option as bio-degradable, cheap, economic and easily available emulsifier in the list of pharmaceutical excipient. [42-44]

CHEMICAL CONSTITUENTS:

The phytochemical constituents isolated so far from the plant *C. dichotoma* is given below.

Seed: α -amyrins, betulin, octacosanol, lupeol-3-rhamnoside, β -sitosterol, β -sitosterol-3-glucoside, hentricontanol, hentricontane, taxifolin-3-5-dirhamnoside, hesperitin-7-rhamnoside and fatty acids such as palmitic acid, stearic acid, arachidic acid, behenic acid, oleic acid and linoleic acid. Four flavonoid glycosides (robinin, rutin, rutoside, datiscoside and hesperidin), a flavonoid aglycone (dihydrorobinetin), p-hydroxybenzaldehyde, 4-hydroxybenzoic acid, p-hydroxyacetophenone, p-hydroxypropiophenone, latifolicinin C and 2 phenolic derivatives (chlorogenic acid and caffeic acid) were isolated from seeds.

Kernel: Fatty acids are present abundantly in the kernels of *C. dichotoma* such as behenic acid and palmitic acid [9]. Also, it contains a large amount of tannic acid and protein i.e. cysteine and methionine

Bark: Allantoin, β -sitosterol and 3', 5-dihydroxy-4'-methoxy flavanone-7-O- α -L-rhamnopyranoside, apigenin.

Fruits and leaves: Presence of pyrrolizidine alkaloids, coumarins, flavonoids, saponins, terpenes and sterols.

Fruit: Arabinoglucan, D-glucose (67.6%) and L-arabinose (13.2%).

Leaves: Flavonoids such as apigenin, rutin, quercetin, quercitrin, (quercetin-3-O-rutinoside, quercetin-3-O-2G-rhamnosylrutinoside), isorhamnetin-3-O-rutinoside, kaempferol-3-O-robinoside, kaempferol-3-O-rutinoside, kaempferol-3-O-2G-rhamnosylrutinoside, flavone (luteolin) and phenols such as methyl rosmarinate, β -sitosteryl-1- β -glucopyranoside-6'-O-palmitate, chlorophyll, octacosanol, pyrrolizidine alkaloids, saponins, terpenes (betulin), and sterols such as β -sitosterol, α -amyrin, 4-hydroxy-transcinnamate ester triterpenoids (0.075 %) and amino acids (1.39 %).

Twigs: β -sitosterol and β -sitosteryl-3-glycoside, 1, 2-dilinoleoyl-3-linolenoylglycerol [45-50].

QUANTITATIVE STANDARDS

The loss on drying at 105°C was 8.5% w/w,

Total ash value 13% w/w,

Acid-insoluble ash 5.07% w/w,

Water-soluble ash 5.49% w/w,

Water-soluble extractive 9.2% w/w,

Alcohol soluble extractive 5.81% w/w

pH (1% aqueous extract):6.88.

PHYTOCHEMICAL SCREENING

Phytochemical screening of leaves showed the presence of steroid, carbohydrate, alkaloid, saponin, cardiac glycosides, flavonoid and phenolic compounds in methanol extract.

HPTLC DETERMINATION OF METHANOL EXTRACT OF LEAVES

The methanol extract of *Cordia dichotoma* leaves) were applied on precoated silica gel GF 60254 aluminum. Toluene: ethyl acetate: formic acid (5:4:1) was used as the mobile phase. After development, densitometric scan was performed at 254 nm and 366 nm. It revealed 3 peaks and 5 peaks at UV 254 nm. and UV 366 nm. Four of the components with max R_f values 0.3, 0.53, 0.60 and 0.65 were found to be predominant as the percentage area was more with 30.97%, 13.18%, 26.23 and 20.91% respectively [51,52].

PHARMACOLOGICAL ACTIVITIES

Acute toxicity studies

The acute toxicity was determined in albino rats (170-200 g) by adopting fixed dose method (OECD guidelines No. 420). Animals were administered with increasing dose of methanol extract (5, 50, 300, 2 000 and 5 000 mg/kg body weight) to determine changes in parameters for assessing toxicity. No mortality was observed up to dose as high as 2 g/kg body weight.

Anti-diabetic activity:

The antidiabetic activity of methanol extract of bark of *C. dichotoma* [MECD] was assessed in alloxan-induced diabetic wistar rats and oral glucose tolerance. The extract significantly reduced the blood glucose levels, including body weight, serum lipid profile and antioxidant enzymes/ biomarkers in the alloxan-induced diabetic rats at the dose levels of 250 & 500 mg/kg as compared with that of the standard drug, glibenclamide (5 mg/kg). In oral glucose tolerance (OGT) test, the pre-treatment of MECD showed partial protection from hyperglycemia induced by a glucose load (2 g/kg, body weight) in rats at the dose levels of 250 and 500 mg/kg, body weight [53].

Similar studies were conducted with methanol extract of fruits of *Cordia dichotoma* in glucose-loaded animals and alloxan induced diabetic animals. In both the models, it reduced the blood glucose level and body weight in comparison to that of standard drug metformin exhibiting significant hypoglycemic and antidiabetic activity [54].

The isolated flavonoids 3, 5, 7, 3', 4'-tetrahydroxy-4-methoxyflavone-3-O-L-rhamnopyranoside and 5, 7, 3'-trihydroxy-4-methoxyflavone-7-O-L-rhamnopyranoside (quercitrin) were evaluated for antidiabetic activity along with docking and ADMET studies. Docking and ADMET studies revealed the promising binding affinity of flavonoid molecules for human lysosomal α -glucosidase and human pancreatic α -amylase with acceptable ADMET properties [55].

The anti-diabetic effect of fruits pulp and peel of *Cordia dichotoma* (*C. dichotoma*) powder against diabetes mellitus type 2 was evaluated. The results showed that supplemented diet with *C. dichotoma* powder caused slight increase in body weight gain, significant decreases in serum levels of blood glucose, AST, ALT, total bilirubin, alkaline phosphatase enzyme and decreased serum levels of (LDL), triglycerides (TG), total cholesterol (TC) levels, malondialdehyde (MDA) and increased in HDL levels and activity of antioxidant enzymes suggesting it helps in controlling of diabetic hazards [56].

Anti-atherosclerotic activity

The anti-atherosclerotic activity of isolated Isorhamnetin from the bark of *Cordia dichotoma* was evaluated in high fat induced atherosclerosis rats. Isorhamnetin produced a significant and dose-dependent anti-atherosclerotic activity in terms of reduction in low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), Total cholesterol (TC), and Triglyceride (TG) level; and elevation of high-density lipoprotein (HDL) [57].

Antihypertensive activity

The anti-hypertensive activity of the isolated Isorhamnetin from the bark of *Cordia dichotoma* in L-NAME induced hypertension model was evaluated. It reduced the elevated arterial pressure of L-NAME induced hypertensive rat significantly to the level of normotensive animal group [57].

Anti hyperlipidemic activity

The effect of 10% and 20% *C.dichotoma* pulp extract (CPD) were evaluated for antihyperlipidemic activity in male albino rats, which were fed high-fat diet (HFD) for 10 weeks. In normal rats, CDP 20% caused significantly decreased of risk to about 57.9% with respect of normal control. Liver and kidney functions of hyperlipidemic rats were improved with two levels supplemented of *Cordia dichotoma* Forst. pulp. The results of pathological indicted that 20% CDP caused decrease in fatty changes in the liver of rats [58].

In another similar experiment performed using the aqueous extract from the uneaten pulp of the fruit from *Cordia dichotoma* (CDNP extract) at a dose of 0.50 and 1.00 g/kg body weight in male albino rats which were

fed high-fat diet (HFD) for 10 weeks. Similar results were obtained with the CDNP extract as above so it can be employed in the management of dietary hyperlipidaemia [59].

The administration of the *C. dichotoma* extract with two dosages (0.5 and 1.0 g/kg body weight/ day) for four weeks in rats fed on high-fat diet caused a significant improvement in the lipid metabolism compared to the hyperlipidemic control. The high dosage of extract. *C. dichotoma* minimized fat and cholesterol intake significantly and maximized those in faecal excretions in comparison with hyperlipidemic control values. *C. dichotoma* extract normalized the lipid profile of the serum and liver compared with hyperlipidemic control [60].

Wound healing activity:

The wound healing activity of ethanol extract of fruits of *C. dichotoma*, which fractionated with Petroleum ether, solvent ether, ethyl acetate, butanol and butanone fractions, was screened using three different models, viz. excision wound, incision wound, and dead space wound in Wistar rats. All the fractions showed significant wound healing property [61].

Anti-fungal and Anti-microbial activity:

Antibacterial and antifungal activity of methanol and butanol extracts of the bark was carried out against two gram negative bacteria (*Escherichia coli*, and *Pseudomonas aeruginosa*); two Gram positive bacteria (*St. pyogenes* and *Staphylococcus aureus*) and *Aspergillus niger*, *A.clavatus*, and *Candida albicans*. The extracts showed remarkable inhibition of zone of bacterial growth and fungal growth when compared with that of different standards like Ampicillin, Ciprofloxacin, Norfloxacin and Chloramphenicol for antibacterial activity, Nystain, and Greseofulvin for antifungal activity [62].

The antibacterial, anti-biofilm and photo catalytic activity of silver nanoparticles synthesized using *Cordia dichotoma* fruits (Cd-AgNPs) was evaluated. It showed significant antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*. Phyto-synthesized Cd-AgNPs exhibited more than 90% inhibition of biofilm activity formed by *S. aureus* and *E. coli*. Furthermore, photocatalytic degradation of crystal violet (CV) under UV light irradiation using Cd-AgNPs which exhibited 85% degradation activity for CV suggesting that Cd-AgNPs, can be used as a novel biocidal agent[63].

Methanolic extract of root fractionated showed Microorganism susceptible index was 100 for *P. vulgaris*, *K. pneumonia* bacteria; *A. fumigates* and *V. myditis* fungi. It exhibited best activity against *M. tuberculosis* with lowest MIC of 30 mg/ml and highest activity index of 0.85 suggesting it to be a potential cure for infectious diseases like tuberculosis [64].

Antifungal activity of the ethanol extract of *Azadiracta indica*, *Allium sativum*, *Cordia dichotoma* *Ocimum sanctum*, *Syzygium cumini* and *Trigonella foenum grecum* were evaluated against a total of 50 *Candida* isolated from clinical specimens. All extracts were effective against all MDR *Candida* isolates with inhibition zone ranging from 10- 18mm in diameter with minimum inhibitory concentration (MIC) of all ethanol plant extract ranging from 1.56-25mg/ml. The percentage inhibition was found to be 84%, 62%, 60%, 76%, 46, 30%, and 22% for fluconazole, clotrimazole, Amphotericin B, itraconazole, ketoconazole, miconazole and nystatin tested respectively against multi-drug resistance in all *Candida* isolates[65].

The antibacterial test of Copper nanoparticles synthesized using *Cordia dichotoma* plant leaf extract conducted on *E. coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, showed good zone of inhibitions 9.60, 9.45 and 9.50 mm, respectively proving potentiality of Cu NPs as a remedy for infectious diseases [66].

The hexane extract of powdered stem bark was evaluated for antibacterial activity using two bacterial pathogens by the disc diffusion method [67].

Standardized surface sterilization methods were employed to isolate thirty-three phenotypically distinguishable endophytic bacteria from the root, stem, and leaf parts of the *Cordia dichotoma*. Shannon Wiener diversity index clearly divulged diverse endophytes in roots (0.85), stem (0.61), and leaf (0.54) belonging to the genera *Bacillus*, *Pseudomonas*, *Paenibacillus*, *Acidomonas*, *Streptococcus*, *Ralstonia*, *Micrococcus*, *Staphylococcus*, and *Alcalignes* predominantly. Interestingly, majority of the bacterial endophytes of *C. dichotoma* showed antimicrobial activity against *Bacillus subtilis* followed by *Klebsiella pneumonia* [68].

The crude ethanol extract of leaves of *Cordia dichotoma* was evaluated for its antibacterial effects against both Gram negative and Gram-positive bacteria against *Streptococcus aureus*, *Streptococcus pyogenes*, *Vibrio*

cholerae, *Streptococcus epidermis*, *Hafnia* and *Escherichia coli*, which is comparable with Kanamycin (30µg/ml) [69].

The medicinal plants *Asphodelus tenuifolius* Cav., *Asparagus racemosus* Willd., *Balanites aegyptiaca* L., *Cestrum diurnum* L., *Cordia dichotoma* G. Forst, *Eclipta alba* L., *Murraya koenigii* (L.) Spreng., *Pedaliium murex* L., *Ricinus communis* L. and *Trigonella foenum graecum* L were tested against occurrence of secondary infections in immuno-suppressed patients. Prevalent bacterial pathogens isolated were *Staphylococcus aureus* (23.2%), *Escherichia coli* (15.62%), *Staphylococcus epidermidis* (12.5%), *Pseudomonas aeruginosa* (9.37%), *Klebsiella pneumonia* (7.81%), *Proteus mirabilis* (3.6%), *Proteus vulgaris* (4.2%) and the fungal pathogens were *Candida albicans* (14.6%), *Aspergillus fumigatus* (9.37%). Out of 40 cases, 35 (87.5%) were observed as neutropenic. All plant extracts showed significant antimicrobial activity ($P < .05$) against most of the isolates with MIC values ranged from 31 to 500 µg/ml [70].

The bioassay-guided fractionation from the 80 % ethanol ultrasonic extracts of *C. dichotoma* fruits was done to determine antimicrobial (*Candida albicans*, *Escherichia coli*, and *Staphylococcus aureus* which showed the inhibition zones of 10.0, 9.0, and 12.0 mm, respectively) activities than other fractions. The EA fraction was lead to the isolation of 45 compounds including 40 phenolics [71].

The eco-friendly synthesized AgNPs from the aqueous extract from *Cordia dichotoma* (*C. dichotoma*) fruits exhibited antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* [72].

The present investigation was carried out for the evaluation of antibacterial activities of *Cordia dichotoma* leaves, stem, fruit peel and fruit pulp extracts. Among them fruit pulp extract was found to have significant antibacterial against gram-negative organisms and possessed antioxidant properties [73].

Analgesic activity:

The crude ethanol extract of leaves of *C dichotoma* at the oral dose of 500 mg/kg body weight was screened for its analgesic activities. The extract produced significant writhing inhibition in acetic acid induced writhing in mice in comparison to diclofenac sodium [69].

The methanol extracts of leaf powder at a dose of 400 mg/kg showed significant analgesic activity in Eddy's hot plate method [74].

Anticancer activity

The crude ethanol extract of leaves of *C dichotoma* was tested for toxicity using brine shrimp lethality bioassay. The extract showed LC₅₀ (20 µg/ml) and LC₉₀ (180 µg/ml) against the brine shrimp *Artemia salina* [69].

The present study evaluated the anticancer effect of the methanol extract of *C. dichotoma* (MECD) bark against Ehrlich ascites carcinoma (EAC) cells induced in albino mice and against human cancer cell lines (malondialdehyde-MB-231 and MCF-7 cells). MECD (500 mg/kg, b.w., p.o.) or 5-Fluorouracil (20 mg/kg b.w., i.p.) in EAC-cell bearing mice caused a significant increase in Hb levels, decrease in WBC levels, tumor volume, tumor weight and body weight when compared to EAC control rats. Furthermore, increase in the concentration of MECD dose-dependently increased the percent cytotoxicity and decreased the cell viability in both cell line types. In treated group, mean survival time (MST) was significantly increased to 29.0 ± 1.98 (% ILS = 69.04), 34.12 ± 1.84 (% ILS = 81.25), and 36.87 ± 1.67 (% ILS = 87.79), respectively, when compared to EAC control group suggesting anticancer activity [75].

Similar studies were conducted with *Cordia dichotoma* fruit pulp extract (CDFP-extract) with EAC cells. Analysis of CDFP-extract showed 112.71 ± 8.40 mg gallic acid/g, 69.76 ± 4.18 mg quercetin/g, 25.65 ± 1.80 mg catechin/g, 70.90 ± 2.92 mg total alkaloids/g extract. The viable Ehrlich cell count, solid tumour weight were significantly reduced, increased non-viable cells, ameliorated all haematological parameters and increasing median survival time by administration of CDFP[76].

The anticancer properties of *Cordia dichotoma* seeds extract (MECD) along with its fractions was determined against Human Cervix Epitheloid (HeLa) and human lung (A549) carcinoma cell lines by MTT assay, nuclear staining assays such as PI-Exclusion and Hoestch/PI double staining for the analysis of induction of apoptosis. Exposure to crude extract and their fractions in the dose ranging from 25 µg/mL to 250 µg/mL, significantly inhibited the cell viability ($p < 0.001$) in a dose-dependent manner [77].

The anticancer activity of the methanol extract of *Cordia dichotoma* leaves (MECD) was evaluated against a human prostate carcinoma cell line, PC3. Flavonoid content was found to be 160 mg QE/g extract. IC₅₀ values for MECD treatment in various assays based on scavenging of 2,2-diphenyl-1-picrylhydrazyl, 2,2-azinobis(3-ethylenebenzothiazoline-6-sulfonic acid), nitric oxide, peroxy radical, superoxide anion, hydroxy radical were found to be 315.5, 38, 476, 523, 197, 82 µg/ml respectively. MECD exposure to PC3 cells significantly

increased the cell death ($IC_{50} = 74.5 \mu\text{g/ml}$), nuclear condensation, apoptosis and induced production of ROS initiating apoptotic cascade in a dose dependent manner [78].

To evaluate the anticancer potential and to assess apoptosis inducing effect of the methanol extract of *Cordia dichotoma* leaves (MECD) against human cervical cancer cell line (HeLa) by MTT assay and DAPI staining test. IC_{50} value obtained with MECD $202 \mu\text{g/}$ as compared to the standard tamoxifen with IC_{50} of $48 \mu\text{g/mL}$ [79].

The in vitro anticancer potential of *Cordia dichotoma* (bark, leaves, pulp and seed) on ten human cancer cell lines MCF-7, MDA-MB-231, N2A, SH-SY5Y, U-251, HCT-116, SW-620, A-549, MIA PaCa-2, Panc-1. The bark portion had in vitro cytotoxicity against the A-549 human lung cancer cell line in a dose-dependent manner [80].

Antiinflammatory Activity

The methanol extracts of leaf powder were evaluated for anti-inflammatory activity against carrageenan-induced rat paw edema method. The methanol extract high dose (400 mg/kg) was found to be highly significant as compared to standard drug.

Transdermal films were prepared using natural polymer (fruit gum) of *C. dichotoma* with different percentage of plasticizer (glycerine 0.10, 0.20 and 0.25% w/v), preservatives (methyl paraben 0.1% w/v) and drug neomycin (0.2% w/v). The films were screened for the anti-inflammatory activity using carrageenan-induced rat paw edema model with standard drug, diclofenac sodium. The percentage of inhibition of odema was found to be highest in 0.20% (w/v) glycerine treated animals, which indicate significant anti-inflammatory activity of cordial dichotoma [81].

Anti pyretic activity

The methanol extracts of leaf powder (400 mg/kg) possess antipyretic activity in yeast-induced pyrexia method as compared to standard drug [74].

Antioxidant activity

The free radical scavenging potential of methanol extract of seeds and leaves of *Cordia dichotoma* was evaluated using *in-vitro* models viz. DPPH and hydrogen peroxide model. The highest concentration exhibits highest ($100\mu\text{g/ml}$) antioxidant activity. This activity was more pronounced in leaves as compared to seeds [82]. *In vitro* antioxidant activity of methanol and butanol extract of *C.dichotoma* bark was determined by 1, 1-diphenyl-2, picrylhydrazyl (DPPH) free radical scavenging assay. The results reveal that the *C. dichotoma* bark has significant radical scavenging activity [83].

The phytochemical composition and antioxidant activity of air-dried *Cordia dichotoma* seeds was determined. The ethanol extracts contained polyphenolic compounds (1.0%), triterpenoids (0.075%), amino acids (1.39%), and rosmarinic acid (0.0028). The ethanol extract of *C. dichotoma* seeds has good antioxidant capacity due to of polyphenolic compounds and amino acids [84].

The bioassay-guided fractionation and isolation of bioactive constituents from the 80 % ethanol ultrasonic extracts of *C. dichotoma* fruits was done to determine antioxidant activity. The preliminary bioassay revealed that the ethyl acetate fraction (EA) of the extract exhibited stronger antioxidant: 2,2'-diphenyl-1-picrylhydrazyl (ABTS) with half inhibitory concentration (IC_{50}) = $6.71 \pm 0.46 \mu\text{g/mL}$, 2,2'-diphenyl-1-picrylhydrazyl (DPPH) with IC_{50} = $34.18 \pm 0.52 \mu\text{g/mL}$, Ferric reducing antioxidant power (FRAP) with the value of $134.35 \pm 2.01 \mu\text{mol Fe}^{2+}/100 \text{ g}$ [71].

Similar results were obtained with the prepared extracts of *Cordia dichotoma* using DPPH (1, 1--Diphenyl-2-Picryl-Hydrazyl) assay [85].

The *Cordia dichotoma* fruit pulp extract (CDFP-extract) showed a powerful effect in scavenging superoxide radicals and chelating metals ions as well as high reduction capability and total antioxidant capacity, dose-dependent manner[76].

Dried bark powder showed antioxidant potential [in DPPH (1,1-diphenyl-2-picrylhydrazyl) assay IC₅₀ value 26.25; trolox equivalent (TE) antioxidant capacity µg/ml TE/g of plant material on dry basis in ABTS (2,2'-azinobis[3-ethylbenzthiazoline]-6-sulfonic acid) and FRAP (ferric reducing antioxidant potential) assay was found to be 2.03 and 2.45 respectively [86].

Antiviral activity

The bioassay-guided fractionation and isolation of bioactive constituents from the 80 % ethanol ultrasonic extracts of *C. dichotoma* fruits was done to determine antiviral activity (with IC₅₀ = 12.84–115.56 µg/mL) against influenza virus A/Hanfang/359/95(H3N2) [71].

Gastroprotective and anti-ulcer effect:

The methanol extract of CD leaves (MECD) was administered orally at doses 50 mg/kg, 100 mg/kg and 200 mg/kg against indomethacin induced gastric ulceration and stress-induced gastric ulceration in Wistar rats. Omeprazole at 10 mg/kg orally was used as the reference standard. The MECD have reduced gastric volume, total acidity and gastric mucosal damage in both models in a dose dependent manner, SOD and CAT were increased, MDA levels were decreased significantly, TNF-α and IL-6 levels were decreased and anti-inflammatory IL-10 levels were increased suggesting significant gastroprotective potential [81].

The seed extracts of *C. dichotoma* was examined for cytoprotective and antiulcer properties. The antiulcer activity was evaluated by using H⁺K⁺-ATPase inhibition assay. The aqueous extract exhibited almost equal potential with respect to pantoprazole (proton potassium ATPase inhibitor) drug. Whereas methanol extract exhibited more potential than that of aqueous, extract [87].

Similar studies were conducted using extract of *Cordia dichotoma* fruit against aspirin induced ulcer. Prevent index was found to be 27.08%. The level of pH of stomach, volume of gastric fluid, free acidity and total acidity levels, showed a significant change suggesting antiulcer activity [88].

Ulcerative colitis activity:

The methanol extract of dried bark powder and fractionated extract were tested for effectiveness against ulcerative colitis (UC). Animals treated with the methanol fraction of the crude methanol extract showed lower pathological scores and good healing. This fraction reduced myeloperoxidase (MPO) and malondialdehyde (MDA) levels significantly in blood and tissue [86].

Apigenin is isolated by column chromatography from methanol fraction of crude methanol extract of *C. dichotoma* bark. Ulcerative colitis was induced and confirmed by observing classical lesions of ulcer *i.e.*, the destruction of epithelia, haemorrhage, infiltration of neutrophils and macrophage. Groups treated with fractions and standard (prednisolone 5 mg/kg, *i.p.*) showed significant healing. Groups treated with ethyl acetate fraction and ethyl acetate/methanol (1:1) fraction showed mild scores of pathological changes but infiltration of neutrophils and presence of oedema was observed. Apigenin (5 mg/kg, *p.o.*) showed significant healing and reduction in inflammatory enzymes when screened for UC [89].

Anaemic effect

In the present study anti-anaemic effect of the petroleum ether, solvent ether, ethyl acetate, butanol and butanone extracts of *Cordia dichotoma* fruits were evaluated in albino rats in the dose of 100, 200 and 300 mg/kg body weight for 15 days *p.o.* The ethyl acetate, butanol and butanone extract of *C. dichotoma* fruits causes significant dose dependent rise in hemoglobin content and RBC count. However, reduction in clotting and bleeding time was not found to be dose dependent. The WBC count was found to rise only in higher doses of extracts (300mg). In case of higher doses (200 and 300mg/kg body weight) the extracts of fruits reduced the clotting and bleeding time, whereas lower dose (100 mg/kg body weight) there was no significant change in bleeding and clotting time [90].

Anthelmintic activity:

Methanol extract of the drug was explored for anthelmintic activity against *Pheretima posthuma*. Worms were exposed to 10 mg/ml, 25 mg/ml, 50 mg/ml, and 75 mg/ml concentrations of extract and standard drug, albendazole. The extract showed dose-dependent effects, affecting worm motility, viability, and mortality the methanol extract was found to possess these phytoconstituents such as octacosanol, lupeol, caffeic acid, and hentricontanol were >0.5 (probable activity > 0.5). The paralysis and mortality of *P. posthuma* might be due to the combined effects different phytoconstituents [91].

Similar study was done with ethanol and aqueous extracts with five concentrations (10-100 mg/ml) were studied for anthelmintic activity by using *Eudrilus euginae* earthworms. Both aqueous and ethanol extracts showed paralysis and death of worms in concentration (10-100 mg/ml) dependent manner. Aqueous extract of *Cordia dichotoma* showed significant activity than ethanol extract. The result showed fruits of *Cordia dichotoma* possessed potential anthelmintic activity [92].

Behavioural changes and hypoperfusion test:

Effect of *C. dichotoma* on long-term cerebral hypoperfusion in rats was investigated. The *C. dichotoma* treatment (250 mg/kg *p.o.* for 28 d) alleviated the behavioural, cognitive, and histopathological changes. The study suggests that *C. dichotoma* may be useful in cerebrovascular insufficiency conditions [93].

Anti-implantation activity:

The present work was carried out to evaluate ethno-contraceptive use of *Cordia dichotoma* G. Forst., Boraginaceae, leaves (LCD). The leaves extract (LD50 5.50 g/ kg bw) showed 100% anti-implantation activity (n=10) at 800 mg/kg dose level suggesting potential antifertility activity [94].

The antifertility activity of hydroalcoholic extract of *Cordia dichotoma* leaves at two dose level (200 and 400 mg/kg, orally) was evaluated in two experimental animal models i.e. anti-implantation and estrogenic/antiestrogenic activity in female rats by observing number of implants, vaginal cornification, body weight, uterus weight and biochemical investigation. A good antiimplantation (81.22%) activity in female rats was observed at the tested dose levels (200 and 400 mg/kg, orally). The extract further showed increase that is more significant in uterine weight and significant change in biochemical parameters in immature rats. Simultaneous administration of extract along with ethinyl estradiol showed significant estrogenic activity [95]. Similar study investigates the effect of *Cordia* fresh fruits hydroethanolic extract on 125, 250, and 500 mg extract/kg bodyweight for 56 days. After day 56, extract at 500 mg/kg significantly reduced sperm total count, motility%, and alive%, to $47.60 \pm 2.27 \times 10^6$ sperm/mL, $43.33\% \pm 1.49$, and $63.67\% \pm 1.19$, respectively, abnormalities% increased considerably ($26.67\% \pm 0.54$), compared to the negative control. Also, significant depletion on follicle-stimulating hormone (2.66 ± 0.21 mIU/L), luteinizing hormone (1.07 ± 0.06 mIU/L), and testosterone (2.69 ± 0.13 nmol/L) level was recorded, compared to the negative control [96].

Hepatoprotective activity

The methanol extract of the leaves of *Cordia dichotoma* at 300 mg/kg and 500 mg/kg were studied for hepatoprotective activity in liver damage caused by carbon tetrachloride (CCl₄). The extract (300 mg/kg) significantly reduced the AST (P<0.001), ALT (P<0.001) and TBR levels (P<0.01) and at 500 mg/kg dose significantly reduced the AST (P<0.001), ALT (P<0.001), TBR (P<0.01) and lipid peroxide levels (P<0.05). The antioxidant parameters like glutathione and total antioxidant levels increased considerably [97].

The hepatoprotective activity of aqueous –methanol (30:70%) extract of *Cordia dichotoma* fruit against paracetamol – induced hepatic damage in rabbits for 18 days. The extract at 300 mg /kg b.w. exhibited significant reduction in biochemical parameters like RBS, ALT, AST, TSB, TSP, BUN and Creatinine suggesting hepatoprotective activity [98].

The present study appraised the hepatoprotective activity of alcoholic and aqueous extract of *Cordia dichotoma* fruits (150 and 300 mg/kg b.w.) against carbon tetrachloride induced liver damage in rats for 14 days. *Cordia dichotoma* (300 mg/kg b.w.) has shown significant reduction in serum hepatic enzymes and increase in the serum total protein and albumin when compared to carbon tetrachloride alone [99].

Antitermite activity

The antitermite responses of *Cordia dichotoma* leaves extracts to *Odontotermes obesus* in various bioassays were evaluated. The methanol extracts and their fractions were evaluated at different dilutions i.e. (0.5%, 1%, 2%) against *Odontotermes obesus*, the test termite. The 2% ethyl acetate extract possesses highest antitermite potential [100].

CONCLUSION

Cordia dichotoma is very useful plant in traditional system of medicine. It is scientifically proven by various researchers to possess activities like antidiabetic, antiatherosclerotic, antihypertensive, antilipidemic, wound

healing, antifungal, antimicrobial, analgesic, anticancer, anti-inflammatory, antipyretic, antioxidant, antiviral, gastroprotective, antiulcer, anthelmintic, antiimplantation and hepatoprotective activity.

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ETHICAL ISSUES

There is none to be applied.

CONFLICT OF INTEREST

None to be declared.

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