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Review Article

Impact of Solvent Extractions and its Pharmacological Potential of *Boerhavia diffusa* L.: An Updated Review

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ABSTRACT

Boerhavia diffusa L. (Punarnava) is a cornerstone of ancient Indian Medicine, historically valued as a Rasayana agent for rejuvenation and vitality. This review provides a comprehensive and comparative analysis of the various pharmacological activities of the whole plant, particularly, the effects of the various solvent-based extraction methods (aqueous, methanol, ethanol) influencing its phytochemical yield and therapeutic efficacy. We have critically reviewed several preclinical and translational studies to summarize the phytoconstituents, correlate solvent-dependent extracts with bioactivities, and discuss the modern pharmacological relevance of *B. diffusa* in complex chronic diseases (diabetes, inflammation, hepatic/renal dysfunction, cardiovascular disorders, and cancer). Results confirm that *B. diffusa* acts by synergistic mechanisms mediated by the essential bioactive compounds (punarnavine, a family of rotenoids (boeravinones A-J), flavonoids (kaempferol, and quercetin), and ecdysteroids). Extraction solvent selection is essential, as methanol extracts consistently exhibited superior yield and antioxidant capacity, reporting the highest levels of phenolic and flavonoid compounds compared to aqueous. Its anti-inflammatory properties (Shothahara) are explained by the ability of punarnavine to inhibit inflammatory cytokines (TNF- α, IL-1b, IL-6), and its strong hepatoprotective effect (Yakrit uttejak) is attributed to restoring antioxidant enzymes and mitigating lipid peroxidation. Furthermore, *B. diffusa* revealed multi-target efficacy (as a potent antidiabetic agent, a neuroprotectant, and an anticancerous agent). In conclusion, the remarkable bioactivity and chemical diversity of *B. diffusa* positions it as a powerful lead to generate novel therapeutic development and holistic care applications.

Keywords: Bioactive compounds, *Boerhavia diffusa*, Chronic disease, Ethnopharmacology, Solvent extraction.

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INTRODUCTION

Nature offers mankind with a vast pharmacopeia of plants, each endowed with distinct bioactive compounds, which sustain human health. Medicinal plants have been treasured as agents of restoring balance and health across cultures and continents, and often surpass their synthetic analogues in safety and efficacy. The vast spectrum of medicinal plants provides a rich and dynamic resource for the discovery of novel therapeutic molecules.

Among these, *Boerhavia diffusa* L., commonly known as Punarnava, is a significant medicinal plant rooted deeply in traditional Indian systems of Medicine, particularly Ayurveda. The name "Boerhavia" honors the 18th-century Dutch physician Hermann Boerhaave, reflecting the plant's early recognition in both European and Asian medicinal histories (Rajpoot and Mishra, 2011). In Ayurvedic literature, *B. diffusa* is classified under the Rasayana category-herbs and therapies that rejuvenate the body, enhance longevity, preserve youth, and improve memory, intelligence, health, complexion, voice, and general immunity by invigorating the body's vital essence (ojas) (Sun W and Shahrajabian M, 2023).

Pharmacognosy

B. diffusa belongs to the family Nyctaginaceae, order Caryophyllales, class Magnoliopsida, division Magnoliophyta, and phylum Angiosperms within the group Dicotyledons (Bremer *et al.*, 2016) and includes several synonyms such as *B. adscendens, B. caribaea, B. repens*, and *B. viscosa*. Six species are common and reported in India - *B. diffusa, B. chinensis, B. erecta, B. hirsute, B. rubicunda*, and *B. rependa. B. diffusa* is the most widely utilized for its medicinal properties (Selvaraj *et al.*, 2012).

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The plant is recognized by numerous vernacular names across India, such as *Varshabhu, Punarnava, Raktakanda, Shothaghni* (Sanskrit), *Rakta Punarnava* (Bengali), *Gadapurna* (Hindi), *Mukurattai* (Tamil), *Erra Galijeru, Atikamamidi* (Telugu), *Ghetuli* (Marathi), *Balavadikae* (Kannada), and *Hog weed, horse purslane* (English) (Rawat *et al.*, 1977).

Macroscopic Characteristics

According to Patil and Bhalsing, *Boerhavia diffusa* L. is a perennial herbaceous plant commonly found across tropical and subtropical regions. It is typically characterized as a prostrate or spreading weed capable of extending over 1 meter in length. The plant exhibits a cylindrical stem that is either woody or succulent in nature, often purplish, thickened at the nodes, and covered with fine hairs. The leaves are simple, thick, fleshy, and arranged oppositely in unequal pairs (Patil *et al.*, 2016 and Poorter *et al.*, 2012).

The plant bears minute flowers, typically arranged in small, axillary clusters. The fruit is an ovate to oblong achene that is pubescent, 3mm long, five-ribbed, and glandular. The seeds generally germinated just before the monsoon season, with the plant flourishing during the rainy period and completing its reproductive cycle by producing mature seeds between October and November (Brindha *et al.*, 2020). Notably, *B. diffusa* possesses a robust and extensive root system, composed of tuberous taproots that are cylindrical to narrow fusiform in shape. These roots are light yellow to brownish-grey, thick, fleshy, and markedly bitter, contributing to their extensive use in traditional medicine (Azeez *et al.*, 2020). The deep perennial taproot is still alive in dry conditions, although the aerial portions may wilt and totally dried (Das *et al.*, 2023).

Biogeographical Mapping

B. diffusa is a very versatile plant species with a pantropical distribution, flourishing in many tropical and subtropical environments worldwide. Its abundantly native and naturalized along the entire Indian subcontinent (including India, Sri Lanka, Nepal, and Pakistan), significant portions of Southeast Asia (e.g., Myanmar, Thailand, Malaysia), southern China, extensive areas of Africa and Australia, various Pacific Islands, and the southern United States (Florida, Texas, and Hawaii), where it is firmly established (USDA 2023). The plant is prevalent throughout its core range in India, thriving as a common weed across all states, from low-lying plains to elevations of 2,000 meters in the Himalayan foothills (Mochanla *et al.*, 2021).

This review aimed to provide an updated, comprehensive and comparative analysis of the pharmacological activities of *B. diffusa*, with particular emphasis on how different solvent extraction (ethanol, methanol, aqueous, and others) affect its therapeutic efficacy, and identified research gaps while proposing future directions, particularly regarding mechanistic studies, standardization of extraction protocols, and exploration of molecular targets and other signaling pathways.

METHODOLOGY

This review was conducted by a comprehensive web-based literature search using PubMed, Google Scholar, Web of Science, Research Gate, and Scopus to identify original research articles, systematic reviews and meta-analyses with terms such as "*Boerhavia diffusa* L.", "Extractions", "solvent", and "Pharmacological activities". Using Boolean operators (AND/OR) the following terms were searched: "*Boerhavia diffusa* and different solvent", "*Boerhavia diffusa* and phytochemistry", "*Boerhavia diffusa* and extractions", "*Boerhavia diffusa* and therapeutic potential", *Boerhavia diffusa* and ethanol extractions", "*Boerhavia diffusa* and methanol extractions". Editorials, case reports, commentaries, letters to the editors and non-English articles were excluded. The full article screening was performed by the authors. This review does not include any experimental research with humans or animals. Furthermore, no independent statistical analysis is required. The numerical data and statistical interpretations were directly taken from the key research articles referenced.

RESULTS AND DISCUSSION

Ancient Remedial Applications

Bioactive compounds of *B. diffusa* like phenolic acid and flavonoids are some good neutralizers of free radicals and thus help reduce oxidative stress, which is one of the main causes of ageing and chronic diseases (Bremer *et al.*, 2016).

Different parts of the plant, including the root, leaves, aerial portions, and the entire plant, are utilized for a wide range of therapeutic purposes. The root is especially valued for its application in treating reproductive and genitourinary conditions such as gonorrhea, menstrual irregularities, and enhancing male fertility. Additionally, it is used to manage inflammatory conditions, dyspepsia, edema, jaundice, anemia, and disorders of the liver, gallbladder, and kidneys. The leaves are used with black pepper (*Piper nigrum* Linn.) to treat piles. In ophthalmic care, the root and leaf preparations are used for corneal ulcers and night blindness (Muley *et al.*, 2023 and Panossian *et al.*, 2021).

Recent research has proposed that diuretic action for addressing dysuria, oedema (Shotha), and nephrolithiasis was caused by bioactive compounds that include potassium salts, flavonoids, and glycosides that facilitate the excretion of water, sodium, and urea without causing much depletion in potassium levels, which is a major adverse effect of synthetic diuretics. The nephroprotective action becomes essential in conditions such as nephrotic syndrome and chronic kidney disease, to mitigate oedema and proteinuria (Trautmann *et al.*, 2023).

The Shothahara (anti-inflammatory) property, utilized for arthritis (Amavata) and other inflammatory disorders, is associated with the inhibition of essential pro-inflammatory enzymes such as COX and LOX. Punarnavine, an alkaloid, and rotenoids such as boeravinone B have demonstrated the ability to inhibit the synthesis of inflammatory cytokines, including TNF-α, IL-1β, and IL-6, thereby establishing a mechanistic foundation for their application in rheumatoid arthritis and other inflammatory conditions (Nunes *et al*., 2020). Its application as a Jvaraghna (antipyretic) is associated with its anti-inflammatory and antibacterial properties, which may alleviate fever induced by illnesses. The Yakrit uttejak (Hepatoprotective) used in treating jaundice and hepatic diseases is one of the most extensively studied areas. Extracts of *B. diffusa* have a notable capacity to shield the liver against damage induced by poisons such as Carbon Tetrachloride (CCl_4) and paracetamol. This is accomplished by reinstating antioxidant enzyme levels (SOD, CAT, GSH), diminishing lipid peroxidation, and facilitating hepatocyte regeneration, thereby regulating functional markers of the liver (AST, ALT, ALP) (Qu *et al*., 2020; Li *et al*., 2015). It also functions as a Cardiac Tonic with positive inotropic effects (enhancing heart muscle contraction), hypotensive properties (reducing blood pressure), and antioxidant benefits, which protect the heart from oxidative damage (Gorniak *et al*., 2019).

Contemporary Pharmacological Applications

Scientific research has rigorously confirmed and broadened the traditional use of *B. diffusa*, making it a multifunctional therapeutic agent with a significant modern pharmacological importance. This plant is effective because it has diverse bioactive chemicals, including alkaloids (e.g., punarnavine), rotenoids (e.g., boeravinones A-J), flavonoids, lignans, and ecdysteroids.

Phytochemical Diversity and Bioactive Constituents of *B. diffusa*

Phytochemical investigations revealed that *B. diffusa* contains bioactive compounds such as alkaloids (punarnavine), flavonoids, rotenoids, steroids, and glycosides, with a variety of biological functions, including antioxidant, anti-inflammatory, anti-diabetic, hepatoprotective, nephroprotective, immunomodulatory, and anticancer properties.

Root Extracts

The roots of *B. diffusa* are a good source of bioactive phytochemicals, primarily complex glycosides, rotenoids, and alkaloids. Punarnavine is the main alkaloid and has been shown to have strong immunomodulatory and anti-inflammatory effects. The methanol, ethanol, water, and 60% aqueous methanol solvent show that phenolic and flavonoid compounds are particularly abundant in root extracts and are linked to high levels of antioxidant activity. The highest levels of flavonoids (131.1 mg QCE/g) and total phenols (239.8 mg GAE/g) were found in methanol extracts (Bhalodiya *et al*., 2020; Oliveira *et al*., 2025).

Leaf Extracts

Traditionally, roots have been the primary focus of medicinal preparations; however, recent research has found that *B. diffusa* leaves contain a variety of bioactive constituents. Large proportions of quercetin 3-O-2-D-rhamnoside and eupalitin 3-O-2-D-galactopyranoside, as well as notable amounts of boeravinone B, 2-amyrin, and kaempferol, are always present in methanol and ethanol leaf extracts that have been analyzed using GC-MS, FTIR, and TLC (Jayachitra *et al*., 2020; Bhardwaj *et al*., 2019). The presence of flavonoids, phenols, terpenoids, glycosides, alkaloids, tannins, and saponins was also verified by TLC and FTIR (Jeena *et al*., 2023). A comparison study also found that methanolic leaf extract had the same antioxidant scavenging ability as ascorbic acid (Tian *et al*., 2021; Muthulingam *et al*., 2018).

Stem extracts

Although limited research has been reported on *B. diffusa* stems, phytochemical analyses utilising methanol, ethanol, and aqueous extracts have yielded results like those of roots and leaves. Flavonoids (particularly quercetin and kaempferol), alkaloids, phenolics, tannins, and glycosides have all been discovered as major constituents. Antioxidant and antibacterial assays support the bioactivity of stem extracts, showing their therapeutic potential, and it also suggests that the stem could be used as an alternate or complementary source (Kaviya *et al*., 2022).

Antioxidant activity

Radical scavenging and redox-based methods have predominated in vitro antioxidant assessments. DPPH is widely used due to its sensitivity and reliability. Other common assays include ABTS radical scavenging, FRAP, nitric oxide, hydrogen peroxide, SOD activity, and lipid peroxidation.

Over the past decade, *B. diffusa* research has transitioned from single-solvent extraction to comparative multi-solvent techniques. Comparative analysis reveals that gradient aqueous methanol shows the highest extractive ability and antioxidant activity compared to ethanol (Chaves *et al*., 2020). Aqueous extracts, are important in traditional medicine, generally exhibits lower total antioxidant activity than alcohol-based solvents, except in decoction. Non-polar solvent extraction (Hexane, Acetone, Chloroform): isolates sterols, triterpenoids, and lipids (Devi *et al*., 2025). Roots are the most extensively studied due to their elevated concentrations of phenolics, flavonoids, alkaloids, and particularly, punarnavine and boeravinones, rutin, syringic acid, and epicatechin, correlating with strong DPPH, FRAP, and ABTS activity. Several studies have reported that methanolic and ethanolic leaf extracts possess equal or higher phenolic and flavonoid contents than roots. Stems show moderate activity linked to polyphenolics and saponins. Whole-plant

extracts exhibit broad-spectrum antioxidant activity attributed to synergistic effects of volatile oils, alkaloids, and secondary metabolites (Yahfoufi *et al.*, 2018).

Anti-inflammatory Activity

The anti-inflammatory efficacy of *Boerhavia diffusa* L. is a long-established pharmacological attribute, supporting its traditional application in addressing several inflammatory disorders, including arthritis, asthma, and general oedema. This activity is not limited to a specific plant portion but is dispersed across the root, leaf, and whole-plant extracts, which act through a variety of bioactive chemicals that regulate essential inflammatory pathways (Table 1).

The roots are most widely researched part, as punarnavine (an immunomodulatory alkaloid), observed to inhibit the synthesis of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, in macrophage models and in vivo (Chen *et al.*, 2020). Also, root extracts have a huge inhibitory effect on COX-2, as well as 5-LOX, decreasing the formation of prostaglandin and leukotrienes (Shin *et al.*, 2020).

Leaves, which are less studied, exhibits strong anti-inflammatory properties due to the presence of flavonoids and phenolic compounds. These metabolites are radical scavengers, diminishing oxidative stress that intensifies inflammation, and extracts of leaves have been indicated to prevent the release of histamine and acute inflammatory mediators, in managing allergic reactions and topical inflammation (Mudgal *et al.*, 1975). Whole-plant extracts have broad-spectrum action, which is usually due to the synergistic relationships of root, leaf, and stem-derived phytoconstituents.

Antidiabetic and Hypoglycemic Activity

B. diffusa roots had been studied for their antidiabetic and hypoglycemic effects. The methanolic root extracts decreased the levels of Fasting Blood Glucose (FBG), glycated Hemoglobin (HbA_{1c}), and oxidative stress of Streptozotin (STZ)-induced diabetic models (Alam *et al.*, 2018). An empirical clinical pilot study by Gopinath *et al*, where *B. diffusa* Q (mother tincture, root-based) reduced fasting blood sugar and HbA1c in prediabetics over three months (Gopinath *et al.*, 2024).

The leaves extracts are also potent antidiabetics. Methanolic fractions increased glucose tolerance, serum insulin, lipid parameters, and augmented insulin receptor expression in Streptozotocin (STZ)-diabetic rats (Sushma *et al.*, 2021). Whole-plant extractions suggest that sterols (stigmasterol, β-sitosterol), triterpenoids, and polyphenols have a role in metabolic regulation, although stem contributions are less documented.

The nanotechnology study revealed a better therapeutic profile of *B. diffusa*. Whole-plant or ethanolic extract-based selenium- and silver-coated nanoparticles have a better enzyme inhibition effect, cell protection, and glucose lowering potential (Sudheer *et al.*, 2023). In addition, callus and cell culture systems have been used to optimize metabolite production to produce boeravinone-B and other analogous rotenoids with high antidiabetic activity (Bhalodiya *et al.*, 2020; Rodrigue, 2018).

Together, solvent selection and extraction technology will play an important role in determining phytochemical yield and bioactivity. The extractions with hydroethanolic and 60% aqueous methanol are always sufficient to extract phenolics and flavonoids and achieve the maximum use of antioxidant and hypoglycemic effects (Figure 1).

Antimicrobial Activity

B. diffusa exhibited varied antibacterial and antifungal properties across various plant parts, with ethanolic and methanolic extracts of the roots and leaves often exhibiting the strongest effects. Bioactive compounds such as kaempferol, quercetin, luteolin, saponins, glycosides, and alkaloids contribute to these activities, primarily through mechanisms including microbial cell wall disruption, inhibition of essential metabolic enzymes, and interference with DNA synthesis or replication (Kaviya *et al.*, 2022).

The ethanolic and methanolic root extracts consistently showed broad antibacterial activity against priority Gram-positives and Gram-negatives (e.g., *S. aureus, E. coli, P. aeruginosa, K. pneumoniae, Salmonella* spp.), with dose-responsive Zones of Inhibition (ZOI). The stem extract showed activity particularly against urinary-tract pathogens (*E. coli, Klebsiella, Serratia, and Acinetobacter*). The leaf extracts (methanol/ethanol > aqueous) inhibited pathogens (*S. aureus, E. coli, K. pneumoniae, P. aeruginosa*) with solvent-dependent potency; several studies reported ZOI and MIC with polar extracts outperforming than aqueous extracts.

The whole-plant ethanolic extracts have shown activity against Multi Drug-Resistant (MDR) urinary-tract isolates in clinical panels, with inhibitory effects reported across species. Green-synthesized AgNPs using *B. diffusa* (commonly leaf or callus extracts as reductant/stabilizer) display size-dependent antibacterial, broad-spectrum antimicrobial effects that frequently exceeds the parent extract. Table 2 summarizes reported antimicrobial activities of *B. diffusa* across different plant parts, extraction techniques, identified compounds, and target organisms.

Anti-fibrinolytic Activity

The roots of *B. diffusa*, owing to their abundant alkaloids like punarnavine, are primarily studied for their antifibrinolytic effects due to their historical use in Ayurveda and traditional medicine for haemostasis and wound care. The root and whole plant extracts showed powerful antifibrinolytic actions using different

solvent extractions, although the most effective were methanol and hydroalcoholic solvents. Leaf extracts were particularly linked to flavonoids and phenolic glycosides, which were acknowledged for their antifibrinolytic properties via interactions with enzymes that facilitate fibrin breakdown (Nicolescu *et al*., 2024).

Aqueous extract, less potent, was nonetheless used in traditional medicine to extract water-soluble glycosides and flavonoids (Nalavade *et al*., 2025). Non-polar extracts of petroleum ether and ethyl acetate included triterpenoids and steroids, which were effective components of antifibrinolytic (Yadav *et al*., 2024). Punarnavine, isolated from root extract, stabilized clots by inhibiting plasmin and flavonoid compounds such as quercetin, kaempferol, and boeravinones (rotenoids) controlled fibrinolysis (Sharma *et al*., 2015).

Multiple mechanisms have been suggested for the antifibrinolytic properties of *B. diffusa*, enzyme inhibition, antioxidant regulation, influences on cytokines and haemostatic mediators, which facilitate less blood loss and improved healing in both experimental and ethnomedicinal. Comparative studies have been performed with various therapeutic plants, including *Centella asiatica* and *Ficus racemosa*. Synthetic antifibrinolytic drugs such as tranexamic acid exhibited superior potency *in vitro*; yet extracts of *B. diffusa* displayed substantial activity due to their intricate phytochemical interactions and multi-targeted effects (Nicolescu *et al*., 2024 and Nalavade *et al*., 2025).

Hepatoprotection

B. diffusa's hepatoprotective potential is one of its most prominent pharmacological effects, and there is compelling evidence that it may reverse liver damage caused by chemicals. Aqueous and methanolic extracts can always alleviate hepatotoxicity induced by chemicals, as indicated by the significant decrease in serum AST, ALT, and bilirubin levels and improved histopathological healing (Rajesh *et al*., 2024). The extracts also reduce hepatotoxin-induced free radical production (e.g., CCl 4, paracetamol), boosted natural antioxidant defenses (GSH, SOD, CAT), and prevented lipid peroxidation (Sravani *et al*., 2024).

CYP2E1 suppression also reduced hepatic pro-toxin metabolism activation, resulting in anti-inflammatory and anti-fibrotic effects by downregulating TNF- 26 IL-6 and hepatic stellar cell activation (Rajesh *et al*., 2024 and Gaur *et al*., 2022). Notably, aqueous extracts showed a higher degree of hepatoprotective impact than crude powders due to the improved solubility and bioavailability of the polar phytochemicals that are biologically active. Toxicological analysis also indicates the safety profile is excellent, with no adverse effects observed in an acute or

Table 1: Anti-inflammatory potential and related bioactive properties of *B. diffusa* extracts across plant parts.

Sl. No.	Plant Part	Extract Type / Preparation	Major Compounds Identified	Pharmacological activity
1.	Leaves and Flowers	Aqueous-insoluble alcoholic extract	Not specified	55.78% reduction in rat paw edema (Hiruma *et al*., 2000).
2.	Roots and Leaves	Isolated fraction	β-sitosterol	61.29% reduction in rat edema (Ibrahima *et al*., 2018).
3.	Stem and Leaves	Methanol extract	Polyphenols, flavonoids	Inhibition of xanthine oxidase and lipoxygenase (Bairwa *et al*., 2013).
4.	Roots	Rotenoid-rich fraction	Boeravinone B, other Rotenoids	Anti-inflammatory: COX-1/2 inhibition; reduced carrageenan paw edema (Goyal *et al*., 2010).
5.	Leaves	Juice; Lyophilized decoction	Flavonoids, alkaloids, glycoproteins, phenolics	Analgesic and anti-inflammatory, antinociceptive effect, opioid vs. non-opioid pathways confirmed by naloxone reversal studies (Asadulla *et al*., 2010).
		Methanol extract	Flavonoids, phenolics	~55.8% reduction of carrageenan-induced paw edema (Srivastava *et al*., 2017).
		Ethanol extract	Eupalitin-3-O-β-D-galactopyranoside (Bd-I)	Immunosuppressive: ↓ IL-2, TNF-α, NF-κB/AP-1, T-cell proliferation (Giresha *et al*., 2017).
6.	Whole Plant	Ethanol extract	Broad phytoconstituents	Inhibition of $sPLA_2$; reduction of oxidative stress and edema, Suppression of signaling pathways (Syk, Src, TRAF6) (Van *et al*., 2015).

sub-chronic trial using therapeutic doses. These findings collectively support the use of *B. diffusa* in ethnomedicine and its potential as a phytotherapeutic agent for liver diseases.

Diuretic Activity

Diuretic effects of *B. diffusa* serve as a crucial foundation for its ethnomedicinal use in treating oedema, ascites, and different urinary ailments. *B. diffusa* exhibited a potassium-sparing effect and promoted natriuresis and diuresis, without inducing electrolyte imbalance as conventional loop diuretics like furosemide do (Panossian *et al.*, 2021).

The *B. diffusa* whole plant, most predominantly study for diuretic effects (multiple solvent). The aqueous extract exhibits growth inhibition of struvite crystal, reduce crystal size, and promote crytal dissolution. Ethanolic extracts promote COD crystal formation more than COM crystals and shrinking crystal size (Chauhan *et al.*, 2009). Notably, the white type has a greater diuretic and enzymatic activity compared to red, indicating that chemotypic characteristics differ and that phytochemical standardization is required.

Enzyme inhibition activity

The enzyme inhibitory potential of *B. diffusa* has been extensively studied, and it has been found to have a role in metabolic disorders as well as neurodegenerative disorders. The solvent used in the extraction process has a significant impact on the yield and potency of the active compounds, and methanol and ethanol are known to extract flavonoids, xanthones, and polyphenols, which are the primary agents of enzyme inhibition (Singh *et al.*, 1988).

In vitro experiments have shown that *B. diffusa* has a high inhibitory capacity against carbohydrate-digesting enzymes, specifically α-amylase and α-glucosidase, important therapeutic targets in diabetes management. Methanolic root extracts showed a strong inhibitory effect on alpha-amylase with high antioxidant capacity and equally, the aerial parts extracts (ethanol and aqueous) inhibited α-glucosidase, pancreatic lipase, and the ex vivo models showed decreased intestinal glucose absorption and increased muscle glucose uptake (Sathyapriya *et al.*, 2009; Oyebode *et al.*, 2018). These effects were mainly attributed to xanthones and stigmasterol, and there was evidence of both competitive and non-competitive mechanisms of inhibition. In addition to metabolic targets, *B. diffusa* has also demonstrated encouraging inhibitory activities on cholinesterases, indicating a neuroprotective effect.

Boeravinone A, boeravinone H, and coccineone B were also discovered as potent Acetylcholinesterase (AChE) inhibitors by use of computational docking and molecular dynamics simulations. Boeravinone A was found to bind persistently at the enzyme's catalytic site with binding affinities comparable to FDA-approved medicines, and it was expected to cross the blood-brain barrier,

Table 2: Evaluation of Antimicrobial Effects in *B. diffusa*.

Sl. No.	Plant Part	Extract Type / Preparation	Antimicrobial activity
1.	Leaves	Methanolic (Soxhlet, 130°C, 24-30 hr)	Antibacterial activity vs. *S. aureus, E. coli, K. pneumoniae, P. aeruginosa* (max inhibition S. aureus, MIC 0.0625-0.25 mg/µL) (Haritha *et al.*, 2023 and Mahajan *et al.*, 2024).
		Aqueous (boiling distilled water, filtered, oven-dried at 40°C)	
		Acetone, Ethanol, Aqueous	
		Ethanol, Methanol, Diethyl Ether, Chloroform, EtOAc, Aqueous	Antibacterial vs. Gram +/- bacteria, S. aureus, B. subtilis, etc. (Arya *et al.*, 2025).
		Silver nanoparticle (using extract)	Potent activity via green synthesis of silver nanoparticles (Dholaria *et al.*, 2019).
2.	Stems and Leaves	Ethanol, n-butyl alcohol	Antibacterial vs. UTI bacteria (Serratia, Acinetobacter, *E. coli, Klebsiella*) (Sharma *et al.*, 2021).
3.	Roots	Decoction (water, Ayurvedic)	Broad spectrum activity (antibiotic-resistant Gram-negatives, *C. glabrata*) (Ibrahima *et al.*, 2018).
		Hexane, chloroform, ethanol, water (sequential Soxhlet)	*In vitro* activity vs. *S. aureus, B. subtilis, E. coli, P. aeruginosa, S. typhi, K. pneumonia* (Umamaheswari *et al.*, 2010).
		Methanolic, chloroform-partitioned alkaloids	Inhibition of *E. coli, B. subtilis, F. oxysporium*; strong effect (Bhardwaj *et al.*, 2019).
4.	Whole Plant	Hydroethanolic	Antimicrobial, antioxidant, anti-inflammatory, hepatoprotective, immunomodulatory (Zahoor *et al.*, 2024).
		Ethanol (Soxhlet)	Antibacterial vs. MDR UTI pathogens (Zahoor *et al.*, 2024).

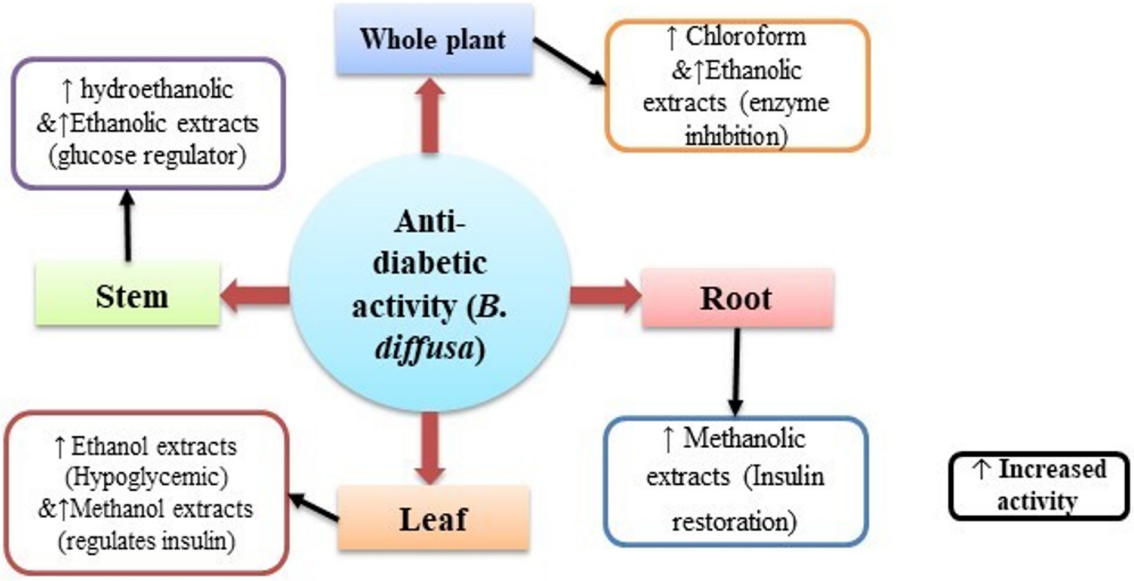

Figure 1: Anti-diabetic activity of *B. diffusa* extracts across plant parts.

indicating potential in Alzheimer's disease therapy (Rafi *et al.*, 2025). The results exhibited that *B. diffusa* acts as a multi-target enzyme inhibitor that has high potential in therapeutic use in diabetes, neurodegeneration, and inflammation.

Anticancer activity

B. diffusa has a long history of ethnomedicinal use, which has been strengthened by increased scientific interest in its anticancer properties. The ethanolic root extracts, exhibit chemopreventive activities in oxaliplatin-induced hepatotoxicity models, lowering blood ALT and AST levels and preventing chemotherapy-induced toxicity (Chaudhary *et al.*, 2021).

Both methanol and aqueous extracts exhibited strong cytotoxicity in a variety of cancerous cell types, such as cervical (SiHa), colorectal (HCT116), Hepatocellular (HepG2), and breast (MCF-7) cancer cells, with fractions containing kaempferol showing a high level of inhibition (IC_{50}: 56.140 g/mL) (Harini *et al.*, 2025). It causes apoptosis, cell arrest, oxidative stress, and is also capable of regulating immune-related genes, including M-CSF and GM-CSF, suggesting both a direct cytotoxic and an immunomodulatory effect.

Phytochemical characterizations through GC-MS transformed into LC-MS and FTIR, revealed punarnavine, boeravinones, kaempferol, beta sitosterol, phytol, and eugenol as prominent bioactive compounds. As indicated by docking studies, punarnavine binds to the apoptosis regulator of Bcl-2 that enhances caspase-dependent apoptosis (Hussain *et al.*, 2014).

The boeravinones disrupt cellular migration and caspase cascades (Kumar *et al.*, 2019), and 2-sitosterol regulates ceramide levels and sensitizes to the action of traditional chemotherapy (Nicolescu *et al.*, 2024). The apoptotic effects and immune-stimulating effects of kaempferol were dual in nature, and methanolic extracts were rich in kaempferol (Rohit *et al.*, 2022).

In mechanistic studies, downregulation of anti-apoptotic (Bcl-2), upregulation of pro-apoptotic (caspases), DNA fragmentation, and cell cycle arrest (G2/M or S phase) were consistently reported by Nisaath *et al.* 2024. Extracts additionally elevated antioxidant enzymes like Superoxide Dismutase (SOD) and Catalase (CAT), which implicates that the regulation of oxidative stress played a role in cytoprotection and antitumor. Further relatability to hormone-sensitive cancers was reported in estrogen receptor modulation of MCF-7 cells (Orisakwe *et al.*, 2023; Rohit *et al.*, 2022).

Notably, cytotoxicity was observed to be selective in malignant cells, leaving behind non-transformed tissues. Clinical trials were few, though *in vivo* models of hepatocellular carcinoma, lymphoma, and colon cancer have shown a regressive effect on tumors, extended survival, and a recovery of hematological and biochemical parameters (Orisakwe *et al.*, 2023).

B. diffusa exhibited anticancer action with a broad spectrum due to the presence of several phytochemicals, which promoted action by mediating apoptosis, cell cycle, redox, and immune interactions (Table 3).

Cardioprotective effect

Boerhavia diffusa L. (Nyctaginaceae), traditionally employed in Ayurveda for *Hridya roga* (cardiac disorders), with multi-modal cardioprotection effects across cellular and animal models. The stem primarily exhibits potent antioxidant actions, mitochondrial stabilization, and anti-remodeling effects. The use of polyphenol-enriched ethanol extracts strongly inhibits cardiac angiotensin II-induced hypertrophy and fibrosis through

the maintenance of mitochondrial membrane potential and prevention of superoxide production by mitochondria, as well as restoring the activity of the electron transport chain complex, and alleviating oxidative (Ali *et al.*, 2021). These effects are mediated by key bioactive constituents, especially rotenoid derivatives e.g. boeravinone B, flavonoids, and other phenolics that process direct Reactive Oxygen Species (ROS) scavenging and mitochondrial Permeability Transition Pore (mPTP) modulation to hinder cytochrome c release, which triggers apoptotic signaling. *In vivo*, pre-treatment with *B. diffusa* extracts (200 mg/kg) prevents isoproterenol, or doxorubicin induced cardiotoxicity, as shown by LDH and CK-MB serum biomarkers and by histopathological evidence of myocardial necrosis, edema, and inflammation (Parthapan *et al.*, 2018; Chen *et al.*, 2021).

The root extract exhibits anti-atherosclerotic potential: ethanolic and aqueous root extracts (250-400 mg/kg) reduce total cholesterol, triglycerides, and LDL while elevating HDL in hyperlipidemic rodent models, implicating lipid-modulating activity as an additional cardioprotective effect (Parthapan *et al.*, 2018). *B. diffusa* also protected against chemotherapeutic cardiotoxicity that is caused by doxorubicin and oxaliplatin, which further supports its therapeutic potential.

These findings suggest that *B. diffusa* is a promising multi-target cardioprotective phytomedicine, with mitochondrial integrity and redox homeostasis as central mechanistic pillars, bridging ancient ethnopharmacological use with modern molecular study.

Neuroprotective effect

The neuroprotective efficacy of *Boerhavia diffusa* L. has been established in a wide range of *in vitro* and *in vivo* neurodegenerative models involving multimodal activities such as oxidative stress, neuroinflammation, mitochondrial dysfunction, and cholinergic deficits. In a scopolamine-induced murine model of amnesia, oral administration of ethanol root extract (100-200 mg/kg) significantly reversed spatial and recognition memory impairments, as evidenced by improved performance in the Morris water maze and novel object recognition tests. The changes in behavior were associated with a decreased activity of brain Acetylcholinesterase (AChE) and elevated levels of endogenous antioxidants (e.g., glutathione, superoxide dismutase), implicating dual cholinergic and redox-modulating effects (Rafi *et al.*, 2025).

The rotenid derivatives, boeravinones B, E, and G, are crucial neuroactive components. Among them, boeravinone B exhibited potent dual inhibitory effects on AChE and Butyrylcholinesterase (BChE) with an IC_{50} value of 8.2 uM, and 12.4 uM respectively, being superior to reference standards on a few enzyme-specific assays (Sinan *et al.*, 2021). This renders boeravinones to be a promising scaffolds of multi-target anti-Alzheimer drugs.

At the molecular level, a standardized hydroalcoholic extract triggers Nrf2/ARE antioxidant pathway, suppressing NF-kB-induced neuroinflammation in LPS-stimulated BV-2 microglial cells. This dual regulation leads to a significant down-regulation of pro-inflammatory mediators (TNF-a, IL-6, and nitric oxide) and neuronal damage microglia-mediated was suppressed (Nimbal *et al.*, 2017).

B. diffusa has antidepressant-like effects in preliminary behavioral experiments, indicating that it may be involved in neuromodulatory pathways besides cytoprotection. These results

Table 3: Anti cancerous efficacy of *B. diffusa* plant.

Sl. No.	Plant Part	Extract Type	Bioactive compounds	Anti-cancerous activity
1.	Leaves	Ethanolic	Vitamin E, phytol, β-sitosterol	Antioxidant, anticancer activity in hepatocellular carcinoma model (rats), restoration of hematological parameters, and reduced liver necrosis (Odion *et al.*, 2025).
		Methanolic, aqueous	Kaempferol, total flavonoids	Significant anticancer activity against HCT116 colon cancer cells, gene regulation of M-CSF and GM-CSF, Potent anticancer activity in HepG2 (liver cancer) cells (Jayachitra *et al.*, 2020; Bano *et al.*, 2019).
		Methanolic, n-hexane, dichloromethane, n-butanol, water	Diverse fractions affecting ER modulation	Modulated oestrogen receptors (ERα, ERβ, GPER) and significant cytotoxicity in MCF-7 breast cancer cells (Saini *et al.*, 2023; Arif *et al.*, 2024).
2.	Roots	Ethanolic	Alkaloids, flavonoids, steroids, triterpenoids	Hepatoprotective, reduced serum enzymes, suggested anticancer potential (Harini *et al.*, 2025).
			Alkaloids, flavonoids, tannins, saponins, terpenes, steroids, anthraquinones	Cytotoxic activity against cervical cancer (SiHa cell line), 96.3% inhibition at 1000 µg/mL (Noudamadjo *et al.*, 2025).

highlight *B. diffusa* as a viable source of neuroprotective chemicals with a wide range of structures and mechanisms. However, additional clinical validation and comprehensive phytochemical characterization are required to support these effects and translate them into therapeutic applications.

Respiratory (Anti-asthmatic/Immunomodulatory) Activity

In Ayurvedic medicine, *Boerhavia diffusa* is used to treat Shwasa (dyspnea) and Kasa (cough) in an allergic inflammation, bronchospasm, and excess production of mucus. Modern preclinical research offers solid experimental support of these ethnomedical applications showing all three anti-asthmatic, bronchodilatory, and immunomodulatory actions in respiratory models.

Oral delivery of an ethanolic extract of the root (200 mg/kg) significantly prevented airway hyper responsiveness and eosinophil inflammation of Bronchoalveolar Lavage Fluid (BALF), resulting decrease in serum IgE levels in an ovalbumin-sensitized murine model of allergic asthma. Casaro *et al* reported that *B. diffusa* extract suppresses an allergic Th2 cytokine responses and downregulation of IL-4 and IL-5 with an up-regulation of IFN-g. Also inhibiting important pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) and preventing cellular inflammatory responses in allergen- and trypsin-induced airway inflammation in mice (Evans *et al*., 2023).

Sharma *et al* reported that an aqueous extract of *B. diffusa* exhibited strong bronchodilatory effects during acetylcholine-induced bronchospasm in guinea pigs, compared to theophylline (Sharma *et al*., 2021). The presence of flavonoids like quercetin and kaempferol stabilized mast cells and blocked the release of histamine, an important pathway in the disease pathogenesis of allergic asthma.

FUTURE DIRECTIONS/RESEARCH GAPS

This review provides a comprehensive and comparative analysis of the various pharmacological activities of the plant, particularly the effects of the varied solvent-based extraction methods (aqueous, methanol, ethanol) influence its phytochemical yield and therapeutic efficacy (Figure 2). Beyond the major biological functions reviewed above, *B. diffusa* has been reported to have a wide range of additional bioactivities, immunomodulatory, nephroprotective, wound-healing, analgesic, antipyretic, and gastroprotective, adaptogenic activities, and insecticidal/biopesticidal effects, documented across ethnopharmacological surveys and experimental studies. The effectiveness of methanolic, chloroform leaf and root extracts in wound repair and antimicrobial effects, and several articles also reported antitoxin effects and the renal and gastroprotective effects in models of toxin-induced diseases (Casaro *et al*., and Kim *et al*., 2019).

The recent translational studies have also extended to the investigations on *B. diffusa*-based nanotechnology study (AgNP, SeNP, CuNP) that could enhance antimicrobial, antioxidant, and wound healing performances and provide a viable pathway to increase the stability and bioavailability of extracts. However, there are critical research gaps in clinical translation: there are only limited well-controlled randomized trials, and extraction and analytical standardization are not uniform. Lack of chemotypic variation based on the geographical, seasonal, and varietal factors leading to inconsistent phytochemical composition and potency. Further, despite various pharmacological properties like antioxidants, antidiabetic, hepatoprotective, anticancer,

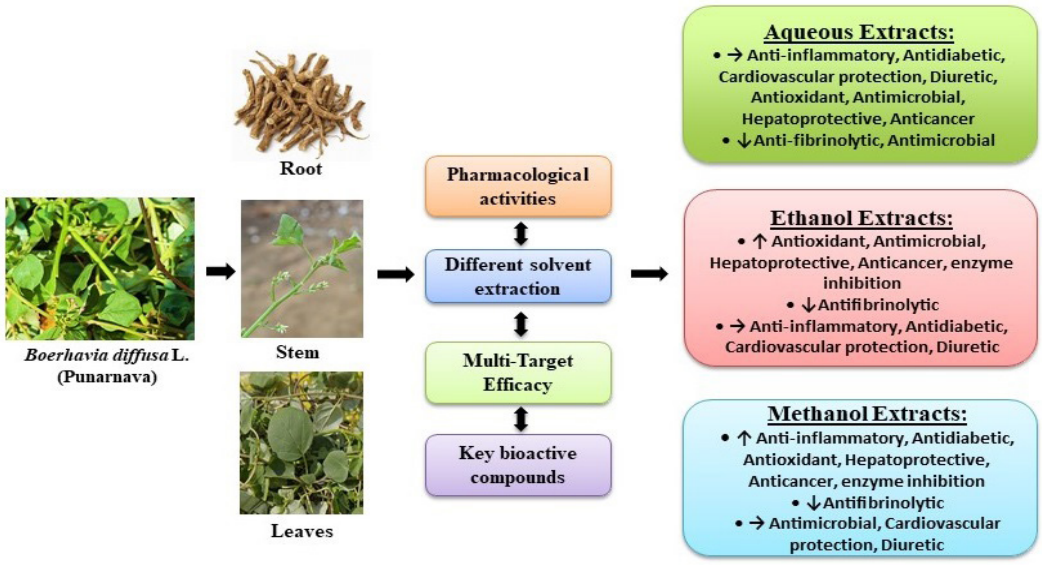

Figure 2: Summary of comparative pharmacological activities of *B. diffusa* plant (root, stem, leaves) by solvent-based extraction.

cardioprotective, and neuroprotective, most of these studies lack a detailed mechanism of action and identification of their target at the molecular level.

Minimal information exists regarding molecular docking, pharmacokinetics (ADME/PK), pharmacodynamics, and chronic toxicity, with limited systematic dose-dependent studies. Most of the research has been restricted to preclinical *in vitro* or *in vivo* models, and there is a lack of well-designed randomized clinical trials. Moreover, the lack of detailed Structural Activity Relationship (SAR) research, bioavailability evidence, and sophisticated formulation development (nanoformulations) limits its use in therapy. Network pharmacology and integrative multi-omics analysis, which link active phytoconstituents to biological pathways, are also mostly unexplored.

Future research must prioritize isolation and structural characterization of key bioactive compounds, boeravinones, and punarnavine, and elucidate their molecular targets, including PI3K/Akt signaling pathways, using target based and omics-driven approaches (e.g., transcriptomics, proteomics, and metabolomics). Another promising field is nanocarrier-based delivery systems to improve the bioavailability of active phytoconstituents, and genomic and metabolic studies to explore variation in plants to affect phytochemical yield. Addressing these gaps will effectively bridge traditional ethnopharmacological with modern drug discovery paradigms, paving the way for *B. diffusa* development into a scientifically validated, multi-target therapeutic agent for complex diseases such as diabetes, cancer, and cardiovascular disorders.

CONCLUSION

B. diffusa is a well-known medicinal plant having a wide range of phytochemicals, including alkaloids, flavonoids, rotenoids, glycosides, and phenolics, whose extraction is strongly influenced by solvents, which contribute to the plant's robust pharmacology. Its antioxidant, anti-inflammatory, antidiabetic, antibacterial, hepatoprotective, nephroprotective, and anticancer properties have been extensively studied and demonstrated. Lipophilic metabolites are isolated using non-polar solvents (hexane, chloroform); rotenoids and terpenoids are isolated using semi-polar solvent (ethyl acetate, acetone, butanol); and phenolics and flavonoids are isolated using polar solvents (water, methanol, ethanol). Despite significant preclinical studies, *B. diffusa* has yet to be translated into universal therapeutic usage due to extraction inconsistencies, a lack of clinical validation, and regulatory deficiencies. Future research efforts should prioritize rigorously planned clinical trials, enhanced nanoformulation-based delivery methods, and integrative investigations that incorporate ethnobotanical knowledge with contemporary pharmacology. In conclusion, the remarkable bioactivity and chemical diversity of *B. diffusa* positions it as a powerful lead to generate novel therapeutic development and holistic care applications.

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ABBREVIATIONS

L.: Linnaeus; **TNF-α:** Tumour Necrosis Factor-alpha; **IL-1β:** Interleukin-1 beta; **IL-6:** Interleukin-6; **SOD:** Superoxide dismutase; **CAT:** Catalase; **GSH:** Glutathione; **AST:** Aspartate transaminase; **ALT:** Alanine transaminase; **ALP:** Alkaline phosphatase; **COX:** Cyclooxygenase; **LOX:** Lipoxygenase; **GC-MS:** Gas chromatography-mass spectrometry; **HPLC:** High-pressure liquid chromatography; **FTIR:** Fourier Transform Infrared spectroscopy; **TLC:** Thin-Layer Chromatography; **DPPH:** 2,2-diphenyl-1-picrylhydrazyl assay; **ABTS:** 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) assay; **FRAP:** Ferric reducing antioxidant power assay; **MDR:** Multidrug-resistant; **AgNPs:** Silver nanoparticles; **SeNP:** Selenium nanoparticles; **CuNP:** Copper nanoparticles; **FBG:** Fasting blood glucose; HbA1c**:** Glycated hemoglobin; **STZ:** Streptozotocin; **ZOI:** Zones of inhibition; **MIC:** Minimum inhibitory concentration; **AChE:** Acetylcholinesterase; **BChE:** Butyrylcholinesterase; **sPLA$_2$:** Secretory phospholipase A2; **SAR:** Structure-activity relationship; **M-CSF:** Macrophage colony-stimulating factor; **GM-CSF:** Granulocyte-macrophage colony-stimulating factor; **LC-MS:** Liquid chromatography-mass spectrometry; **IC$_{50}$:** Half maximal inhibitory concentration; **mPTP:** Mitochondrial permeability transition pore; **ROS:** Reactive oxygen species; **LDH:** Lactate dehydrogenase; **CK-MB:** Creatine kinase-MB; **LDL:** Low-density lipoprotein; **HDL:** High-density lipoprotein; **Nrf2/ARE:** Nuclear factor erythroid 2-related factor 2/antioxidant response element; **NF-κB:** Nuclear factor kappa B; **BALF:** Bronchoalveolar lavage fluid; **IgE:** Immunoglobulin E; **IFN-γ:** Interferon-gamma; **Th2:** T helper type 2; **PI3K/Akt:** Phosphoinositide 3-kinase/protein kinase B; **ADME/PK:** Absorption, distribution, metabolism, excretion/pharmacokinetics; **ER:** Estrogen receptor; **UTI:** Urinary tract infection.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHOR'S CONTRIBUTIONS

Chalini Vijayakumar: Conceptualization, Data Collection, Methodology, Writing - Original Draft.

Saramma Mini Jacob: Analysis, Writing - Review and Editing.

Jamuna Rani: Visualization, Supervision.

SUMMARY

Boerhavia diffusa L. (Punarnava) is renowned in traditional medicine for its rich chemical diversity and potent pharmacological properties, such as antioxidant, anti-inflammatory, antidiabetic, antibacterial, hepatoprotective, nephroprotective, and anticancer. The choice of extraction method is important to isolate a particular bioactive, with non-polar solvent extraction targeting lipophilic metabolites, semi-polar solvent extraction optimal for rotenoids and terpenoids, and polar solvent extraction for phenolics and flavonoids. Notably, the methanol extracts yield the highest pharmacological potential, surpassing other solvents. Despite strong preclinical evidence, widespread clinical use is hindered by variable solvent extraction and insufficient clinical validation. Moving forward, a standardized extraction approach, intensive clinical trials, and novel nanoformulations, combined with ethnopharmacology, are required in the future for the therapeutic potential of *B. diffusa*.

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