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## Phytopharmacological Effects of *Pergularia Daemia*: A Comprehensive Review

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### ABSTRACT

*Pergularia daemia* (Forssk.) Chiov., commonly known as Veliparuthi or Utranmul, is a perennial climbing herb belonging to the Asclepiadaceae family. This plant has been extensively used in traditional medicinal systems including Ayurveda, Unani, and Siddha for treating various ailments. This comprehensive review synthesizes current knowledge on the ethnobotanical uses, phytochemical composition, and pharmacological properties of *P. daemia*. The plant contains diverse bioactive compounds including alkaloids, flavonoids, glycosides, saponins, tannins, and steroids. Extensive pharmacological studies have demonstrated multiple therapeutic properties including antidiabetic, anti-inflammatory, antimicrobial, antioxidant, hepatoprotective, anticancer, wound healing, and immunomodulatory activities. This review critically evaluates the scientific evidence supporting traditional uses and discusses the molecular mechanisms underlying the observed pharmacological effects. Despite promising preclinical findings, clinical trials are needed to validate therapeutic efficacy and safety. This review provides a comprehensive foundation for future research aimed at developing evidence-based phytopharmaceuticals from *P. daemia*.

**Keywords:** *Pergularia daemia*, ethnobotany, phytochemistry, pharmacology, traditional medicine, bioactive compounds

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## INTRODUCTION

Medicinal plants have served as primary sources of therapeutic agents throughout human history and continue to play vital roles in modern healthcare systems (Fabricant & Farnsworth, 2001). The World Health Organization estimates that approximately 80% of the global population relies on traditional plant-based medicines for primary healthcare needs (Ekor, 2014). *Pergularia daemia* (Forssk.) Chiov., synonymously known as *Pergularia extensa* (Jacq.) N.E.Br., represents a significant medicinal plant with extensive ethnobotanical documentation across tropical and subtropical regions (Suresh et al., 2011).

The genus *Pergularia* belongs to the family Asclepiadaceae (Apocynaceae sensu lato) and comprises approximately 12 species distributed primarily in tropical Africa and Asia (Goyder, 2006). *P. daemia* is a perennial, laticiferous, twining herb characterized by opposite leaves, greenish-yellow flowers in umbellate inflorescences, and paired follicular fruits (Khare, 2007). The plant exhibits remarkable adaptability, thriving in diverse ecological niches from coastal regions to semi-arid zones.

Traditional medical systems have employed various parts of *P. daemia* for treating respiratory disorders, digestive complaints, skin diseases, inflammatory conditions, and metabolic disorders (Chopra et al., 1956). In Ayurvedic medicine, the plant is recognized as 'Veliparuthi' and valued for its bitter, acrid properties with applications in treating fever, asthma, and bronchitis (Warrier et al., 1996). Unani practitioners utilize the plant as 'Utranmul' for its stomachic and purgative properties (Said, 1969). The Siddha system employs the plant for treating diabetes, skin disorders, and snake bites (Nadkarni, 1976).

Recent decades have witnessed intensified scientific investigation into *P. daemia*, revealing diverse bioactive constituents and validating numerous traditional therapeutic claims through rigorous pharmacological studies. This comprehensive review synthesizes current knowledge on the phytochemistry and pharmacological properties of *P. daemia*, critically evaluating the scientific evidence and identifying gaps for future research.

### **Botanical Description and Distribution**

#### ***Taxonomic Classification***

Kingdom: Plantae

Division: Magnoliophyta

Class: Magnoliopsida

Order: Gentianales

Family: Asclepiadaceae (Apocynaceae)

Genus: *Pergularia*

Species: *P. daemia*

### ***Morphological Characteristics***

*P. daemia* is a perennial, slender, glabrous or pubescent climber that can extend several meters in length (Hooker, 1885). The stems are cylindrical, twining, and exude white latex when injured. Leaves are opposite, simple, ovate-cordate to lanceolate, measuring 2.5-8 cm in length and 1.5-5 cm in width, with entire margins and acute to acuminate apices. Leaf venation is reticulate with prominent midribs. Petioles are slender, 1-3 cm long, and pubescent (Gamble, 1935).

The inflorescence consists of extra-axillary umbellate cymes bearing 3-15 flowers. Flowers are small, greenish-yellow to white, approximately 6-8 mm in diameter, with five sepals and five petals united at the base. The corona is distinctly five-lobed with stamens inserted on the corolla tube. The gynoecium consists of two superior ovaries with a common style (Cooke, 1958). The fruit comprises paired follicles, cylindrical to lanceolate, 5-10 cm long, tapering at both ends, and containing numerous comose seeds. Seeds are ovate, compressed, approximately 5 mm long, with a tuft of silky hairs (coma) facilitating wind dispersal (Matthew, 1983).

### ***Geographical Distribution***

*P. daemia* exhibits pan-tropical distribution, occurring naturally throughout Africa, Asia, and Australia (Khare, 2007). In the Indian subcontinent, the species is widely distributed across tropical and subtropical regions, particularly abundant in coastal areas, wastelands, agricultural field margins, and disturbed habitats from sea level to approximately 1000 m altitude (Hooker, 1885). The plant demonstrates remarkable ecological plasticity, colonizing diverse soil types including sandy, loamy, and lateritic soils with pH ranges from slightly acidic to alkaline conditions. Its drought tolerance and ability to thrive under various moisture regimes contribute to its extensive geographical range (Suresh et al., 2011).

### **Traditional and Ethnobotanical Uses**

*P. daemia* holds significant positions in various traditional medical systems and folk medicine practices across its geographical distribution. Ethnobotanical documentation reveals extensive therapeutic applications spanning multiple organ systems and disease conditions (Nadkarni, 1976).

### ***Ayurvedic Medicine***

In Ayurvedic medicine, *P. daemia* is documented as 'Veliparuthi' and classified under the category of bitter (tikta) and pungent (katu) herbs. The plant is attributed with properties including digestive stimulation (deepana), toxin elimination (vishaghna), and fever reduction (jvaraghna) (Warrier et al., 1996). Classical Ayurvedic texts describe its use in respiratory disorders including asthma

(shwasa), cough (kasa), and bronchitis. The root is particularly valued for treating intermittent fevers and as an antidote for various poisons. Leaf paste is applied externally for treating skin diseases, wounds, and inflammatory conditions (Chopra et al., 1956).

### ***Unani Medicine***

Unani practitioners recognize the plant as 'Utranmul' and classify it as hot and dry in the second degree. The root is employed as a stomachic, expectorant, laxative, and anthelmintic. Unani formulations incorporate *P. daemia* for treating chronic fevers, digestive disorders, hepatic and splenic enlargement, and as a blood purifier. The latex is used topically for treating skin eruptions, scabies, and inflammatory dermatoses (Said, 1969). Decoctions of the root are prescribed for bronchial asthma and as a febrifuge in malaria (Ghani, 1920).

### ***Siddha Medicine***

The Siddha system of medicine employs *P. daemia* extensively for diabetes management, where it is considered to possess significant hypoglycemic properties. Fresh leaf juice is administered orally for diabetes mellitus, often in combination with other medicinal plants (Nadkarni, 1976). The plant is also utilized in formulations for treating snake bites, scorpion stings, and other venomous bites. Root powder is prescribed for amenorrhea, dysmenorrhea, and as an emmenagogue. External applications include poultices for treating boils, abscesses, and chronic ulcers (Anonymous, 1992).

### ***Folk Medicine***

Ethnobotanical surveys across various geographical regions document diverse folk medicinal uses. In rural India, leaf juice mixed with honey is administered for treating cough and cold in children. Root decoction is used as an antipyretic in intermittent fevers (Jain, 1991). Tribal communities in central India employ the latex as a vesicant and counter-irritant for rheumatic pains. In African traditional medicine, the plant is used for treating gonorrhoea, dysentery, and as a galactagogue (Burkill, 1985). Southeast Asian folk medicine utilizes the plant for treating malaria, intestinal worms, and as a general tonic (Perry, 1980). These widespread traditional uses provide valuable leads for pharmacological investigations and drug development.

### **Phytochemistry**

Phytochemical investigations of *P. daemia* have revealed a diverse array of bioactive secondary metabolites contributing to its pharmacological properties. The chemical composition varies among different plant parts, with roots, leaves, and aerial parts exhibiting distinct phytochemical profiles (Suresh et al., 2011).

### ***Alkaloids***

Alkaloids represent significant bioactive constituents in *P. daemia*. Several indole alkaloids have been isolated and characterized from various plant parts. Pergularinine, an indole alkaloid, was isolated from the roots and demonstrated significant biological activity (Alam et al., 2006). Other alkaloids identified include pergularine, daemidonin, and pergulavoline. These alkaloids exhibit diverse structural features and are implicated in various pharmacological activities including antimicrobial and cytotoxic properties (Suresh et al., 2011).

### ***Glycosides***

Cardiac glycosides constitute important secondary metabolites in *P. daemia*. Calotropin, a cardenolide glycoside, has been isolated from aerial parts and demonstrates cardiogenic activity (Habib & Karim, 2011). Uscharin and voruscharin are other glycosides identified from the plant. These compounds possess characteristic steroid nuclei with lactone rings and sugar moieties, contributing to their biological activities. The presence of cardiac glycosides necessitates careful dose consideration in therapeutic applications (Akhtar et al., 1992).

### ***Flavonoids***

Flavonoids contribute significantly to the antioxidant and anti-inflammatory properties of *P. daemia*. Quercetin, kaempferol, and their glycosides have been detected in leaf extracts through chromatographic and spectroscopic analyses (Kumar et al., 2010). Rutin, a flavonoid glycoside, was isolated from aerial parts and exhibited notable antioxidant activity. Other flavonoid compounds including myricetin, apigenin, and luteolin derivatives have been reported. These polyphenolic compounds act as free radical scavengers and modulate various signaling pathways involved in inflammation and oxidative stress (Goyal et al., 2012).

### ***Steroids and Triterpenoids***

Steroidal compounds isolated from *P. daemia* include  $\beta$ -sitosterol, stigmasterol, and campesterol. These phytosterols exhibit cholesterol-lowering and anti-inflammatory properties. Triterpenoid compounds identified include  $\alpha$ -amyrin,  $\beta$ -amyrin, and lupeol. These pentacyclic triterpenoids demonstrate various pharmacological activities including hepatoprotection, anticancer, and anti-inflammatory effects (Sharma et al., 2013). Ursolic acid and oleanolic acid derivatives have also been reported from leaf extracts (Bhaskar & Balakrishnan, 2009).

### ***Saponins***

Saponins present in *P. daemia* contribute to its foam-forming properties and biological activities. Both steroidal and triterpenoid saponins have been detected. These amphipathic glycosides exhibit hemolytic activity, antimicrobial properties, and immunomodulatory effects. Saponins also

enhance the bioavailability of other phytochemicals through membrane permeabilization (Goyal et al., 2012).

### ***Tannins and Phenolic Compounds***

Tannins, including both condensed and hydrolyzable types, are present in significant quantities in *P. daemia* leaves and stems. These polyphenolic compounds exhibit astringent properties and contribute to antimicrobial and antioxidant activities. Gallic acid, ellagic acid, and catechin derivatives have been identified as major phenolic constituents. Total phenolic content varies with plant part, extraction solvent, and geographical origin, with methanolic extracts generally exhibiting higher phenolic content than aqueous extracts (Kumar et al., 2010).

### ***Other Constituents***

Additional phytochemicals identified from *P. daemia* include terpenoids, proteins, carbohydrates, and fixed oils. Essential oil analysis revealed the presence of various volatile compounds including monoterpenes and sesquiterpenes. Latex composition analysis identified proteolytic enzymes, resin, and rubber-like substances. Amino acid analysis detected both essential and non-essential amino acids. These diverse chemical constituents collectively contribute to the plant's medicinal properties and therapeutic potential (Suresh et al., 2011).

## **PHARMACOLOGICAL ACTIVITIES**

Extensive pharmacological investigations have validated numerous traditional therapeutic claims for *P. daemia*, demonstrating diverse biological activities through in vitro, in vivo, and limited clinical studies. The following sections critically evaluate the scientific evidence for various pharmacological properties.

### ***Antidiabetic Activity***

The antidiabetic potential of *P. daemia* has received considerable scientific attention, substantiating its traditional use in diabetes management. Ahmad et al. (2012) demonstrated that methanolic leaf extract significantly reduced blood glucose levels in streptozotocin-induced diabetic rats at doses of 200 and 400 mg/kg body weight. The hypoglycemic effect was comparable to glibenclamide, a standard antidiabetic drug. Histopathological examination revealed partial regeneration of pancreatic  $\beta$ -cells and reduced pancreatic damage in treated animals.

Bhaskar and Balakrishnan (2009) investigated the mechanism of antidiabetic action using alloxan-induced diabetic rats. The aqueous leaf extract (250 mg/kg) administered for 30 days significantly decreased fasting blood glucose, glycosylated hemoglobin (HbA1c), and improved glucose tolerance. Biochemical analyses revealed increased hepatic glycogen content and enhanced activities of glucokinase and glucose-6-phosphate dehydrogenase, suggesting improved glucose

utilization. Furthermore, the extract decreased activities of glucose-6-phosphatase and fructose-1,6-bisphosphatase, key gluconeogenic enzymes, indicating suppression of hepatic glucose production.

Antioxidant enzyme activities including superoxide dismutase, catalase, and glutathione peroxidase were significantly elevated in diabetic rats treated with *P. daemia* extract, suggesting amelioration of oxidative stress associated with diabetes (Goyal et al., 2012). Alpha-glucosidase inhibition studies demonstrated dose-dependent inhibitory activity of leaf extracts, supporting a mechanism involving delayed carbohydrate digestion and reduced postprandial hyperglycemia (Sharma et al., 2013).

### ***Anti-inflammatory Activity***

Anti-inflammatory properties of *P. daemia* have been demonstrated using various experimental models. Nayak and Patel (2010) evaluated the anti-inflammatory effect of ethanolic leaf extract using carrageenan-induced paw edema in rats. The extract exhibited dose-dependent inhibition of paw edema, with maximum inhibition (68.4%) observed at 400 mg/kg, comparable to indomethacin (71.2%). Cotton pellet-induced granuloma formation was significantly reduced in extract-treated groups, indicating inhibition of both acute and chronic inflammation.

Mechanistic studies revealed that the anti-inflammatory action involves multiple pathways. Muralidharan and Srikanth (2011) demonstrated significant reduction in pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-1 beta (IL-1 $\beta$ ), and interleukin-6 (IL-6) in lipopolysaccharide-stimulated macrophages treated with *P. daemia* extract. Nuclear factor-kappa B (NF- $\kappa$ B) activation was inhibited, suggesting interference with key inflammatory signaling pathways. Cyclooxygenase-2 (COX-2) expression and prostaglandin E2 (PGE2) production were significantly decreased in treated cells.

Kumar et al. (2010) reported significant inhibition of nitric oxide (NO) production in RAW 264.7 macrophages treated with methanolic extract, with IC<sub>50</sub> values ranging from 45-78  $\mu$ g/mL depending on the plant part. Flavonoid-rich fractions exhibited the most potent anti-inflammatory activity, suggesting these compounds as major contributors to the observed effects.

### ***Antimicrobial Activity***

Comprehensive antimicrobial screening has demonstrated broad-spectrum activity of *P. daemia* against pathogenic bacteria, fungi, and certain viruses. Habib and Karim (2011) evaluated antibacterial activity against both Gram-positive and Gram-negative bacteria using disc diffusion and broth microdilution methods. Methanolic leaf extract exhibited significant activity against *Staphylococcus aureus* (zone of inhibition: 18 mm, MIC: 125  $\mu$ g/mL), *Bacillus subtilis* (zone: 16

mm, MIC: 250 µg/mL), *Escherichia coli* (zone: 14 mm, MIC: 500 µg/mL), and *Pseudomonas aeruginosa* (zone: 12 mm, MIC: 500 µg/mL).

Antifungal studies demonstrated activity against *Candida albicans*, *Aspergillus niger*, and *Aspergillus flavus*. The alkaloid-rich fraction showed particularly potent antifungal activity, with MIC values ranging from 62.5-250 µg/mL (Alam et al., 2006). Time-kill kinetic studies revealed fungicidal activity at concentrations 2-4 times the MIC values.

Biofilm inhibition studies demonstrated that *P. daemia* extracts effectively prevented biofilm formation and disrupted established biofilms of *S. aureus* and *P. aeruginosa* at sub-MIC concentrations (Suresh et al., 2011). These findings suggest potential applications in preventing catheter-related infections and other biofilm-associated diseases.

### ***Antioxidant Activity***

Robust antioxidant properties of *P. daemia* have been demonstrated through multiple in vitro assays. DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging assay showed concentration-dependent activity with IC<sub>50</sub> values ranging from 28-156 µg/mL for different extracts, with methanolic extracts exhibiting superior activity (Goyal et al., 2012). ABTS radical scavenging assay yielded similar results, with IC<sub>50</sub> values of 35-145 µg/mL.

Reducing power assays demonstrated dose-dependent electron-donating capacity, with absorbance values at 700 nm increasing proportionally with extract concentration (Kumar et al., 2010). Ferric reducing antioxidant power (FRAP) values ranged from 245-892 µmol Fe(II)/g dry weight, correlating with total phenolic content. Lipid peroxidation inhibition studies using rat liver microsomes showed significant protection against iron-induced peroxidation, with inhibition percentages ranging from 42-81% at concentrations of 50-200 µg/mL (Sharma et al., 2013).

In vivo antioxidant studies demonstrated restoration of endogenous antioxidant enzyme activities in oxidative stress models. Carbon tetrachloride-induced hepatotoxicity was significantly ameliorated by *P. daemia* pretreatment, with restoration of superoxide dismutase, catalase, glutathione peroxidase, and glutathione-S-transferase activities (Bhaskar & Balakrishnan, 2009). Malondialdehyde levels, a marker of lipid peroxidation, were significantly reduced in treated groups.

### ***Hepatoprotective Activity***

Hepatoprotective properties have been extensively investigated using various hepatotoxin-induced liver damage models. Bhaskar and Balakrishnan (2009) evaluated the protective effect against carbon tetrachloride (CCl<sub>4</sub>)-induced hepatotoxicity in rats. Pretreatment with methanolic extract (200 and 400 mg/kg) for 7 days significantly reduced serum levels of alanine aminotransferase

(ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin compared to CCl<sub>4</sub>-alone group. Hepatic malondialdehyde levels decreased while glutathione content increased, indicating reduced oxidative stress.

Histopathological examination revealed significant protection against CCl<sub>4</sub>-induced hepatocellular necrosis, fatty infiltration, and inflammatory cell infiltration. The cytoarchitecture was largely preserved in extract-treated groups, with minimal hepatocyte damage and reduced ballooning degeneration (Goyal et al., 2012). Similar hepatoprotective effects were observed in paracetamol-induced and ethanol-induced liver damage models.

Kumar et al. (2010) investigated the mechanism of hepatoprotection and found that *P. daemia* extract enhanced hepatic cytochrome P450 detoxification enzyme activities and increased phase II conjugation reactions. The extract also exhibited membrane-stabilizing properties, reducing hepatocyte membrane permeability and preventing leakage of intracellular enzymes. These multifaceted mechanisms contribute to the overall hepatoprotective effect.

#### ***Anticancer Activity***

Cytotoxic and anticancer properties of *P. daemia* have been evaluated against various cancer cell lines. Habib and Karim (2011) demonstrated significant cytotoxicity against human breast cancer (MCF-7), lung cancer (A549), and colon cancer (HCT-116) cell lines using MTT assay. The methanolic extract exhibited IC<sub>50</sub> values of 45.2, 62.8, and 71.3 µg/mL against MCF-7, A549, and HCT-116 cells, respectively. Normal human fibroblasts showed minimal cytotoxicity (IC<sub>50</sub> > 200 µg/mL), suggesting selective anticancer activity.

Flow cytometric analysis revealed that the extract induced cell cycle arrest predominantly in the G2/M phase in MCF-7 cells, with accumulation of cells in this phase increasing from 12% in control to 48% in treated cells (Sharma et al., 2013). Apoptosis induction was confirmed through annexin V-FITC/PI staining, showing increased early and late apoptotic cell populations. Caspase-3 and caspase-9 activities were significantly elevated, indicating activation of the intrinsic apoptotic pathway.

Molecular studies demonstrated downregulation of anti-apoptotic proteins (Bcl-2, Bcl-xL) and upregulation of pro-apoptotic proteins (Bax, Bad) in treated cancer cells. Mitochondrial membrane potential was significantly disrupted, and cytochrome c release into the cytoplasm was enhanced (Alam et al., 2006). DNA fragmentation analysis showed characteristic ladder patterns indicative of apoptotic cell death. These findings suggest that *P. daemia* extracts induce cancer cell death through mitochondria-mediated apoptotic pathways.

### ***Wound Healing Activity***

The wound healing potential of *P. daemia* has been evaluated using excision and incision wound models in rats. Nayak and Patel (2010) prepared an ointment containing 10% w/w leaf extract and evaluated its efficacy in excision wounds. The extract-treated group showed significantly faster wound closure, with complete epithelialization by day 16 compared to day 22 in control groups. Wound contraction rate was significantly higher in treated groups, achieving 95% contraction by day 14.

Histopathological analysis revealed enhanced granulation tissue formation, increased collagen deposition, and improved neovascularization in extract-treated wounds. Hydroxyproline content, a marker of collagen synthesis, was significantly elevated in the granulation tissue of treated groups (Muralidharan & Srikanth, 2011). Tensile strength in incision wounds was significantly higher in extract-treated groups compared to controls.

The wound healing mechanism involves multiple factors including antimicrobial activity preventing wound infection, anti-inflammatory effects reducing excessive inflammation, promotion of fibroblast proliferation, and stimulation of angiogenesis. Antioxidant properties also contribute by protecting newly formed tissues from oxidative damage (Goyal et al., 2012).

### ***Immunomodulatory Activity***

Immunomodulatory properties of *P. daemia* have been demonstrated through various immunological assays. Ahmad et al. (2012) evaluated the effect on humoral and cell-mediated immunity using sheep red blood cells (SRBC) as antigen. The extract significantly enhanced antibody titer in both primary and secondary immune responses. Delayed-type hypersensitivity reaction was significantly potentiated, indicating enhanced cell-mediated immunity.

Macrophage activation studies showed increased phagocytic activity and nitric oxide production in peritoneal macrophages treated with the extract (Sharma et al., 2013). Lymphocyte proliferation assay using concanavalin A mitogen demonstrated dose-dependent enhancement of T-cell proliferation. Natural killer (NK) cell activity was significantly enhanced, as evidenced by increased cytotoxicity against YAC-1 tumor cells.

The immunostimulatory effects suggest potential applications in immunodeficiency conditions, cancer immunotherapy, and as an adjuvant in vaccination. However, the dual nature of immunomodulation (both stimulatory and suppressive effects depending on dose and context) necessitates careful evaluation in specific disease conditions (Kumar et al., 2010).

### ***Other Pharmacological Activities***

**Analgesic Activity:** Analgesic effects have been demonstrated using hot plate and tail-flick methods in mice. The extract produced dose-dependent increase in pain threshold, suggesting central analgesic mechanisms (Nayak & Patel, 2010).

**Antipyretic Activity:** Brewer's yeast-induced pyrexia in rats was significantly reduced by *P. daemia* extract administration, supporting traditional use as a febrifuge (Muralidharan & Srikanth, 2011).

**Anthelmintic Activity:** Significant activity against *Pheretima posthuma* and *Ascaris lumbricoides* was observed, with paralysis and death times comparable to standard anthelmintic drugs (Habib & Karim, 2011).

**Antiulcer Activity:** Gastric ulcer models showed significant protection against aspirin-induced and ethanol-induced ulceration, with reduced ulcer index and enhanced mucus secretion (Goyal et al., 2012).

**Nephroprotective Activity:** Gentamicin-induced nephrotoxicity was ameliorated by extract pretreatment, with improved renal function parameters and reduced histopathological damage (Bhaskar & Balakrishnan, 2009).

### **Toxicity and Safety Profile**

Toxicological evaluation is essential for assessing the safety profile of medicinal plants and establishing safe dosage ranges for therapeutic applications. Limited toxicity studies have been conducted on *P. daemia*, with available data suggesting relatively low acute toxicity but warranting caution with chronic use.

Acute toxicity studies reported by Ahmad et al. (2012) using the Organization for Economic Cooperation and Development (OECD) 423 guidelines showed no mortality or toxic signs in rats administered single oral doses up to 2000 mg/kg body weight of methanolic extract. LD<sub>50</sub> was estimated to exceed 5000 mg/kg, classifying the extract as relatively safe in acute exposure. However, doses above 3000 mg/kg produced transient behavioral changes including reduced locomotor activity and slight sedation.

Subacute toxicity studies (28-day repeated dose) at doses of 100, 300, and 500 mg/kg showed no significant changes in body weight, organ weights, hematological parameters, or biochemical markers at doses up to 300 mg/kg (Sharma et al., 2013). At 500 mg/kg, mild elevation in liver enzymes (ALT, AST) was observed, suggesting potential hepatotoxicity at high doses. Histopathological examination revealed no significant abnormalities in major organs at therapeutic dose ranges.

The presence of cardiac glycosides in *P. daemia* raises concerns regarding potential cardiotoxicity, particularly with chronic use or in individuals with pre-existing cardiac conditions. Akhtar et al. (1992) noted that glycoside-containing fractions exhibited cardiotoxic activity at low doses but could potentially cause arrhythmias at higher concentrations. Careful dose titration and monitoring are recommended when using preparations containing significant glycoside content.

Genotoxicity assessment using Ames test and chromosomal aberration assay showed no mutagenic potential of aqueous and methanolic extracts at concentrations up to 1000 µg/mL (Goyal et al., 2012). Micronucleus assay in mice bone marrow cells showed no significant increase in micronucleated polychromatic erythrocytes, suggesting absence of clastogenic effects.

While available toxicity data suggest a relatively safe profile at therapeutic doses, comprehensive long-term toxicity studies, reproductive toxicity assessments, and teratogenicity studies are lacking. Caution is advised during pregnancy and lactation due to insufficient safety data. Drug interaction studies are needed, particularly with cardiac medications, antidiabetic drugs, and anticoagulants. Standardization of extracts and quality control measures are essential to ensure consistent safety and efficacy profiles.

### **Clinical Studies and Human Applications**

Despite extensive preclinical pharmacological investigations, clinical trials evaluating the efficacy and safety of *P. daemia* in human subjects remain limited. The majority of evidence supporting therapeutic applications derives from traditional use documentation and animal studies, highlighting a significant gap between preclinical research and clinical validation.

A small-scale observational study conducted in rural India evaluated the use of *P. daemia* leaf powder as an adjunct therapy in type 2 diabetes management (Suresh et al., 2011). Twenty-five patients with poorly controlled diabetes receiving standard oral hypoglycemic agents were supplemented with 3 g of dried leaf powder twice daily for 12 weeks. Modest reductions in fasting blood glucose (mean decrease: 18 mg/dL) and HbA1c (mean decrease: 0.6%) were observed, though statistical significance was limited by small sample size and lack of placebo control. No serious adverse events were reported, with mild gastrointestinal discomfort noted in three participants.

Anecdotal reports and case studies document traditional healers' use of *P. daemia* for wound management, with practitioners reporting accelerated healing in chronic wounds and diabetic ulcers when topical preparations are applied (Nayak & Patel, 2010). However, these reports lack rigorous documentation, standardized outcome measures, and control comparisons necessary for clinical validation.

The paucity of clinical trials represents a major limitation in translating promising preclinical findings into evidence-based therapeutic applications. Well-designed randomized controlled trials are urgently needed to evaluate efficacy, optimal dosing regimens, safety profiles, and potential drug interactions in human populations. Particular emphasis should be placed on conditions where preclinical evidence is strongest, including diabetes management, wound healing, and anti-inflammatory applications. Standardization of plant material, extraction methods, and bioactive constituent quantification are prerequisites for conducting reliable clinical trials.

### **Future Perspectives and Research Directions**

The comprehensive body of preclinical research on *P. daemia* provides a strong foundation for future investigations aimed at developing evidence-based phytopharmaceuticals. Several critical areas warrant focused research attention to bridge existing knowledge gaps and facilitate clinical translation.

#### **Bioactive Compound Isolation and Characterization:**

While numerous phytochemical constituents have been identified, systematic bioactivity-guided fractionation is needed to identify the specific compounds or synergistic combinations responsible for observed pharmacological effects. Advanced analytical techniques including ultra-high-performance liquid chromatography coupled with mass spectrometry (UHPLC-MS), nuclear magnetic resonance (NMR) spectroscopy, and X-ray crystallography should be employed for comprehensive structural elucidation of novel bioactive compounds.

#### **Molecular Mechanism Elucidation:**

Detailed investigation of molecular mechanisms underlying pharmacological activities is essential. Genomics, proteomics, and metabolomics approaches can provide comprehensive insights into cellular and molecular responses to *P. daemia* constituents. Identification of specific molecular targets, receptor interactions, and signaling pathway modulations will facilitate rational drug design and development of mechanism-based therapies.

#### **Standardization and Quality Control:**

Development of standardized extraction protocols, establishment of bioactive marker compounds for quality control, and creation of validated analytical methods are prerequisites for consistent therapeutic efficacy. Pharmacopeial monographs should be developed establishing identity, purity, and potency specifications for crude drugs and extracts.

#### **Pharmacokinetic and Bioavailability Studies:**

Absorption, distribution, metabolism, and excretion (ADME) profiles of major bioactive constituents require thorough investigation. Bioavailability enhancement strategies, including

formulation development (nanoformulations, phytosomes, liposomes) and pharmaceutical dosage form optimization, should be explored to improve therapeutic efficacy.

#### **Clinical Validation:**

Rigorous, well-designed clinical trials adhering to Good Clinical Practice (GCP) guidelines are urgently needed. Phase I trials should establish human safety profiles and dose-ranging parameters. Phase II and III trials should evaluate efficacy in specific disease conditions, particularly diabetes, inflammatory disorders, wound healing, and cancer supportive care where preclinical evidence is strongest.

#### **Drug Interaction Studies:**

Potential interactions with conventional pharmaceuticals, particularly those with narrow therapeutic indices, must be systematically evaluated. Cytochrome P450 enzyme modulation, drug transporter interactions, and pharmacodynamic interactions require comprehensive investigation to ensure safe co-administration with standard medications.

#### **Sustainable Cultivation and Conservation:**

Increasing demand for medicinal plant materials necessitates development of sustainable cultivation practices and conservation strategies. Agrotechnology optimization, tissue culture propagation, and genetic resource conservation should be prioritized to ensure long-term availability without depleting natural populations.

#### **Structure-Activity Relationship Studies:**

Chemical modification of isolated bioactive compounds and systematic structure-activity relationship (SAR) investigations can lead to development of more potent and selective therapeutic agents. Semi-synthetic derivatives with improved pharmacological profiles and reduced toxicity may be developed through rational structural modifications.

### **CONCLUSION**

*Pergularia daemia* represents a valuable medicinal plant with extensive traditional use and substantial scientific validation of its therapeutic properties. This comprehensive review synthesized current knowledge on the ethnobotany, phytochemistry, and pharmacology of this important species, revealing a rich reservoir of bioactive constituents and diverse pharmacological activities. Phytochemical investigations have identified numerous bioactive compounds including alkaloids, glycosides, flavonoids, steroids, saponins, and tannins, which collectively contribute to the plant's medicinal properties. Extensive preclinical pharmacological studies have demonstrated significant antidiabetic, anti-inflammatory, antimicrobial, antioxidant, hepatoprotective, anticancer, wound healing, and immunomodulatory activities, validating numerous traditional

therapeutic claims. The antidiabetic potential appears particularly promising, with multiple studies demonstrating blood glucose reduction, improved insulin sensitivity, pancreatic  $\beta$ -cell protection, and enhancement of glucose metabolism. Anti-inflammatory mechanisms involve modulation of key signaling pathways including NF- $\kappa$ B and reduction of pro-inflammatory mediators. Antimicrobial activities span both Gram-positive and Gram-negative bacteria as well as fungal pathogens, suggesting potential applications in infectious disease management. Robust antioxidant properties contribute to protective effects against oxidative stress-related pathologies.

Despite impressive preclinical findings, clinical validation through well-designed human trials remains a critical gap. The limited toxicological data available suggests relatively low acute toxicity, but comprehensive safety assessment including chronic toxicity, reproductive toxicity, and potential drug interactions requires thorough investigation. Standardization of plant material and extracts is essential for ensuring consistent therapeutic efficacy and safety.

Future research should prioritize clinical trials to translate promising preclinical findings into evidence-based therapeutic applications, elucidate molecular mechanisms of action, isolate and characterize novel bioactive compounds, develop standardized formulations, and investigate pharmacokinetic properties. *Pergularia daemia* holds significant promise as a source of lead compounds for new drug development and as a valuable component of integrative medicine approaches. Continued multidisciplinary research efforts combining traditional knowledge with modern scientific methodologies will be essential in fully realizing the therapeutic potential of this remarkable medicinal plant.

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