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A REVIEW OF PHARMACOLOGY OF LEPTADENIA RETICULATA: THE PLANT THAT GIVES LIFE

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ABSTRACT

The traditional medicinal plant species *Leptadenia reticulata* is used to cure a broad range of illnesses, including cancer, dysentery, hematopoiesis, emaciation, coughing, dyspnoea, fever, burning sensation, night blindness, and TB. It is well-known in Ayurveda for its lactogenic, restorative, and revitalizing qualities. Numerous commercial herbal preparations, such as Speman, Envirocare, Calshakti, Antisept, and Chyawanprash, contain this plant as one of their main constituents. A variety of bioactive chemicals, including α-amyrin, β-amyrin, ferulic acid, luteolin, diosmetin, rutin, β-sitosterol, stigmasterol, hentricontanol, a triterpene alcohol called simiarenol, apigenin, reticulin, deniculatin, and leptaculatin, are responsible for this herb's medicinal potential. A wide range of pharmacological activities, including antibacterial, anticancer, lactogenic, antioxidant, anti-implantation, anti-asthmatic, modulating, hepatoprotective, antifungal, antidiabetic, and anti-inflammatory properties, have been discovered in the plant. To support the traditional applications of *L. reticulata* with evidence-based data, many physiologically active chemicals have not yet been found, and the majority of biological investigations on the plant are limited to crude extracts. Due to habitat degradation, irresponsible harvesting, and overexploitation, *L. reticulata* is currently considered a vulnerable endangered plant. Its widespread spread has been spurred by the veterinary, pharmaceutical, and nutraceutical sectors growing demand. However, the paucity of information on its agronomical procedures and the unavailability of authentic planting material hinders its commercial cultivation. Biotechnological techniques including genetic transformation, cell culture, cryopreservation, and synthetic seed technology can aid in conservation and boost *L. reticulata* metabolite production.

Keywords: *Leptadenia Reticulata*, Bioactive Chemicals, Traditional Applications, Pharmacological Activities.

I. INTRODUCTION

Many different chemical scaffolds that have developed particularly to interact with biological targets are produced by plants, which have long been used as traditional treatments to heal ailments. Many medications used in contemporary therapy are based on compounds obtained from plants. These include galantamine from Galanthus nivalis, which is used to treat Alzheimer's illness, the antimalarial artemether made from artemisinin extracted from Artemisia annua, the anticancer medication paclitaxel from the Taxus species, and the anticancer Vinca alkaloids from the Catharanthus roseus. An estimated 15% of plant species have undergone phytochemical investigation, while just 6% have had their medicinal potential examined. This indicates that there are still a lot of compounds generated from plants that may have some medicinal use. The identification of bioactive chemicals from plants depends on preserving ethnobotanical knowledge, both in the West and in developing nations where plants are still frequently utilized as traditional remedies. Additionally, it is critical that ongoing efforts to protect plant biodiversity—which is now declining as a result of overexploitation of natural resources and climate change—be connected to bioprospecting for medications derived from plants. Interesting biological characteristics of plant extracts and ingredients continue to inspire the creation of novel medications. Combining methods from ethnobotany, phytochemistry, medicinal chemistry, and pharmacology is necessary to find plant-derived compounds that may be helpful for a variety of therapeutic uses. The sustainable bioprospecting of plants is essential to future discoveries in this sector. (1)

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PLANT PROFILE

TAXONOMY

Kingdom Viridiplantae
Phylum Streptophyta
Class Magnoliopsida
Order Gentianales
Family Apocynaceae
Sub-family Asclepiadoideae
Genus *Leptadenia*
Species *reticulata* (2)

Synonyms: *Asclepias javanica, Asclepias suberosa, Asclepias volubilis, Asclepias zeylanica, Curinila rheedei, Curnilia sarmentosa, Leptadenia brevipes, Secamone canescens.* (3)

Vernacular names

English Cork Swallow-Wort
Hindi Dori
Bengali Bhadjivai
Gujarati Methidodi, Dodi saka/Dodi Saag, Dori
Marathi Haranvel, Hiranvel
Sanskrit Madhusrava, Jivniya, Jivapushpa, Jivani (2, 3)

Description

The species is a laticiferous twining shrub with many branches and extensively broken, yellowish-brown bark. The leaves are coriaceous, oval, cordate, glabrous on top, and rather slightly hairy on the underside. A cyme with several blooms that are greenish-yellow is called an inflorescence. The fruit (follicle) is thin and horned. The seeds are comose and lanceolate. While fruiting starts in October and lasts until November, flowering takes place in May and June. (4)

Distribution

The plant needs moderate rainfall and relative humidity to thrive in tropical and subtropical climates. Additionally, this plant thrives in dry areas, which are defined by poor organic matter, sandy soil, and little rainfall. Red laterite soil is also excellent for its decent growth, although black soil is determined to be ideal for cultivation. For robust and healthy growth, open sunshine and assistance are essential.

In India, it is mostly found up to 2000 meters above sea level in the following regions: Rajasthan, Gujarat, Punjab, the Himalayan ranges, Khasi Hills, Sikkim, Deccan Plateau, Konkan mountains, Karnataka, and Kerala. In addition to India, it is said to be found in Burma, Nepal, Sri Lanka, the Malay Peninsula, Cambodia, the Philippines, Mauritius, Madagascar, and tropical and subtropical regions of Africa. (2)

Traditional uses

The traditional medicinal plant *Leptadenia reticulata* is used to cure a broad range of conditions, including cancer, night blindness, hematopoiesis, emaciation, coughing, dyspnoea, fever, burning feeling, and dysentery.

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It's renewing, lactogenic, and revitalizing qualities are well-known in Ayurveda. This plant is a key component of several commercial herbal preparations, such as Chyawanprash, Speman, Envirocare, Calshakti, and Antisept. (2)

Phytochemistry

Acetyl alcohol, leptidine, luteolin, diosmtin, β-sitosterol, β-amyrin, lupanol 3-O diglucoside, and tannin are present in the plant. In addition to two resins, leaves also include albuminous and coloring matter, calcium oxalate, glucose, carbohydrate, tartaric acid, and bitter neutral principal. Additional chemical components that have been reported include rutin, stigmasterol, apigenin, α-amyrin, hentriacontanol, ferulic acid, and simiarenol. Additionally, leptaculatin, deniculatin, and reticulatin have been identified from the aerial parts. (5) Glycoflavones (6C-Glucosyl acacetin), phenolic acids (vanillic acid, syringic acid, p-coumaric acid, ferulic acid, p-hydroxy benzoic acid, melilotic acid, and phloretic acid), and flavones (apigenin, 4'-Methoxy apigenin, diosmetin, chrysoeriol, and 3',4'-Dimethoxy luteolin) are also found in Leptadenia reticulata. (6)

Pharmacology

The formalin-induced paw edema test and λ-carrageenan were used to conduct the anti-inflammatory assay. Using quantitative ELISA, the levels of pro-inflammatory mediators (IL2, IL6, and TNF-α) in the serum of the treated and control organisms were measured. The test known as thiobarbituric acid reactive substances (TBARS) was used to determine the inhibition of lipid peroxidation. flavonoids (quercetin and rutin) and phenolic components (p-coumaric acid) were found in the most active fraction, which was also quantitatively quantified. At 600 mg/kg, the ethyl acetate fraction dramatically reduced the paw edema caused by formalin and λ-carrageenan by 60.59% and 59.24%, respectively. The strong analgesic action of acetic acid is indicated by the notable decrease in the proportion of writhing (76.25%). At 4 hours after λ-Carrageenan injection, a lower level of pro-inflammatory cytokines (IL-2, IL-6, and TNF-α) in blood suggested that cyclooxygenase-2 (Cox-2), nitric oxide (NO), and prostaglandin production were inhibited to avoid inflammation. The study also showed that the plant's ability to reduce lipid peroxidation was evidenced by a decrease in malonaldehyde (MDA) levels. (7)

Among the notable phytocompounds identified by the HR-LCMS/MS(Q-TOF) investigation were Brassilexin, Kaempferol, Ferulic acid, Ellagic acid, Neuraminic acid, Hydroquinidine, Catechin, Madasiatic acid, Luteolin, Caulerpin, Methyl N-methylanthranilate, Lamprolobine, malic acid, quercitrin, albuterol, colnelenic acid, 2-hexaprenyl-3-methyl-6-methoxy-1,4 benzoquinone, Pyrenyl sulfate, 14,19-Dihydroaspidospermatine, Tetradecyl Sulphate, Muricatalin, Hexazinone, Isocarbostyril, methylquinoline, 2,4,6-triethyl-1,3,5-trioxane, and L-tryptophan. SwissADME and ProTox II were used to assess these compounds' drug-likeness using Lipinski's rule of five. The Genecard, TTD, and CTD databases were used to identify possible inflammatory targets, which were made easier by Swiss Target Prediction. Among the hub proteins identified by a network pharmacology study are CCR2, ICAM1, KIT, MPO, NOS2, and STAT3. According to drug-like principles, the findings showed adequate solubility and absorption properties as well as excellent oral absorption. To identify the molecules principally responsible for the phytocompounds' anti-inflammatory properties, network pharmacology was employed. Eighteen compounds were selected for target prediction after passing through the ADME filter process and following Lipinski's rule of five. Hub genes, including CCR2, ICAM1, KIT, MPO, NOS2, and STAT3, were identified using MCODE analysis of the protein-protein interaction (PPI) network. These genes are essential for inflammation, directing immune cell movement, adhesion, and activation. They have a variety of activities, from controlling inflammatory responses and signaling (STAT3) to promoting leukocyte endothelial transmigration (ICAM1). By modifying immune responses, targeting these proteins may have a substantial influence on the treatment of autoimmune and inflammatory illnesses. (8)

Acute toxicity studies were performed and the aqueous extract was found to be safe up to 2000 mg/kg. The antipyretic activity was evaluated using baker's yeast-induced pyrexia in albino rats and cow milk-induced pyrexia in albino rabbits. Anti-inflammatory activity was evaluated using carrageenan-induced paw edema and turpentine oil-induced paw edema in albino rats. In all the animal models Aqueous Extract of *Leptadenia reticulata* (AELR) at the dose of 200 mg/kg and 400 mg/kg showed significant antipyretic and anti-inflammatory activity. (9)

The methanol leaf extract of *L. reticulata* was used to biosynthesize silver nanoparticles (Ag Nps). X-ray diffraction (XRD) analysis, transmission electron microscopy, and UV-visible spectroscopy measurements were

used to characterize Ag Nps. These Ag Nps were examined for antioxidant activity using the DPPH assay and for antibacterial activity against several pathogenic microbes using the agar well diffusion method. At 150 µg/ml of Ag NPs, the largest zone of inhibition was seen with B. subtilis (24.3 ± 1.3 mm), followed by E. coli (20.0 ± 0.4 mm). At a dose of 25 µg/ml of Ag NPs, the M. luteus showed the lowest zone of inhibition (08.7 ± 1.4 mm). The zone of inhibition increased as the concentration of Ag NPs, regardless of the microorganisms that were examined. At 500 µg/ml, Ag NPs exhibited the maximum radical scavenging activity (64.81%). Ag NPs and plant extract both progressively enhanced their DPPH radical scavenging capabilities in a dose-dependent manner. Additionally, the HCT15 cancer cell line was used to screen for the in vitro cytotoxic effects of Ag Nps, and the MTT assay was used to determine the viability of tumor cells. Propidium iodide staining was used to investigate the nuclear condensation. The development of nanoparticles was demonstrated by the color shift from green to dark brown and the absorbance peak at around 420 nm. (10)

The larvicidal effects of endophytic fungi isolated from *Psoralea corylifolia* and *Leptadenia reticulata* against Aedes aegypti were examined. *Trichodermata viride* and *Candida albicans* from *L. reticulata* leaves had the greatest larvicidal activity, with 85.71% and 90.47 percent, respectively, at 20 ppm. Similarly, *Aspergillus niger* and *Piriformospora* indica species were detected in 66.66% and 83.33% of *P. corylifolia* leaves, respectively. *Aspergillus niger* from *Psoralea corylifolia* leaves and Candida albicans from L. reticulata leaves demonstrated the greatest death percentages, 90.47 and 83.33 at 20 ppm, respectively. (11)

The purpose of the study is to assess the antioxidant and immunomodulatory effects of an ethanolic extract of *L. reticulata* leaves in rats. In vivo investigations were used to examine the haemagglutinating antibody (HA) titre, haematological profile (Hb, WBC, RBC), decreased GSH, LPO, SOD, CAT, DTH response, neutrophil adhesion test, and carbon clearance assay. *L. reticulata* (100, 200 mg/kg, p.o.) significantly increased antibody titre values in a dose-dependent manner; SRBC-induced DTH response and increased the proportion of neutrophils adhering to nylon fibers and phagocytosis in the carbon clearance experiment. In cyclophosphamide-induced immunosuppressed rats, it also dramatically reduced LPO levels and increased the hematological profile, GSH, SOD, and CAT activity. According to the findings, *L. reticulata* may significantly lower the chance of developing immunodeficiency problems. (12)

Using the 3-(4, 5-dimethyl thiazol–2–yl)–5-diphenyl tetrazolium bromide assay, several extracts were evaluated for cytotoxicity against the human breast adenocarcinoma cell line MCF-7, the human colon adenocarcinoma grade II cell line HT-29, and the non-cancerous skeletal muscle cell line L6. Three distinct antioxidant models—diphenyl picrylhydrazyl free radical scavenging activity, H_2O_2 scavenging activity, and $FeCl_3$ reducing activity—were used to assess the overall antioxidant potential. With IC_{50} values of 21 µg/mL, 26 µg/mL, and 22 µg/mL; 20 µg/mL, 30 µg/mL, and 18 µg/mL, respectively, the ethyl acetate extract of both naturally occurring and tissue-cultured plants demonstrated notable cytotoxicity against three cell lines. The ethyl acetate extract exhibited the strongest diphenyl picrylhydrazyl free radical scavenging activity, with an IC50 value of 267.13 µg/mL. There was a strong positive link found between the plant's cytotoxic action and antioxidant capacity. (13)

The petroleum ether and ethanol of bark of *L. reticulata* were administered orally to male rats for 60 days at a dosage of 250 mg/kg body weight/day. Histological alterations, lipid profile, testosterone and antioxidants, body and organ weight, hematology, serum biochemical chemistry, and sperm parameters (density and motility) were also noted. In the treatment groups (TP and bark petroleum ether extract), sperm motility and density, reproductive organ weight, serum testosterone, and serum antioxidant markers like SOD were all shown to be significantly lower than in the control group. Histological examinations showed that spermatogenesis had stopped, and that mature Leydig cells, secondary spermatogonia, spermatids, and seminiferous tubule diameter had all decreased. This resulted in a significant rise in LPO and GSH. It is possible to infer that *L. reticulata bark* petroleum ether extract can operate as a safe and reversible oral contraceptive for male albino rats. (14)

Experimental settings (high temperature and 25°C; ultrasonic vibrations) and solvent systems (water, methanol, water: methanol (1:1), chloroform: methanol (1:1)) were used to obtain the extracts. The Folin-Ciocalteu technique was used to assess the total phenolic content; the AlCl method was used to estimate the total flavonoids; and the DPPH and phosphomolybdenum assays were used to measure the antioxidant activity.

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The highest phenolic content (69.39 ± 1.22 mg GAE/g of dry extract), flavonoid content (44.50 ± 1.11 mg RE/g of dry extract), and free radical scavenging capacity (57.01 ± 1.57%) were found in Bauhinia variegata prepared at 25°C. Additionally, the highest total antioxidant capacity was found in methanol extract prepared at elevated temperatures (135.24 ± 4.37 mg AAE/g of dry extract). The phenolic content (24.60 ± 0.65 mg GAE/g of dry extract), flavonoid content (6.44 ± 0.21 mg RE/g of dry extract), and free radical scavenging capacity (66.83 ± 0.91%) of the water: methanol extract of *Leptadenia reticulata* were the highest, while the sonication-prepared methanol extract had the highest total antioxidant capacity (52.88 ± 1.34 mg AAE/g of dry extract). (15)

DPPH radical, nitric oxide and hydroxyl radical scavenging activities were used to assess the methanolic extract of *Leptadenia reticulata* (LRM) for in vitro antioxidant activity. By scavenging or reducing the DPPH, nitric oxide, and hydroxyl radicals, LRM demonstrated strong antioxidant activity. Additionally, the potential protective impact of LRM against adriamycin-induced (ADR) cardiotoxicity in rats was examined. Wistar rats received intraperitoneal injections of adriamycin (10 mg/kg) after receiving LRM at dosages of 250 mg/kg and 500 mg/kg for 28 days. Reduced levels of the diagnostic enzymes alanine transaminase, aspartate transaminase, lactate dehydrogenase, and creatine kinase in cardiac homogenate, together with corresponding increases in these enzyme levels in the blood, indicated oxidative stress in the myocardium of rats treated with ADR. ADR also decreased the baseline levels of cardiac antioxidant enzymes such as glutathione peroxidase, glutathione reductase, glutathione-S-transferase, catalase, and superoxide dismutase. It emerged that the injection of ADR caused a reduction in myocardial glutathione and an increase in lipid peroxidation. The changes in the previously described biochemical parameters were considerably suppressed by pretreatment with LRM. The Bonferroni test was used to evaluate for statistical significance after a one-way ANOVA. According to the histology, LRM pretreatment prevented cellular infiltrations and degenerative alterations brought on by adriamycin in the heart in a dose-dependent way. The findings showed that ADR therapy significantly hampered heart function, but LRM avoided this toxicity, possibly as a result of its antioxidant properties. (16)

Streptozotocin (STZ) with a high-fat diet (HFD) caused diabetes in Wistar rats. Metformin (50 mg/kg) and an isolated ETLR (100 mg/kg) from *Leptadenia reticulata* leaf were given orally. Column chromatography separated a pure chemical from an isolated fraction exhibiting greater anti-diabetic efficacy. This molecule was given the trivial name LR-1. In diabetic rats, it was discovered that the ETLR fraction D considerably reduced the FBG level, which confirms that the substances linked to D have anti-diabetic properties. Using a variety of solvent systems, additional column chromatographic analysis was performed with D, which was given the unimportant designation LR-1. Spectral analysis verified that LR-1 was a phenolic component (flavonoids). (17)

The goal of the current study was to create capsule formulations using isolated components from *Leptadenia reticulata* and *Dregea volubilis*. to determine the anti-diabetic impact of DVLR (DV and LR separated fraction was blended in a 1:1 ratio) capsules on STZ and HFD-induced diabetic rats. The bulk density and angle of repose of the preformed capsules were noted. Weight variation, pH, moisture content, disintegration time, in vitro drug release percentage, and in vivo anti-diabetic studies were all assessed for completed capsule formulations. The goal of the current study was to create capsule formulations using isolated components from Leptadenia reticulata and Dregea volubilis. to determine the anti-diabetic impact of DVLR (DV and LR separated fraction was blended in a 1:1 ratio) capsules on STZ and HFD-induced diabetic rats. The bulk density and angle of repose of the preformed capsules were noted. Weight variation, pH, moisture content, disintegration time, in vitro drug release percentage, and in vivo anti-diabetic studies were all assessed for completed capsule formulations. (18)

Hepatotoxicity was induced using a 1.25 ml/kg dosage of the toxicant CCl4 in a 1:1 combination with olive oil. For seven days, 250 and 500 mg/kg/day of ethanolic and aqueous extracts of *L. reticulata* stems were taken orally. The standard medication was silymarin (50 mg/kg). By restoring the architecture of the liver, as demonstrated by decreased levels of blood bilirubin and protein as compared to the normal and silymarin-treated groups, the administration of ethanolic and aqueous extracts to animals considerably decreased liver damage and the symptoms of liver injury. The liver sections' histology, which showed normal hepatic cords, no necrosis, and no fatty infiltration, verified that the extracts stopped the hepatic damage caused by CCl_4. (19)

Experimental rats were given oral dosages of 100 mg/kg p.o. of aqueous and ethanolic extracts of entire *Leptadenia reticulata* plants. In the trial, furosemide (100 mg/kg) served as the positive control. Urine volume, salt, potassium, and chloride concentration were measured to assess the extract's diuretic impact. Both the ethanolic and aqueous extracts considerably raised urine volume when compared to the control group, but this

impact was not as strong as that of furosemide. Both the treated and standard groups showed a significant increase in renal clearance of sodium, potassium, and chloride ions. (20)

The extracts of fresh aerial parts of *Leptadenia reticulata* were evaluated. Petroleum ether extract showed antibacterial action against *Klebsiella pneumoniae*, alcoholic extract demonstrated strong antibacterial activity against *Pseudomonas aeruginosa*, and chloroform extract demonstrated high antimicrobial activity against *E. coli*. Out of all the examined microorganisms, chloramphenicol had the strongest antibacterial action. (21)

Using the fission yeast *Schizosaccharomyces pombe* as a model, the antiproliferative properties of crude extracts from the leaves of *Bauhinia variegata* and *Leptadenia reticulata* were investigated. Three experimental settings (25°C, increased temperature, and ultrasonic waves) and four solvent systems (water, methanol, water: methanol (1:1), and chloroform: methanol (1:1)) were used to obtain the crude extracts of both plants. Cell viability was estimated using the MTT test, and the findings were reported as a percentage of growth inhibition. Overall, according to the MTT experiment conducted on yeast cells, extracts of water: methanol, methanol, and water demonstrated additional antiproliferative activity in a dose-dependent manner than the positive control, Paclitaxel. (22)

Since no implants were seen in the whole treated animal, the ethanolic extract of *Leptadenia reticulata* roots administered orally to rats at doses of 300 mg/kg demonstrated a very strong anti-implantation effect. The uterotropic effects of LRA in immature female rats and its capacity to raise the weight of genital organs in ovariectomized rats demonstrate its strong oestrogenic activity. The potentiation of ethinyl estradiol action verified both activities. It also has a very powerful anti-implantation activity, which might be because of its oestrogenic activity. (23)

In a rat animal model, the 50% ethanolic extract of the aerial piece of *Leptadenia reticulata* was tested for antifungal efficacy against *Aspergillus flavus* in vivo. The treated wound had obvious signs of healing, and the fungal hyphae were absent from the swab taken from the area of the site that was healing. However, the wound had worsened and the animal was in pain in the infected but untreated group, which might have resulted in 40% death in just eight days. *A. flavus* hyphae were found in the swab taken from the area of the rats' wounds that survived. When compared to the untreated group, the treated group's WBC, polymorphs, and lymphocyte count increased while the eosinophil count decreased. (24)

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