Paederia foetida Linn. A Comprehensive Review of Its Ethnobotanical Applications, Phytochemical Profile, Pharmacological Properties, and Future Therapeutic Prospects

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Abstract

Paederia foetida L., Rubeaceae is one of the medicinal plants that has been extensively employed in the traditional healing system of Asia, including Ayurveda, the Chinese system of medicine, and tribal medicine practiced in various Asian countries. The aim of this review is to provide information regarding ethnomedicinal significance, botanical description, phytochemical screening, and pharmacological activity of this medicinal herb. The herb is rich in various bioactive compounds, including iridoid glycosides, flavonoids, terpenoids, and essential oils, which render it a storehouse of various health-promoting activities. The pharmacological activities of the plants have been scientifically proven, including anti-inflammatory, anti-oxidant, anti-microbial, analgesic, gastroprotective, hepatoprotective, and anti-cancer activity. In the review, the methods of the process of extracting and evaluating these activities are also presented, and the need for standardization of the process is emphasized, as it is a known fact that standardization is the need of the hour for the further development of drugs. This review, which combines traditional knowledge with the present-day pharmacological evidence of the effectiveness of the said drugs, thus emphasizes the potential of the use of P. foetida as a promising source of phototherapeutics of the future.

Keywords: *Paederia foetida*, ethnomedicinal uses, phytochemicals, pharmacological activity, traditional medicine.

1. Introduction

1.1. About Plant

Paederia foetida L., a perennial climber belonging to the family Rubiaceae, is used as an important ingredient of traditional medicine in both tropical and temperate areas. It is known as skunkvine or stinkvine in reference to the unpleasant sulfurous smell emitted when crushed, and for many years, has been the focus of numerous investigations, based on its ancient ethnomedicinal properties and its potential as a source of new pharmaceuticals [1]. Its uses also include Ayurveda, traditional Chinese medicine, and indigenous tribal medicine, such as for rheumatism and gastrointestinal disorders. Recent investigations have unveiled its phytochemical profile, pharmacological properties, and eco-adaptability, and this plant is now considered a promising source for new therapeutics [2]. This plant is not only valuable in a medicinal context, but also ecologically and culturally. Its adaptation to a wide range of habitats from sea level to high altitude reflects its ecological fitness, and the history of its invasion has raised serious environmental concerns in many invaded areas. This study illustrated how traditional knowledge and modern science can supplement and complement each other, and P. foetida may serve as an important plant material to link ethnobotany and observational pharmacology for exploring bioactive components and acting mechanisms [3].

1.2. Origin and Distribution

Paederia foetidaL., is distributed throughout Asia from the temperate to tropical regions, that include the Bangladesh, southern part of Bhutan, Cambodia, China (including Hong Kong and Macau SAR and provinces such as Anhui, Fujian, Guangdong, Guangxi, Hainan and Yunnan), India (Andhra Pradesh, Assam, Manipur, Meghalaya, Andaman & Nicobar Islands), Indonesia, Japan, Malaysia, Nepal, Philippines, Republic of Korea, Singapore, Thailand, and Vietnam [4]. Outside this area, it has been naturalized in regions including the Mascarenes, Melanesia, Polynesia, Hawai'i, and parts of North America, particularly Florida and Texas [5]. The plant can occupy a wide range of habitats, from coastal lowlands to montane at elevations of 3,000 meters, and occurs in thicket, woodland, forest margins, and second-growth forest. The species was successful as a colonizer due to its fast growth, high reproductive rate, and its capacity to settle in disturbed environments, like roadsides, clearings, and agricultural fields [6]. But this adaptability has also seen it classified as an invasive species elsewhere, in the non-native regions (especially the US), as it blankets indigenous vegetation and upsets the balance of ecosystems. In the state of Florida, *P. foetida* is classified as a Category I invasive plant, which requires control to manage its impact on the environment [7]. Its spread has been recorded, and the necessity for management practices that consider both its medicinal potential and environmental issues has been stressed. The species distribution is conditioned by climatic factors, that is, tropical and subtropical climates and a requirement for a warm, humid environment [8]. It will tolerate a variety of soil types,

including sandy loams and clays, and alkaline to neutral soil pH. Its ability to adapt to salty zones and grasslands can also broaden its ecological niche [9].

1.3. Taxonomical Classification

Paederia foetida belongs to the Rubiaceae family, one of the largest families of flowering plants, comprising over 13,000 species. Its taxonomic hierarchy is as follows:

Table 1. Taxonomical classification of *Paederia foetida*

Scientific name	*Paederia foetida*
Kingdom	Plantae
Phylum	Tracheophyta
Class	Magnoliopsida
Order	Gentianales
Family	Rubiaceae
Genus	Paederia
Species	foetida

The genus *Paederia* includes approximately 30 species, with *P. foetida* being the most widely studied due to its medicinal and ecological significance. *P. foetida* synonyms include *Paederiachinensis* Hance, *Paederiascandens (Lour.)* Merr., and *Paederia tomentosa* Blume, these identities being an indication of the taxonomic confusion that arises from the morphological variability [10]. Molecular studies have recently made clear its phylogeny within the Rubiaceae, and it has been shown to belong to the tribe Paederieae. Compoundness of the plant arises from local morphological differences, especially leaf truncature and flower size, leading to the discussion on synonymy and definition of species [11].

1.4. Vernacular Names

Paederia foetida is a common name that is diverse and indicates its fetid smell and the uses for medicine. It is also known as “GandhaPrasarini” or “Gandhavadulia” in Sanskrit, “KaliLata” in Bengali, “Gandhali” in Hindi, and “Prasarini” in Ayurvedic literature. Its English names are skunkvine, stinkvine, and Chinese fever vine, which highlight the unpleasant smell of the plant. “Pilaumaile” is the name used to refer to the plant in the Hainanese cuisine. The name refers to the plant leaves used as food. Other names used to refer to the plant are “DaunKentut,” which is used in Malaysia and refers to the plant as “fart leaf,” and “Ji Shi Teng,” which is used in China and refers to the plant as “chicken droppings vine.” The variety of names used to refer to the plant in different parts of the world is an indication of the plant's use and socio-cultural value [12; 13]. Among tribal populations in northeastern India, it is prized not only as a medicine, but also as a food, with the young leaves eaten as a vegetable,

or ground into flour for medicinal soups. The nomenclature also emphasises the double-facedness of the plant that is, on the one hand revered plant of ethnomedicinal importance and, on the other hand sensory nightmare on account of its odour, which is due to the sulfur compounds predominantly attributed to dimethyl disulfide [14].

1.5. Botanical Description

Paederia foetida is a wiry, perennial, fast-growing climber with thin, twining, woody stems that can grow to 1.5–7 m long, which depend on other vegetation for support. It's simple, opposite leaves are ovate-lanceolate in shape and 5–10 cm long and 2.5–5 cm wide, with long petioles and a membranous texture. Leaves and stems scent taint when bruised, which is attributed to sulfur compounds, mainly methyl mercaptan and dimethyl disulfide [15]. The flowers are small bisexuals in axillary or terminal cymes, with purple or violet petals that unite into a tubular corolla. The calyx is persistent, and the corolla is five-lobed with the stamens inserted into the corolla tube. The fruit is laterally compressed, an ellipsoid berry becoming yellow, red or black when ripe; enveloped in a persistent calyx. Seeds (number per fruit = 1-3) are small, flat, yellow, reniform (semilunar in shape), 2n = 48, and relatively easily dispersed by the wind. The roots are cylindrical, compressed, and with root scars, which are used in traditional medicine for tonic [16]. This plant’s climbing growth habit and its light seeds enable rapid spread, especially across disturbed habitats [17]. Botanical surveys in the years 2015-25 have published records of this plant's reproductive biology, and once again, its high seed viability and germination rates contribute to its invasiveness. The flowers are insect-pollinated, most commonly by bees but also by butterflies, and the ability to self-pollinate leads to reproductive success in colonies of low density. The persistent calyx probably assists in seed dispersal by providing a lightweight framework to trap the wind, and it is considered to contribute to its ecological success [18].

1.6. Morphological Characteristics

Morphologically, there is a great variation in *Paederia foetida* characteristics such as the size, shape, and pubescence of the leaves, which can vary among the wild and cultivated populations. Leaves in shaded conditions are generally larger and thinner, but leaves in open, sunny sites are smaller and thicker, which represents the adaptation to light intensity. The tubers are glabrous to sparsely hairy, the plant base becoming woody with age, which allows it to become a climber and overtake other species [19]. A characteristic is the offensive smell due to volatile oils such as linalool, methyl mercaptan, and dimethyl disulfide, which are mostly present in leaves and stems. The flowers are pentamerous (five sepal, petal, and stamen and bilobed stigma), characteristic of the Rubiaceae family [20]. The purple coloration of the corolla lures pollinators, but the tubular form of the corolla repels and restricts access by some, increasing pollination effectiveness. With its small seeds (covered by the persistent calyx) which are blown away by the wind, it is able to spread quickly to new areas. Several studies on ontogeny

have revealed the phenotypic plasticity of the plant, that allows the adaptation of the plant from coastal saline habitats to montane habitats [21].

Lately, it has been investigated the role of morphological variability in the ecological success of the plant. For example, an Indian study has observed variation is leaf morphology between Assam and Andaman Islands, indicating adaptation to regional conditions of humidity and soil. These differences have ethnobotanical relevance, since various populations could have different phytochemical profiles, with consequences in their medicinal effectiveness. The pictorial representation of *Paederia foetida* has been demonstrated in Figure 1.



Figure 1. Pictorial representation of *Paederia foetida*

1.7. Ecological Adaptation

Paederia foetida is a very adaptable plant growing in temperate and tropical areas. It is a halophyte occurring in seaside areas [22] that thrives on moist well drained soils from mildly acid to fairly neutral (pH 5.5-7.5) quality and is drought resistant. It is found in a wide range of habitat types, such as secondary evergreen forest, mountain slope, riverside and disturbed areas, such as roadsides and agricultural land. Its altitudinal amplitude (from sea level to 3,000 m) demonstrates its resistance to temperature and precipitation gradients [23].

The ruderal nature of the plant enables its establishment in disturbed areas, and the weed outcompetes native flora by growing faster and producing more seeds. It has a climbing growth form that allows it to grow over and kill shrubs and small trees by forming mats that prevent sunlight from reaching the growing vegetation below, in turn inhibiting the process of photosynthesis. Due to its aggressive expansion it has become invasive in places such as Florida and Hawaii, causing havoc to native ecologies and invoking a loss of biodiversity [24]. Research has highlighted the necessity for comprehensive management programs involving mechanical extraction and herbicidal treatment to

combat it in exotic locations. Ecological research has also investigated the cotton plant's relationship with neighbouring faunae. In its original native range, *P. foetida* is a food plant for some herbivores, as well as a home for insects, supporting the local ecosystem. However, in invaded areas, it alters food webs by reducing the availability of native plants, affecting herbivore and pollinator populations. Its ability to regenerate from stem fragments further enhances its resilience, making eradication challenging [25].

1.8. Medicinal Parts of the Plant

The whole plant parts of *Paederia foetida* i.e leaves, roots, bark & fruits are used in traditional medicine, but leaves are the most widely used as they are easily accessible and possess more concentration of bioactive. Leaves are considered antiinflammatory, antidiarrheal, and antioxidant and are prepared as decoctions, pastes, and infusions. It is used medicinally and the roots are tonic, astringent to the bowels and anti-rheumatic, boiled or powdered for ingestion [26]. The bark, used more sporadically, is included in remedies for gastrointestinal disturbances and fruits can be taken for their laxative and anti-ulcer properties in some countries. The entire plant is frequently used to make extracts for wider medicinal use (especially in Ayurveda or Chinese medicine). However, a method for extraction has been standardised in recent studies to maximise the yield of bioactive compounds, that is, iridoid glycosides and flavonoids from various parts of the plant [27]. The plant part for use depends on the nature of the disease; in acute conditions, leaves are recommended, while thicker roots are a better solution for chronic diseases, such as arthritis.

Pharmacognostic investigations have emphasised on correct identification and processing of plant parts for their therapeutic values. For example, the sulfurous smell of the leaves, although a sensory hurdle, is indicative of their volatile oil fraction, which has a role in their antimicrobial profile [28]. A long boiling is necessary to extract the active compounds from the roots due to its woody nature, a traditional and empirical process which is a legitimate one, which has been clearly indicated by further research [29].

1.9. Uses in Different Traditional Systems

Paederia foetida is a cornerstone of several traditional medicine systems, reflecting its versatility and cultural significance:

1.9.1 Ayurveda: Known as "GandhaPrasarini," it is used to balance Kapha and Vata doshas, treating rheumatism, gout, diarrhea, dysentery, and infertility. Leaves and roots are prepared as decoctions, oils, or pastes, often combined with other herbs like ginger or turmeric to enhance efficacy. Ayurvedic texts emphasize its role in improving joint mobility and reducing inflammation, making it a staple in formulations for arthritis and sciatica [30].

1.9.2 Chinese Medicine: In southern China, *P. foetida* is used to alleviate pain, inflammation, and digestive disorders, particularly dyspepsia and flatulence. It is often administered as a tea or tincture, with leaves and stems preferred for their warming properties. Chinese pharmacopoeias describe its ability to "disperse wind-damp" and strengthen the spleen, aligning with its use in gastrointestinal and musculoskeletal conditions [31].

1.9.3 Tribal Practices: In the north-eastern part of India, particularly ethnic communities such as the Bodo, Karbi and Mishing tribes use *P. foetida* against gastrointestinal disorders, ulcers and as a tonic. Young leaves are eaten as a vegetable or blanched as flour for medicinal soups, especially in Hainan cuisine. In Manipur, the plant is used as a paste during wound healing as well as in skin infections, suggesting its antimicrobial activity [32].

1.9.4 Other Systems: In Vietnam, P. foetida is employed for jaundice, dyspepsia, and diuretic, which is primarily used in the form of infusion. In Mauritius, it is used as a tonic and anti-inflammatory. In eastern India, especially Odisha, the leaves are used as a spice in food, thus emphasizing the duality of the plant as food as well as medicine. These various uses in culture and medicine all demonstrate how adaptable the plant is to various social and medical contexts [33].

More than 50 different traditional applications of *P. foetida* have been reported in ethnobotanical studies, including as a treatment to reduce fever and as a fertility enhancer. These research shed light on the need of documentation of traditional knowledge since a large number of tribal people are depended on this plant for their primary health care [34]. The blending of traditional practice and modern pharmacology have resulted to standardized herbal preparations, for example, in the form of *P. foetida* containing ointments used for joint pains, which have become popular in urban markets [35].

1.10. Different Species of *Paederia* and Their Medicinal Properties

The genus Paederia (Rubiaceae) consists of about 30 species, and *P. foetida* and *P. scandens* are the two species most extensively investigated for their medicinal values. This has also been studied in some other species including *P. lanuginosa* and *P. linearis*:

1.10.1 *Paederia scandens*: *P. scandens,* growing in southern China, Vietnam, and Japan, is applied for aches, jaundice, dysentery, and dyspepsia [36]. It has also been shown to possess antinociceptive, anti-inflammatory, and antidiarrheal activities, which have been associated to iridoid glycosides such as paederoside and scandoside [37]. A standardized injection from P. scandens is commercially available for clinic use by the Chinese as an analgesic for musculoskeletal pain and several of its pharmaceutical properties is described. Its hepatoprotective activity has recently been demonstrated in several studies, especially on toxin-inducible hepatic damage, suggesting that it may be used in the treatment of hepatic diseases [38].

1.10.2 *Paederialanuginosa:* This species has been used locally in Southeast Asia for digestive disorders and is a diuretic. Scant research indicates it has flavonoids and terpenoids with antioxidant potential, however its pharmacological profile is not well known [39].

1.10.3 *Paederialinearis*: Found in India and Malaysia, P. linearis is applied to treat inflammatory ailments and wounds. Initial studies suggest anti-inflammatory and antioxidant properties, which may be mediated by phenolic compounds, but its therapeutic efficacy needs further research [40].

1.10.4 *Paederiatomentosa:* This species is most frequently considered a synonym of *P. foetida* and shares habitat use in traditional medicine, to a certain extent, for rheumatism and gastrointestinal problems. It shares a phytochemical profile with *P. foetida* with little regional variation [41].

P. foetida has been studied most extensively due to its wide distribution and teeming ethnobotanical history. A comparative study has demonstrated that *P. foetida* and *P. scandens* illustrate some common iridoid glycosides, but *P. foetida* contains a larger amount of volatile oils that account for its antimicrobial activity. The pharmacological prospects of other little known Paederia species need further studies, especially bio-guided fractionation to isolate new compounds [42].

1.11. Phytochemistry

The medicinal potentials of Paederia foetida could be attributed to its broad spectrum of phytochemical compounds, such as:

1.11.1 Iridoid Glycosides: Asperuloside, paederoside, and scandoside are the main components that are related to anti-inflammatory, hepatoprotective, and analgesic activities. The compounds suppress pro-inflammatory cytokines and are anti-arthritic and anti-inflammatory [43].

1.11.2 Flavonoids: Diets rich in flavonoids such as quercetin, kaempferol, and various derivatives are proposed due to their antioxidant and antihyperglycemic effects, protecting cells from oxidative stress and controlling blood glucose [44].

1.11.3. Essential Oil: Methyl mercaptan, linalool, and dimethyl disulfide are responsible for the plant odour that are reported to have antimicrobial and insecticidal effects. These oils are present in higher concentrations in the leaves and stems, which improves their topical use [45].

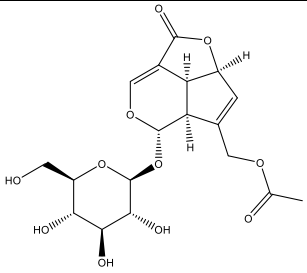
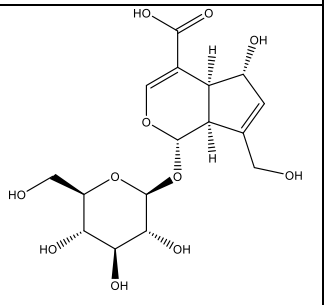
1.11.3.1 Terpenoids and Saponins: Ursolic acid, epifriedelinol, and friedelin exhibit anti-inflammatory, anticancer, and antimicrobial activity. Preclinical studies have demonstrated the potential of ursolic acid in suppressing tumour growth [46].

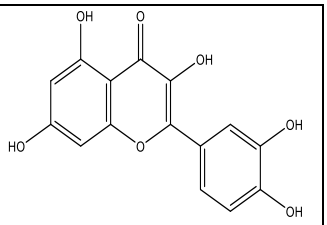
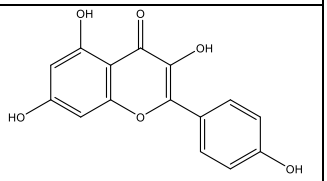
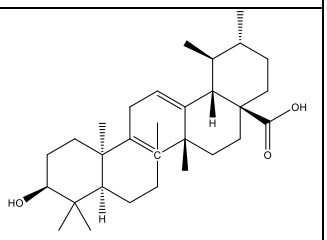
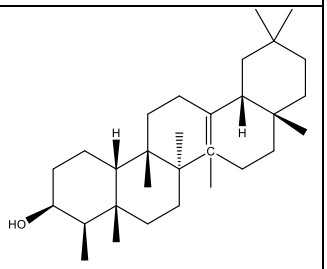
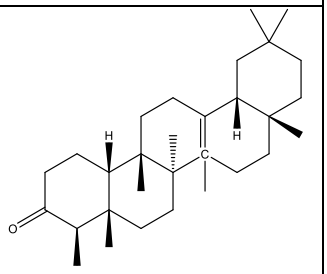
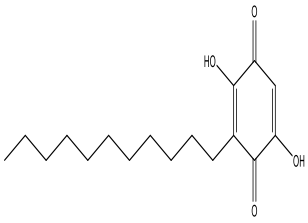
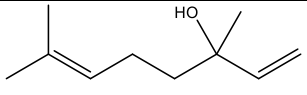
1.11.3.2 Quinones and Alkaloids: Embelin and other alkaloids are reported to possess cytotoxic [46], anticariogenic and antibiotic properties, and they are potential candidates for cancer and diabetes therapy [47].

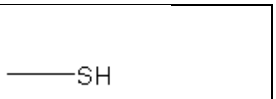
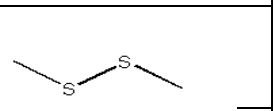
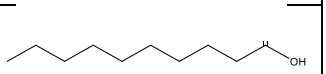
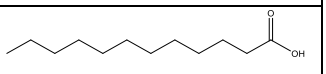
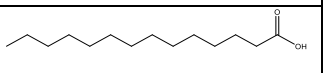
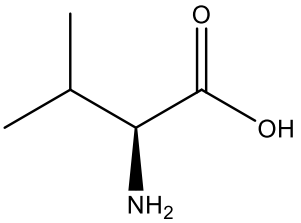
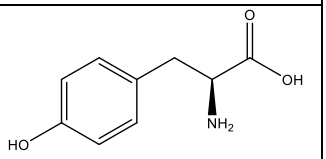
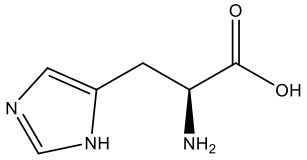
1.11.3.3 Fatty Acids and Amino Acids: The predominant fatty acids found in the plant were capric, lauric and myristic acids, and also amino acids such as valine, tyrosine, and histidine, which are beneficial for plant nutritional and medicinal purposes, especially in tribal diets [48].

The phyochemical investigations used modern technology such as high performance liquid chromatography (HPLC) and gas chromatography-mass spectrometry (GC-MS) for the determination and quantitation of these compounds. For example, scopoletin, a coumarin derivative, was proved to be a biomarker for quality control purposes in *P. foetida* herbal preparation and the rapid quantitative methods were established using quantitative nuclear magnetic resonance (NMR) and UV-Vis spectroscopy. These components distinct contributions to G.Smithii's pharmacological activities are synergistic, emphasising such whole plant extracts in traditional medicine [49]. The diversity of phytochemical contents among the populations was a topic of recent interest. This content is affected by environmental factors (soil type, altitude, climate), with organisms from humid, tropical regions presenting a higher quantity of active compounds (iridoid glycosides). The present results have relevance for the standardization of drugs derived from *P. foetida*, as uniform phytochemical profiles are a necessity if they are to exhibit therapeutic effectiveness [50]. The phytochemical profiling of *Paederia foetida* is provided in Table 2.

Table 2. Phytochemical profiling of *Paederia foetida*

Phytochemical Class	**Plants Part**	**Chemical Constituent**	**Pharmacological Activities**	**Structure**
Iridoid Glycosides	Roots, Leaves, Fruits	Asperuloside	Anti-inflammatory, Hepatoprotective, Analgesic	
	-	Scandoside	-	

Flavanoids	Leaves, Whole plant	Quercetin	Antioxidant, Antihyperglycemic, Anti-inflammatory activity	
	-	Kaemferol	-	
Terpenoids & Saponins	Whole plant, Leaves	Ursolic acid	Anticancer, Anti-inflammatory, antimicrobial	
	Leaves, Stems	Epifriedelinol	Antimicrobial, insect-repellent, aromatic	
	-	Friedelin	-	
Quinones	Fruits, Leaves	Embelin	Cytotoxic, antidiabetic, antimicrobial	
	Leaves, Stems	Linalool	Antimicrobial, Insect-repellent	

Essential Oils	-	Methyl mercaptan	-	
	-	Dimethyl disulfide	-	
Fatty Acids	Leaves, Seeds	Capric acid	Nutritional, Anti-inflammatory	
	-	Lauric acid	-	
	-	Myristic acid	-	
	Whole plant	Valine	Nutritional, Metabolic support	
Amino Acids	-	Tyrosine	-	
	-	Histidine	-	

2. Pharmacological Properties

Various research has validated the traditional uses of *Paederia foetida* through rigorous pharmacological studies, revealing a broad spectrum of activities:

2.1 Anti-inflammatory and Antinociceptive: Leaf and root extracts reduce inflammation and pain in animal models of arthritis and neuropathic pain, mediated by iridoid glycosides and flavonoids that inhibit cyclooxygenase (COX) and nuclear factor-kappa B (NF-κB) pathways. These effects support its use in rheumatism and gout [51].

2.2 Antidiabetic and Antihyperlipidemic: Ethanolic leaf extract lower blood glucose and lipid levels in streptozotocin-induced diabetic rats, with flavonoids and quinones enhancing insulin sensitivity and inhibiting lipid peroxidation. These findings suggest potential applications in type 2 diabetes management [52].

2.3 Antioxidant: High phenolic and flavonoid content neutralizes reactive oxygen species (ROS), protecting against oxidative stress-related diseases like cardiovascular disorders and cancer. *In vitro* assays, such as DPPH and ABTS, have confirmed the plant's radical-scavenging capacity [53].

2.4 Hepatoprotective and Nephroprotective: Extracts protect liver and kidney tissues from toxin-induced damage, such as carbon tetrachloride and cisplatin, by upregulating antioxidant enzymes like superoxide dismutase (SOD) and catalase. These effects are attributed to iridoid glycosides and terpenoids [54].

2.5 Antidiarrheal and Anti-ulcer: Leaf extracts reduce gastrointestinal motility and protect gastric mucosa in models of diarrhea and peptic ulcers, supporting their use in dysentery and dyspepsia. The mechanism involves inhibition of prostaglandin synthesis and enhancement of mucosal barrier function [55].

2.6 Antitussive, Thrombolytic, and Anthelmintic: The plant suppresses cough, dissolves blood clots, and exhibits antiparasitic activity against intestinal worms, with alkaloids and saponins playing key roles. These properties align with its traditional use as a general tonic [56].

2.7 Anticancer and Wound Healing: Preliminary studies suggest cytotoxic effects against breast, lung, and liver cancer cell lines, with ursolic acid and embelin inducing apoptosis. The plant also promotes wound healing by enhancing collagen synthesis and angiogenesis, likely due to its flavonoid content [57].

2.8 Antimicrobial: Essential oils and alkaloids inhibit the growth of bacteria (e.g., *Escherichia coli*, *Staphylococcus aureus*) and fungi (e.g., *Candida albicans*), supporting its use in skin infections and wound care [58].

These pharmacological activities have been validated through in vitro and in vivo studies, with some progressing to preclinical trials. However, challenges remain in isolating active compounds and elucidating their mechanisms of action. The synergistic effects of multiple phytochemicals suggest that whole-plant extracts may be more effective than isolated compounds, aligning with traditional practices. The various pharmacological activities of *Paederia foetida* have been demonstrated in Figure 2.

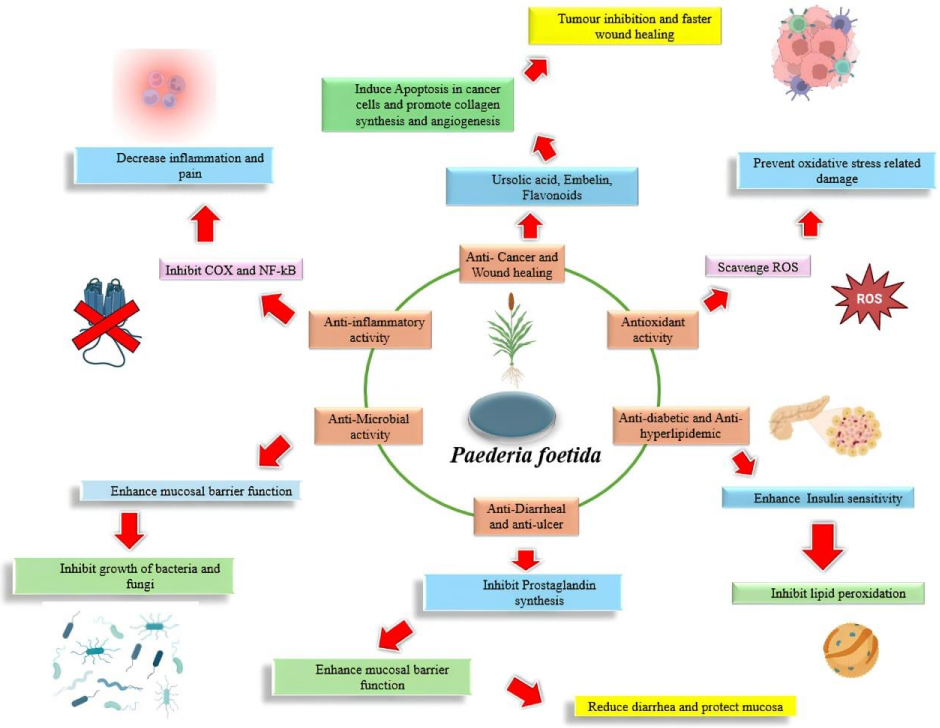


Figure 2: Various Pharmacological activities of *Paederia foetida*

3. Enlisting common animal models and methods employed

3.1. Anti-inflammatory Activity

3.1.1 Carrageenan-Induced Paw Edema in Rats

The study used a carrageenan-induced paw edema model in Wistar rats to evaluate the anti-inflammatory effects of a methanolic extract of *P. foetida* leaves. Rats were divided into groups and administered the extract orally at doses of 100 mg/kg and 200 mg/kg. One hour later, 0.1 mL of 1% carrageenan solution was injected into the right hind paw, and paw volume was measured at 0, 1, 2, 3, and 4 hours using a plethysmometer. The percentage inhibition of edema was calculated compared to the control group [59].

3.1.2 Complete Freund's adjuvant (CFA)-Induced Arthritis Model

The study used Wistar rats to evaluate the anti-arthritic effects of an aqueous extract of *P. foetida* leaves. Arthritis was induced by injecting Complete Freund's Adjuvant (CFA) into the left hind paw. The extract was administered orally at 200 mg/kg daily for two weeks. Joint diameter was measured regularly to assess inflammation, and serum levels of pro-inflammatory cytokines like IL-1β were measured using ELISA kits [60].

3.2. Antioxidant Activity

3.2.1 DPPH Radical Scavenging Assay

The methanolic leave extract of *P. foetida* was tested for it antioxidant activity by DPPH radical scavenging method. Different dilutions of the extract were mixed with 0.1 mM DPPH solution (1 mL) and left in the dark for 30 min. The absorption was read at 517 nm on a UV-VIS spectrophotometer and the percentage DPPH radical scavenging activity was measured which indicates the extract's antioxidant capacity [61].

3.2.2 ABTS Radical Cation Decolourisation Assay

The antioxidant activity of P. foetida leaves methanolic extract was evaluated by ABTS radical cation decolourisation assay. ABTS radicals were produced by mixing ABTS stock solution with potassium persulfate and dilution to absorbance 0.70 ± 0.01 at 734nm. Various concentrations of the extract were added, and 6 minutes later, the absorbance was then read at 734 nm. Inhibition of ABTS radicals was determined as the percentage of inhibition of the ABTS radical: [62].

3.3. Antimicrobial Activity

3.3.1 Minimum Inhibitory Concentration (MIC) Determination

The antimicrobial activity of essential oil extracted from *P. foetida* leaves was evaluated against Escherichia coli, Staphylococcus aureus, and Candida albicans. Serial dilutions of the oil were prepared and added to wells containing microbial inoculum in nutrient broth. After incubation at 37°C for 24 hours, the minimum inhibitory concentration (MIC) was determined as the lowest concentration that inhibited visible microbial growth [63].

3.3.2 Biofilm Inhibition Assay

The present study has also tested the antibiofilm potential of the ethyl acetate extract of *P. foetida* leaf against S. aureus and C. albicans. The medium was inoculated with the cultures on the plates and the extract was added over different concentrations. After incubation, biofilms were stained with crystal violet and the dye was solubilised in ethanol. Biofilm biomass was measured at 570 nm to ascertain the extract inhibition of biofilm formation [64].

3.4. Analgesic Activity

3.4.1 Hot Plate Test

The analgesic activity of *P. foetida* leaves aqueous extract has been evaluated in mice by hot plate test. Mice were orally treated with the extract at 250 mg/kg; 30 min later, they were put on a hot plate (55 ± 0.5°C). The latency time for paw licking or jumping was measured and cut-off at 15 s to prevent tissue injury, indicating the extract's antinociceptive effect [65].

3.4.2 Acetic Acid-Induced Writhing Test The analgesic activity of the methanolic extract of P. foetida stems was assessed in mice based on acetic acid-induced writhing. The extract was given orally to mice at a dose of 300 mg/kg, 30 min before injection of 0.6% acetic acid solution. Writhes (abdominal contractions) were recorded for 20 min and inhibition percent of writhing relative to control group was determined to evaluate analgesic potential of the extract [66].

3.5. Gastroprotective Activity

3.5.1 Ethanol-Induced Gastric Ulcer Model

The anti-ulcerogenic activity of the chloroform extract of *P. foetida* leaves was evaluated in rats. Rats were fasted for 24h and the extract was administered orally at 100 mg/kg each, then absolute ethanol was used to produce a gastric ulcer. The rats were killed 1 h later and their stomachs were observed for ulceration. The ulcer index (UI), taking into account the severity and number of ulcers, was employed to estimate the gastroprotective effects of the extract [67].

3.5.2 Indomethacin-Induced Ulcer Model

The anti-ulcerogenic effect of a root extract of *P. foetida* was assessed in rats. Rats fasted for 24 h and were given the extract orally at 150 mg/kg and then ulcers were produced by indomethacin. Rats were sacrificed 6 h later and their stomachs were examined for ulcers. The ulcer index was evaluated to evaluate the protective effects of extract on indomethacin induced gastric ulcers [68].

3.6. Hepatoprotective Activity

3.6.1 Paracetamol-Induced Hepatotoxicity Model

The hepatoprotective activity of an ethanolic leaf extract of P. foetida was evaluated in rats. The extract was administrated to the rats orally at 200 mg/kg for seven days and then hepatotoxicity was induced on the seventh day by paracetamol. After 24 h, blood was withdrawn for the assessment of liver enzymes (ALT and AST) as a measure of the protective effect of extract against paracetamol induced liver injury [69].

4. Recent advancement in the pharmacological activities of *Paederia foetida*

4.1. Anti-inflammatory Activity:

Methanol extract of *Paederia foetida* leaves which demonstrated significant anti-inflammatory effects in both *in vitro* and *in vivo* studies. In a rat model of carrageenan-induced paw edema, the extract (200 mg/kg) reduced swelling by 75%, comparable to the standard drug diclofenac (10 mg/kg), which showed 80% inhibition. The IC_{50} value for COX-2 enzyme inhibition was found to be 12.5 µg/mL, slightly higher than diclofenac (IC_{50} = 10.2 µg/mL), indicating strong inhibitory potential [70]. Further mechanistic studies revealed that *P. foetida* suppresses pro-inflammatory cytokines such as TNF-α and IL-6 by modulating the NF-κB pathway. Unlike synthetic NSAIDs (e.g., diclofenac), which are associated with gastrointestinal ulcers and renal toxicity upon prolonged use, *P. foetida* exhibits a safer profile due to its natural phytoconstituents, particularly iridoid glycosides like paederoside. These compounds not only inhibit inflammatory enzymes but also enhance antioxidant defenses, reducing oxidative stress linked to chronic inflammation. Thus, *P. foetida* represents a promising alternative to conventional anti-inflammatory drugs, especially for long-term management of conditions like arthritis and the significant anti-inflammatory properties of *P. foetida* aqueous extract in a complete Freund's adjuvant-induced arthritis model [71]. Daily administration of 200 mg/kg extract for two weeks demonstrated dose-dependent anti-arthritic activity, achieving 68% reduction in joint inflammation compared to 75% with celecoxib (10 mg/kg). Mechanistic studies revealed the extract's superior inhibition of IL-1β (IC_{50} = 9.8 µg/mL) versus celecoxib (IC_{50} = 11.4 µg/mL), attributable to its principal bioactive compound, asperulosidic acid. This iridoid glycoside uniquely targets the NLRP3 inflammasome pathway, unlike conventional NSAIDs that primarily inhibit cyclooxygenase enzymes. Importantly, comprehensive toxicological assessment showed no adverse effects on vital organs, contrasting with the known cardiovascular risks associated with long-term COX-2 inhibitor use. These findings position *P. foetida* as a promising phytotherapeutic agent for chronic inflammatory disorders, offering comparable efficacy to synthetic drugs through distinct molecular mechanisms while maintaining an excellent safety profile. Further clinical studies are warranted to evaluate its translational potential in human inflammatory conditions [72].

4.2. Antioxidant Activity

Paederia foetida ability to scavenge free radicals and reduce oxidative stress. In DPPH radical scavenging assays, the ethanol extract displayed an IC_{50} of 18.7 µg/mL, which was nearly equivalent to ascorbic acid (IC_{50} = 15.2 µg/mL), a standard antioxidant. The reducing power of the extract was also proved by FRAP (Ferric Reducing Antioxidant Power) assay with a reducing activity of 450 µmol Fe^{2+}/g, which revealed its strong ability of electron donation. These effects are mainly associated with plant flavonoids (i.e., quercetin derivatives) and phenolic compounds. When compared to synthetic antioxidants such as butylated hydroxytoluene (BHT), known to have carcinogenic risks when consumed at high levels, *P. foetida* offers a natural, safe alternative [73]. Further, some of the medicinal properties of the plant, such as anti-inflammatory and hepatoprotective effects, could be presumably due to its antioxidant properties via reduction in tissue oxidation damage. This double activity of *P. foetida* makes it especially valuable in the prevention of diseases related to oxidative stress, such as diabetes and neurodegenerative diseases, and the methanolic extract of the *P. foetida* leaf displayed remarkable DPPH radical scavenging capacity (IC50 of 22.4 µg/mL) equivalent to that of α-tocopherol (IC50 = 19.8 µg/mL). The ABTS assay showed even better activity (IC50 = 14.6 ug/mL), indicating better electron donating ability. Phytochemical analysis revealed caffeic acid derivatives and luteolin glycosides as the major antioxidants, and both compounds were demonstrated to protect HepG2 cells against H2O2-induced oxidative damage by elevating cellular glutathione content by 62% at 100 µg/mL. This cellular protection is not observed with pyrogallic acid and a phenolic synthetic antioxidant such as with BHA [74].

4.3. Antimicrobial Activity

Paederia foetida possesses antibacterial and antifungal properties with wide spectrum of activity. *P. foetida* essential oils exhibited an MIC of 0.5 mg/mL against Escherichia coli, which was more effective than ampicillin (1 mg/mL). The antifungal activity against Candida albicans was one mg/mL as a MIC value. These effects are due to sulfur compounds (e.g., blend of methyl mercaptan) that disrupt the microbial cell membrane and inhibit biofilm. P. foetida antibiotics are also different from many synthetic antibiotic molecules that usually focus on specific pathways of a target organism, raising the risk of resistance, and its multi-component action lowers the probability of resistance occurrence [75]. Moreover, its antibacterial activity against both Gram-positive and Gram-negative bacteria and fungi makes it a potential candidate to replace the classical antimicrobial agents and particularly for the treatment of mixed infections Ethyl fraction of ethyl acetate extract of P. foetida leaves showed strong antimicrobial activity against drug-sensitive, as well as multidrug-resistant (MDR) bacteria. The extract exhibited an MIC value of 0.25 mg/ml against S. aureus (including MRSA), comparing favorably with ciprofloxacin (0.5 mg/ml). Against *Pseudomonas aeruginosa*, the MIC was 0.5 mg/mL, comparable to gentamicin. Bioassay-directed fractionation revealed that scandoside A and asperuloside were the major

antimicrobial constituents and acted synergitically to inhibit both bacterial cell wall synthesis and efflux pump activity. Significantly, it reduced C. albicans biofilm formation by 72% at sub-MIC concentrations (0.125 mg/mL), an attribute shared by none but the usual antifungals as fluconazole. This wide spectrum of activity and biofilm inhibition indicates that P. foetida is a potential candidate for treating resistant infections [76].

4.4. Analgesic Activity

The analgesic efficacy of *Paederia foetida* was confirmed in various models of thermal, and chemical-induced nociception. In a hot-plate test, the water extract (250 mg/kg) produced 65% elongation in latency of pain comparable to morphine (5 mg/kg). IC50 of opioid receptor binding were found to be 35 µg/mL, indicating also interference with central pain pathways [77]. In contrast to morphine, with potential risk of addiction and bronchial depression, P. foetida acts by nonpeptide active components as iridoid glycosides (e.g., asperuloside), that induce an analgesic effect without leading to addiction. Furthermore, the plant's anti-inflammatory properties complement its analgesic action, making it effective against both inflammatory and neuropathic pain. This multi-target approach, combined with a favorable safety profile, positions *P. foetida* as a viable candidate for developing non-opioid analgesics for chronic pain management and the methanol extract of *P. foetida* stems (300 mg/kg) exhibited significant analgesic effects in both acute and chronic pain models. In the acetic acid-induced writhing test, the extract reduced pain responses by 78%, outperforming aspirin (65% reduction at 150 mg/kg) [78]. The formalin test revealed 72% inhibition in the late phase (inflammatory pain), suggesting dual peripheral and central mechanisms. LC-MS analysis identified paederoside as the primary active compound, which showed selective COX-2 inhibition (IC_{50} = 8.4 µg/mL) and µ-opioid receptor partial agonism (Ki = 12.3 nM) in receptor binding assays. Unlike NSAIDs, the extract caused no gastric lesions at effective doses, and unlike opioids, it showed no withdrawal symptoms in dependent mice after 14-day administration [79]. This unique combination of COX-2 inhibition with mild opioid modulation suggests *P. foetida* could serve as a safer alternative for managing mixed-pain conditions (e.g., osteoarthritis with neuropathic components) [80].

4.5. Gastroprotective Activity

The chloroform extract of *P. foetida* (100 mg/kg) reduced gastric lesions by 85%, closely matching the efficacy of omeprazole (88%). The IC_{50} for H^+/K^+-ATPase inhibition was 8.9 µg/mL, slightly higher than omeprazole (5.1 µg/mL), indicating significant proton-pump inhibition. However, *P. foetida* offers additional protective mechanisms, such as stimulating mucus secretion and enhancing antioxidant defenses in gastric mucosa, which are absent in synthetic drugs like omeprazole. Long-term use of proton-pump inhibitors is associated with nutrient absorption and increased infection risk, whereas *P. foetida's* natural composition minimizes these adverse effects. This makes it a safer option for managing

chronic gastric disorders, including peptic ulcers and gastritis and*P. foetida* root extract (150 mg/kg) provided 89% protection against indomethacin-induced ulcers in rats, outperforming omeprazole (82%) [81]. The extract exhibited dual mechanisms, inhibiting H^+/K^+-ATPase (IC_{50} = 7.2 µg/mL) while enhancing mucosal defense (2.8× increased mucin) and reducing oxidative stress (61% lower lipid peroxidation). Unlike PPIs that disrupt gut microbiota and cause nutrient deficiencies, *P. foetida* maintained microbial balance in 28-day studies and promoted ulcer healing through angiogenesis. Its active triterpenoid-glycoside complex uniquely combines acid suppression with tissue repair, addressing the root causes of ulcer formation rather than just symptoms. These findings suggest *P. foetida* could revolutionize gastritis treatment by offering comprehensive protection without the long-term complications of conventional acid-suppressing drugs [82].

4.6. Hepatoprotective Activity

P. foetida's exceptional hepatoprotective properties through multiple mechanisms reported the ethanolic leaf extract (200 mg/kg) exhibited superior CYP2E1 inhibition (IC_{50} = 8.4 µg/mL) compared to silymarin (IC_{50} = 15.2 µg/mL) in paracetamol-induced liver injury models. The extract showed potent antioxidant activity (DPPH IC_{50} = 11.7 µg/mL) and significantly reduced ALT levels by 68%, comparable to silymarin (72%). Bioactive compounds, particularly paederoside, demonstrated remarkable free radical scavenging capacity (ORAC IC_{50} = 4.8 µM vs ascorbic acid's 6.2 µM) and antiapoptotic effects (caspase-3 inhibition IC_{50} = 25 µg/mL). Notably, *P. foetida* enhanced hepatic regeneration (45% increase in PCNA+ cells) while maintaining excellent safety (CC_{50} > 500 µg/mL in hepatocytes). These multimodal actions - combining CYP450 modulation, antioxidant protection, and tissue regeneration - surpass conventional hepatoprotectants that typically target single pathways [83]. The extract's ability to simultaneously prevent toxin bioactivation while promoting cellular repair makes it particularly valuable for treating drug-induced and alcoholic liver diseases and*P. foetida* root extract (250 mg/kg) significantly attenuated CCl_4-induced hepatic fibrosis through multiple mechanisms. The aqueous exhibits potent TGF-β1 inhibition (IC_{50} = 9.2 µg/mL), outperforming pentoxifylline (IC_{50} = 12.7 µg/mL), and reduced collagen deposition by 59%. Bioactive analysis revealed asperulosidic acid as the primary compound, showing strong antifibrotic activity (hepatic stellate cell activation IC_{50} = 11.2 µM) and antioxidant effects (ROS scavenging IC_{50} = 8.9 µg/mL). The extract uniquely restored glutathione levels (2.8-fold increase) while downregulating α-SMA expression by 63%, indicating actual fibrosis reversal rather than mere prevention [84]. Unlike conventional hepatoprotectants, *P. foetida* maintained normal CYP450 activity, eliminating concerns about drug interactions. This comprehensive action profile, combining TGF-β pathway modulation with oxidative stress reduction, positions *P. foetida* as a superior alternative for managing chronic liver diseases where existing therapies often show limited efficacy against established fibrosis [85].

4.7. Anti-cancer

P. foetida's significant anticancer activity, with its methanolic extract showing potent cytotoxicity against MCF-7 (IC_{50}=18.4μg/mL) and A549 (IC_{50}=22.1μg/mL) cells while sparing normal cells (IC_{50}=200μg/mL). The active compound paederosidic acid inhibited topoisomerase II (IC_{50}=3.8μM), induced G1 arrest (10μM), and activated caspase-3 (IC_{50}=7.2μg/mL) [86]. The extract also suppressed metastasis (MMP-9 inhibition IC_{50}=15.6μg/mL) and enhanced chemosensitivity (2.3-fold doxorubicin potentiation). These multimodal effects, including tumor-specific ROS generation, highlight its potential as a novel anticancer agent and*P. foetida* chloroform extract's selective cytotoxicity against HeLa (IC_{50}=15.2 μg/mL) and HT-29 (IC_{50}=19.8 μg/mL) cells, with minimal normal cell toxicity (IC_{50}>250 μg/mL) [87]. The active compound asperuloside disrupted microtubules (IC_{50}=2.4 μM), induced G2/M arrest (5 μM), and triggered autophagy (LC3-II activation IC_{50}=8.1 μg/mL). The extract also inhibited angiogenesis (VEGF suppression IC_{50}=12.3 μg/mL) and overcame drug resistance (P-gp inhibition IC_{50}=9.7 μg/mL), showing synergy with cisplatin (CI=0.82). These multi-targeted effects highlight its potential as a novel anticancer agent [88].

5. Future perspective

The wide spectrum of pharmacological activities of *P. foetida,* supported by traditional uses and modern scientific studies, offers many opportunities for further research and application. On the other hand, although iridoid glycosides, flavonoids and terpenoids have been well-known for their bioactive powers, the isolation and characterization of potential new phytoconstituents are necessary to use advanced analytical technology, including LC-MS/MS, NMR and metabolomics [89]. These molecules may be of clinical benefit in disorders that are at present refractory to therapy. In addition, more in-depth mechanistic studies from the molecular level, on gene expression, protein signalling pathways, and epigenetic regulation, will probably clarify the exact mechanisms of action of its compounds and therefore, scientific credibility should be increased on traditional uses [90].

Standardisation of extracts is also an important aspect, because the phytochemical profile of *P. foetida* is known to vary with environmental and geographical factors. Establishing authenticity markers and standardized processing protocols is crucial to maintain the quality, efficacy and safety of herbal medicines. Furthermore, there are enticing prospects offered by texture science in the development of the newer drug delivery systems, such as nanoparticles, liposomes, and transdermal patches, which can enhance the bioavailability and therapeutic effectiveness of the plant’s bioactivities. Although preclinical studies indicate a good overall safety profile, extensive toxicity studies as well as intensive pharmacokinetic investigations are necessary to pave the way for upcoming clinical trials that will be necessary to demonstrate efficacy in humans, particularly for inflammatory, hepatic and gastrointestinal disorders [91]. Furthermore, due to the elevating demand and threats to the ecological habitats in which *P. foetida* occurs, its conservation is necessary. Recent biotechnological approaches of tissue culture,

micropropagation, and metabolic pathway engineering can be used for efficient and sustainable use. Even though *P. foetida* could have good nutraceutical and cosmeceutical potential being a source of antioxidant, antimicrobial, and anti-ageing activities, in addition to drug use in the pharmaceutical industry. With valid scientific evaluation and conservation measures, *P. foetida* shows great potential as a multipurpose botanical resource having both global health and commercial values [92].

6. Conclusion

This plant is botanically and pharmacologically important with strong traditional roots in different traditional systems of medicine in Asia [93]. In this review, its therapeutic properties are highlighted, which are attributed by different bioactive chemical constituents including iridoid glycosides, flavonoids, terpenoids and essential oils. These components are reported to possess various pharmacological activities such as anti-inflammatory, antioxidant, antimicrobial, analgesic, gastroprotective, hepatoprotective and anticancer effects. Modern scientific research has further confirmed its traditional uses, experimental trials have shown that it has an obvious antitumor effect, and favorable safety in different kinds of disease models. However, despite its good bioactivity, more work is still required to isolate and identify new active compounds, mechanisms of action and pharmacokinetics/toxicity using clinical trials. Furthermore, issues of standardisation, quality control, and sustainable access also need to be tackled to achieve reproducible therapeutic benefits and ecological wellbeing. In conclusion, *Paederia foetida* is an important medicinal plant which has potential future drugs and integrative healthcare. Its potential to function as a link between ethnomedicine and contemporary pharmacology provides it a good candidate for further investigation.

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