International Journal of Pharmaceutical Science and Research
www.pharmacyjournal.net
ISSN: 2455-4685
Received: 19-03-2026, Accepted: 19-04-2026, Published: 04-05-2026
Volume 11, Issue 2, 2026, Page No. 22-31

Integrative evaluation of *Boerhavia diffusa* in cancer therapy: Bridging Siddha Medicine and modern Oncology

Akash S[1*], Thangadurai K[1], Nithya S[1], Madhumitha M[1], Yuvadharshini V[2]
[1] JSA Medical College for Siddha and Research Centre, Tamil Nadu, India
[2] Department of Botany, Arignar Anna Govt Arts College, Namakkal, Tamil Nadu, India

Abstract
Cancer continues to be a major global health challenge, with rising incidence and significant mortality, highlighting the need for safer and more effective therapeutic approaches. Traditional medical systems such as Siddha Medicine offer holistic treatment strategies that utilize plant-based remedies with multi-targeted actions. Boerhavia diffusa (Punarnava) is a widely used medicinal herb known for its rejuvenating and disease-modifying properties in traditional practice.
Recent experimental studies have revealed that Boerhavia diffusa exhibits notable anticancer activity through multiple mechanisms, including antioxidant defence, immune system modulation, inhibition of tumour cell proliferation, and suppression of metastasis. Its diverse phytochemical profile contributes to these biological effects, making it a promising candidate for integrative cancer therapy.
This review aims to synthesize traditional Siddha knowledge with contemporary scientific findings to provide a comprehensive understanding of the therapeutic potential of Boerhavia diffusa. The evidence suggests that it may serve as a valuable complementary agent alongside conventional cancer treatments, supporting a more holistic and effective approach to cancer management.

Keywords: *Boerhavia diffusa*, Siddha medicine, cancer therapy, anticancer activity, phytochemicals, integrative oncology, medicinal plants, immunomodulation, antioxidant activity, complementary medicine

Introduction

Cancer is a complex and multifactorial disease characterized by uncontrolled cellular proliferation, evasion of programmed cell death (apoptosis), sustained angiogenesis, and metastatic progression. (Aggarwal BB, *et al*., 2021) [1]. It remains a major global health burden despite significant advancements in conventional treatment modalities such as chemotherapy, radiotherapy, and targeted therapies. While these approaches have improved survival outcomes, their clinical utility is often limited by challenges including systemic toxicity, drug resistance, high cost, and tumour recurrence. (Ahmad I, *et al.,* 2021) [2]. These limitations highlight the urgent need for safer, more effective, and multi-targeted therapeutic strategies.

In recent years, increasing attention has been directed toward plant-based therapeutics derived from traditional medical systems. (Sharma R, *et al*., 2025) [21]. Among these, Siddha medicine—one of the oldest indigenous systems of medicine—emphasizes a holistic approach cantered on maintaining physiological balance, detoxification, and rejuvenation. According to Siddha principles, disease arises from disturbances in the equilibrium of the three humours (Vatham, Pitham, and Kapham), along with the accumulation of metabolic toxins (Amar) and impaired digestive/metabolic function (Agni). (Ahmad I, *et al*., 2021) [2].Therapeutic interventions in Siddha aim not only to treat disease but also to restore systemic harmony and enhance the body's intrinsic healing capacity.

Medicinal plants play a central role in Siddha therapeutics due to their multi-component and multi-targeted actions. One such important herb is *Boerhavia diffusa*, commonly known as Punarnava, which has been widely used in traditional medicine for the management of inflammatory disorders, liver diseases, and chronic conditions (Atanasov AG, *et al.,* 2021) [4] The name "Punarnava," meaning "renewal of the body," reflects its well-documented rejuvenate properties. Traditionally classified as a *Kayakalpa* (rejuvenate) drug, it is valued for its ability to promote tissue repair, detoxification, and immune enhancement.

In the context of modern biomedical research, *Boerhavia diffusa* has attracted considerable attention due to its diverse pharmacological activities, including antioxidant, anti-inflammatory, immunomodulatory, anti-proliferative, and anti-metastatic effects. (Bibi Y, *et al.,* 2026) [5] Emerging evidence suggests that its bioactive constituents can modulate key molecular pathways involved in cancer progression, thereby supporting its potential role as an adjunct in cancer therapy.

Thus, integrating the holistic principles of Siddha medicine with contemporary molecular insights offers a promising framework for developing effective and less toxic cancer treatment strategies. (Sinan KI, *et al.,* 2003). In this regard, *Boerhavia diffusa* represents a valuable candidate for bridging traditional knowledge and modern oncology, warranting comprehensive scientific evaluation (Das S, Dutta S, Paul S, *et al.,* 2023) [6].

Siddha Perspective on Cancer (Putru Noi)

Concept of Tridosha (Vatham, Pitham, Kapham)

Siddha medicine is based on the principle of Tridosha, comprising Vatham, Pitham, and Kapham, which regulate physiological functions and maintain internal balance. Vatham controls movement and regulatory activities, Pitham governs metabolism and biochemical transformations, and Kapham provides structural stability and immune support (Das S, *et al*., 2023) [6].

Disease arises when these humours become imbalanced. In the context of cancer (*Putru Noi*), Siddha describes a disturbance predominantly involving *Pitham* and *Kapham*, leading to abnormal tissue growth, inflammation, and accumulation. This imbalance is often associated with impaired metabolic function (*Agni*) and the build-up of toxic substances (*Ama*), which further contribute to disease progression. (Das S, *et al.,* 2023) [6].Therapeutic approaches in Siddha aim to restore Tridosha equilibrium, eliminate toxins, and promote tissue rejuvenation, forming the basis for the use of medicinal plants such as *Boerhavia diffusa* in cancer management. (Dina J, *et al*., 2024) [9].

Role of Ama (Toxins) and Agni (Metabolism)

In Siddha medicine, Agni represents the body's metabolic capacity responsible for digestion, transformation, and cellular energy balance, while Ama refers to improperly processed metabolic by-products that accumulate due to impaired Agni. When metabolic efficiency declines, these toxic substances build up, disrupting physiological functions and promoting disease development. (Dina J, *et al*., 2024) [9]In the context of cancer, this imbalance can be correlated with metabolic deregulation, oxidative stress, and the accumulation of harmful intermediates that favour abnormal cell growth and inflammation. Siddha therapeutics therefore emphasize strengthening Agni and eliminating Ama to restore systemic balance. (Fulda S, *et al*., 2024).Medicinal plants such as *Boerhavia diffusa* are traditionally used to support metabolic function and detoxification, thereby contributing to disease prevention and management. (Greenwell M, Rahman Greenwell M, Rahman. 2020) [12].

Therapeutic Role of Punarnava in Siddha

In Siddha medicine, *Boerhavia diffusa* (Punarnava) is valued as a Kayakalpa (rejuvenative) herb used to restore physiological balance and vitality. It is traditionally prescribed for conditions involving inflammation, fluid accumulation, and chronic disorders. (Gunaseelan D, *et al*., 2022) [13].Punarnava is believed to help regulate Tridosha, particularly by reducing *Pitham* and *Kapham*, while supporting metabolic function and detoxification.Its therapeutic actions include promoting tissue repair, improving digestion, enhancing elimination of toxins, and strengthening overall immunity. These properties make it relevant in managing chronic and degenerative conditions, including those resembling tumor-like growths described in Siddha literature. (Gunaseelan D, *et al*., 2022) [14].

Botanical and Pharmacognostic Profile of *Boerhavia diffusa:*

Boerhavia diffusa L., commonly known as Punarnava, belongs to the family Nyctaginaceae and is a perennial, creeping herb widely distributed in tropical and subtropical regions. It typically grows close to the ground with diffusely spreading branches and thrives in wastelands, roadsides, and cultivated fields. (Hanahan D., 2022) [15].

Botanical Characteristics

- **Habit:** Prostrate or ascending perennial herb
  Roots: Thick, cylindrical, fusiform, and yellowish-brown; medicinally important
- **Stem:** Slender, branched, often purplish, with swollen nodes
- **Leaves:** Opposite, ovate or sub orbicular, unequal in pairs, smooth or slightly hairy
- **Flowers:** Small, pink to reddish, arranged in clusters
- **Fruits:** Small, glandular, one-seeded (Anthrocarp)

Pharmacognostic Features

- **Macroscopic**
  The roots are elongated, tapering, and exhibit a characteristic odour with a slightly bitter taste. The outer surface appears rough and light brown.

- **Microscopic**
  Transverse sections of the root reveal a well-developed cork, secondary cortex, and vascular bundles with xylem vessels and phloem tissues. Presence of starch grains and calcium oxalate crystals is commonly observed.

- **PowderCharacteristics**
  Powdered root shows fragments of cork cells, lignified vessels, fibres, and starch granules, which serve as diagnostic features.

Identification and Standardization Parameters

- Organoleptic properties (colour, odour, taste)
- Microscopic markers (vascular tissues, crystals)
- Physicochemical constants (ash values, extractive values)

This botanical and pharmacognostic profile is essential for correct identification, quality control, and standardization of *Boerhavia diffusa*, ensuring its safe and effective use in both traditional Siddha formulations and modern phytopharmaceutical applications.

Phytochemical Profile

Major Bioactive Compounds

Table 1: Major Bioactive Compounds of *Boerhavia diffusa*

Compound / Class	Biological Activity	Mechanism of Action
Punarnavine (Alkaloid)	Immunomodulatory, anti-inflammatory	Enhances immune cell activity; suppresses inflammatory mediators
Boeravinones (Retinoid)	Cytotoxic, anti-proliferative	Inhibits cancer cell growth; interferes with cell cycle progression
Quercetin (Flavonoid)	Antioxidant, pro-apoptotic	Scavenges free radicals; activates apoptotic pathways (capsizes)
Kaempferol (Flavonoid)	Anti-inflammatory, anticancer	Modulates signalling pathways; inhibits proliferation and angiogenesis
Phenolic compounds	Antioxidant	Neutralizes reactive oxygen species; protects DNA from oxidative damage
Lignin's	Anti-inflammatory, anticancer	Regulates cell signalling and reduces inflammatory responses
β-sit sterol (Sterol)	Anti-inflammatory, anti-tumour	Stabilizes cell membranes; modulates immune and inflammatory pathways

Summary Insight

These compounds act synergistically, targeting multiple pathways such as oxidative stress, inflammation, and apoptosis. This multi-component nature supports the role of *Boerhavia diffusa* as a multi-target therapeutic agent in integrative cancer therapy.

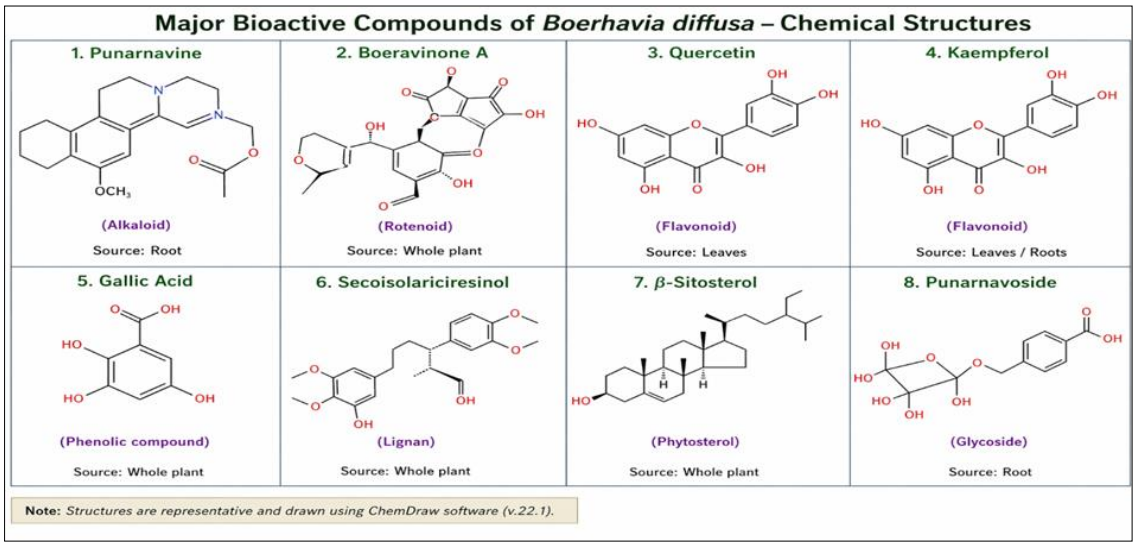

Fig 1: Major compounds of *Boerhavia diffusa* – chemical structures

Pharmacognostic Characteristics

Table 2: Pharmacognostic Characteristics of *Boerhavia diffusa*

Parameter	Macroscopic (Organoleptic Features)	Microscopic (Anatomical Features)	Powder Characteristics
Root	Cylindrical, tapering, yellowish-brown; rough surface; bitter taste	Cork layer present; secondary cortex well developed; vascular bundles with xylem and phloem	Fragments of cork cells, lignified vessels, fibres
Stem	Slender, branched, purplish; swollen nodes	Epidermis with cuticle; vascular bundles arranged in a ring	Epidermal fragments, vascular tissues
Leaves	Opposite, ovate, smooth or slightly hairy; green	Presence of stomata; mesophyll with chloroplasts; vascular strands	Leaf fragments, trachoma's, epidermal cells
Crystals	Not visible macroscopically	Calcium oxalate crystals present	Crystal fragments visible
Storage Materials	Not visible	Starch grains present in parenchyma cells	Starch granules observed
Diagnostic Features	Characteristic odour and bitter taste	Distinct cork cells and vascular tissues	Mixed fragments of fibres, vessels, and starch grains

Phytochemical Significance of *Boerhavia diffusa*

The therapeutic efficacy of *Boerhavia diffusa* is largely attributed to its rich and diverse phytochemical composition, which includes alkaloids, flavonoids, retinoid, phenolic, lignins, and sterols. (James JM, *et al*., 2025) [16]These bioactive constituents collectively contribute to its broad spectrum of pharmacological activities, particularly in the context of cancer.

The presence of flavonoids and phenolic compounds provides strong antioxidant properties, enabling the neutralization of reactive oxygen species and protection against oxidative DNA damage (Krishnamoorthy S, *et al*, 2025) [17]. Alkaloids such as punarnavine exhibit immunomodulatory and anti-inflammatory effects, which are important in regulating tumour-associated inflammation. Retinoid (boeravinones) have been reported to possess cytotoxic and anti-proliferative activities, directly inhibiting cancer cell growth. (Milošević N, *et al*., 2022) [28].

Fig 1: Major Bioactive compounds of Boerhavia diffusa-Chemical Structures.

Additionally, these phytochemicals influence multiple cellular signalling pathways involved in carcinogenesis, including those regulating apoptosis, cell cycle progression, and inflammation. The combined action of these compounds results in a multi-target therapeutic effect, which is a key advantage over single-target synthetic drugs. (Newman DJ, Cragg GM., 2020) [19].From an integrative medicine perspective, the synergistic interaction of these phytoconstituents aligns with Siddha principles of holistic treatment, where multiple components act together to restore balance and enhance the body's natural defence mechanisms. (Patel N, *et al.,* 2025) [20] Thus, the phytochemical richness of *Boerhavia diffusa* underpins its potential as an effective adjunct in cancer therapy.

Summary Insight

These compounds act synergistically, targeting multiple pathways such as oxidative stress, inflammation, and apoptosis (Patel N, *et al*., 2025) [20]. This multi-component nature supports the role of *Boerhavia diffusa* as a multi-target therapeutic agent in integrative cancer therapy.

Mechanisms of Anticancer Activity

Antioxidant Effects

DPPH Radical Scavenging Assay

A 0.1 mm DPPH solution was prepared in methanol. To 1.0 mL of this solution, 1.0 mL of various concentrations of the plant extract (50–300 µg/mL) was added. The reaction

mixture was incubated in the dark at room temperature for 30 min, and the absorbance was measured at 517 nm against a methanol blank. Ascorbic acid was used as the standard. (Sahu SN, *et al*., 2025).The percentage of inhibition was calculated using the formula:

% Inhibition= [Ac−As/Ac] ×100

Where Ac is the absorbance of control and as is the absorbance of sample**.**

ABTS Radical Cat ion Decolourization Assay

The ABTS radical was generated by mixing 7 mm ABTS solution with 2.45 mm potassium per sulfate and allowing the mixture to stand in the dark for 12–16 hr at room temperature. Before use, the ABTS solution was diluted with ethanol to an absorbance of 0.70 ± 0.02 at 734 nm. Then, 1.0 mL of ABTS solution was mixed with 100 µL of the extract at different concentrations and incubated for 6 min, and absorbance was recorded at 734 nm. Ascorbic acid was used as standard. (Sinan KI, *et al.,* 2003).

Hydrogen Peroxide (H_2O_2) Scavenging Assay

Hydrogen peroxide scavenging activity was determined by using solution of H_2O_2 (40 mm) was prepared in phosphate buffer (50 mm, pH 7.4). Plant extract (1 mL) at various concentrations was added to 0.6 mL of H_2O_2 solution. After 10 min of incubation at room temperature, the absorbance was read at 230 nm against a blank solution containing phosphate buffer without H_2O_2. Ascorbic acid was used as a reference compound. (Sinan KI, Zengin G, 2021) [24].

Superoxide Anion Scavenging Assay

The reaction mixture contained 1 mL of nitroblue tetrazolium (NBT, 156 µM), 1 mL of NADH (468 µM), and 1 mL of plant extract at different concentrations. (Sushma B, *et al*.2023). The reaction was initiated by adding 100 µL of phenazine methosulfate (PMS, 60 µM). After 5 min of incubation at 25°C, the absorbance was measured at 560 nm against the corresponding blank. Decreased absorbance indicated increased superoxide scavenging activity.

Hydroxyl Radical Scavenging Assay

The reaction mixture contained 0.45 mL of phosphate buffer (50 mm, pH 7.4), 0.15 mL of 10 mm $FeSO_4$-EDTA, and 0.15 mL of 10 mm deoxyribose, 0.15 mL of 10 mm H_2O_2, and 0.525 mL of distilled water. Plant extract (0.15 mL) at various concentrations was added, and the mixture was incubated at 37°C for 1 hr. After incubation, 0.75 mL of 2.8% trichloroacetic acid and 0.75 mL of 1% thiobarbituric acid were added, and the tubes were heated at 90°C for 15 min. The absorbance was measured at 532 nm. (Milošević N, *et al.,* 2022) [18].

Nitric Oxide (NO) Radical Scavenging Assay

Sodium nitroprusside (10 mm) in phosphate buffer (0.5 mL, pH 7.4) was mixed with 0.5 mL of plant extract at different concentrations and incubated at 25°C for 150 min. After incubation, 0.5 mL of the reaction mixture was added to 0.5 mL of Gris reagent (1% sulfanilamide, 0.1% naphthyl-ethylene-diamante hydrochloride, and 2% phosphoric acid). The absorbance was read at 540 nm. (Vander Heiden MG, *et al*., 2021) [26]. Ascorbic acid served as standard**.**

Anti-inflammatory Actions

Anti-inflammatory assay

200 µL of 1% BSA was added to 800 µL of cold normal saline, and dissolved completely under gentle shaking. 1.3 mL of PBS buffer and 0.2 mL standard (Diclofenac sodium) and sample extract, at different concentration was prepared and mixed with above BSA solution. Only distilled water was combined to make a total volume of 5 mL of the control. After 30 min of incubation at 37±2°C, the reaction tubes were placed in a water bath set at 70±5°C for 15 min. An appropriate UV/visa spectrophotometer was used to determine the absorption at 280 nm following cooling down, using PBS serving as the blank. (Krishnamoorthy S, *et al., 2025*) [17].

% of inhibition = OD of Control- OD of Test/ OD of Control x 100

Cell Viability Assay (MTT Assay)

Cell viability was assessed using the MTT assay. Cells were seeded in 96-well plates and treated with varying concentrations of *Boerhavia diffusa* extract. After incubation (24–48 h), MTT reagent was added and incubated further. (Zitvogel L, *et al.*, 2021) [27]. The resulting Formosan crystals were dissolved in DMSO, and absorbance was measured at 570 nm using a micro plate reader.

Apoptosis Assays

Annexin V–FITC/PI Staining

Apoptotic cells were quantified using Annexin V–FITC/PI staining followed by flow cytometry. Treated and control cells were collected, washed with PBS, and stained with Annexin V–FITC and propidium iodide. Cells were analyzed to determine early and late apoptotic populations. (Gunaseelan D, *et al.,* 2021).

TUNEL Assay

DNA fragmentation was assessed using the TUNEL assay. Cells were fixed, permeabilized, and incubated with TUNEL reaction mixture. Fluorescence microscopy was used to detect apoptotic cells.

Capsize Activity Assay

Caspase-3 and caspase-9 activities were measured using colorimetric or fluorometric assay kits according to the manufacturer's protocol. Increased enzyme activity indicated apoptosis induction. (James JM, *et al.,* 2025) [16].

Mitochondrial Membrane Potential (ΔΨm) Assay

Changes in mitochondrial membrane potential were evaluated using JC-1 dye. Cells were stained and analysed under a fluorescence microscope. A shift from red to green fluorescence indicated mitochondrial depolarization. (Sahu SN, *et al*., 2022) [22].

Cell Cycle Analysis

Cells were fixed in ethanol, stained with propidium iodide, and analysed by flow cytometer. The percentage of cells in different phases of the cell cycle was determined, with a sub-G1 peak indicating apoptosis.

Preclinical Studies: (*In Vitro* Studies)

***In Vitro* Antioxidant Activity**

Ethanol leaf and stem extracts of *Boerhavia diffusa* exhibited significant, dose-dependent antioxidant activity across multiple free radical scavenging assays, including DPPH, ABTS, hydrogen peroxide, superoxide, hydroxyl, and nitric oxide assays. Leaf extracts showed lower IC_{50} values than stem extracts, indicating superior antioxidant efficacy, likely due to higher phenolic and flavonoid

content. The activity was comparable to ascorbic acid, highlighting the strong natural antioxidant potential of Boerhavia *diffusa*.

The antioxidant potential of *Boerhavia diffusa* leaf and stem extracts was evaluated through multiple *in vitro* radical scavenging assays, namely DPPH, ABTS, Hydrogen Peroxide (H_2O_2), superoxide, Hydroxyl (OH), and Nitric Oxide (NO) scavenging assays (Table 1). Antioxidant activity was found to increase in a concentration-dependent manner for both stem (SE) and Leaf (LE) extracts, indicating the presence of phytoconstituents capable of donating electrons or hydrogen atoms to neutralize reactive free radicals. At 50 µg/mL, the scavenging activities were relatively low, ranging from 12.31 ± 0.38% (DPPH) to 17.60 ± 0.44% (NO) for the stem extract and from 16.52 ± 0.55% (OH) to 24.65 ± 0.60% (H_2O_2) for the leaf extract. However, at 300 µg/ mL, both extracts exhibited significantly enhanced activity, with the leaf extract showing the highest inhibition values across all assays - 88.32 ± 1.66% (DPPH), 91.29 ± 1.70% (H_2O_2), and 85.40± 1.53% (NO) - closely approaching that of the standard ascorbic acid (96.09 ± 1.85% NO scavenging at 300 µg/mL).

The DPPH assay reflects the extract's ability to neutralize the stable DPPH radical by hydrogen or electron transfer. The high activity of the leaf extract *Boerhavia diffusa* suggests the presence of potent hydrogen-donating antioxidants such as phenolic and flavonoids, which are well-known in Similarly, the ABTS assay, which evaluates both lipophilic and hydrophilic antioxidant capacity, showed strong activity (88.40 ± 1.88%), further confirming the extract's broad radical-neutralizing potential.

Hydrogen peroxide and superoxide scavenging activities also increased markedly with concentration, indicating the capacity of. *Boerhavia diffusa* phytochemicals to act as reducing agents and metal cheaters that prevent the formation of highly reactive hydroxyl radicals via the Fenton reaction. Hydroxyl radical scavenging activity (83.72 ± 1.55% for the leaf extract) demonstrated efficient quenching of the most damaging ROS species, preventing oxidative damage to biomolecules such as DNA, proteins, and lipids. Nitric oxide scavenging activity was also substantial (85.40 ± 1.53% at 300 µg/mL for both extracts), suggesting *Boerhavia diffusa* that. Constituents may modulate NO-related oxidative stress, which contributes to inflammation and tissue damage. The leaf extract consistently outperformed the stem extract across all assays, implying that leaves are richer in antioxidant phytochemicals such as flavonoids, tannins, alkaloids, and phenolic acids. This aligns with prior reports on other Boerhavia *diffusa* which possess significant antioxidant, anti-inflammatory, and antimicrobial properties attributed to similar classes of compounds. Antioxidant and anti-inflammatory effects than other plant parts due to higher total phenolic and flavonoid contents.

Table 3: Free radical scavenging activity of Boerhavia diffusa.

Concentration µG	DPPH	ABTS	H2O2	Superoxide	OH	Nitric oxide
Stem extract (SE) 50 µg	12.31±0.38	12.51±0.50	14.51±0.55	16.62±0.51	13.24±0.41	17.60±0.44
SE 300 µg	72.37±1.40	80.11±1.52	80.72±1.52	82.73±1.57	78.40±1.37	85.40±1.53
Leaf extract (LE) 50 µg	24.39±0.51	18.62±0.81	24.65±0.60	18.52±0.67	16.52±0.55	17.60±0.44
LE 300 µg	88.32±1.66	88.40±1.88	91.29±1.70	87.50±1.69	83.72±1.55	85.40±1.53
Ascorbic acid 50 µg	30.68±0.89	25.13±0.83	36.52±0.89	28.62±0.80	25.33±0.60	34.41±0.70
Ascorbic acid 300 µg	95.47±1.85	92.70±1.82	96.40±1.75	93.45±1.78	90.19±1.70	96.09±1.85

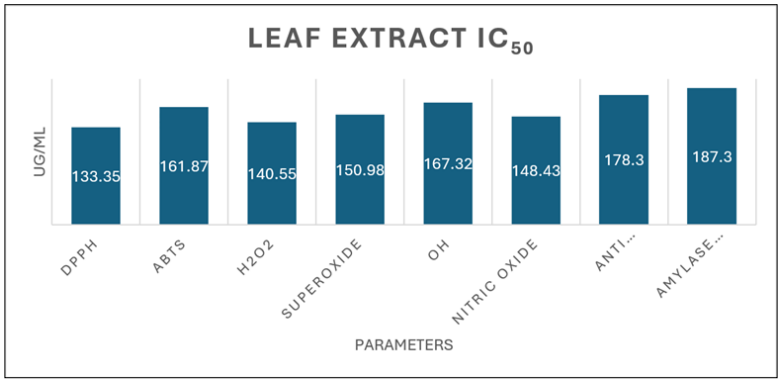

Fig 2: The bar graph presents the IC_{50} values (µg/mL) of various biological and antioxidant assays for the leaf extract of Boerhavia *diffusa*

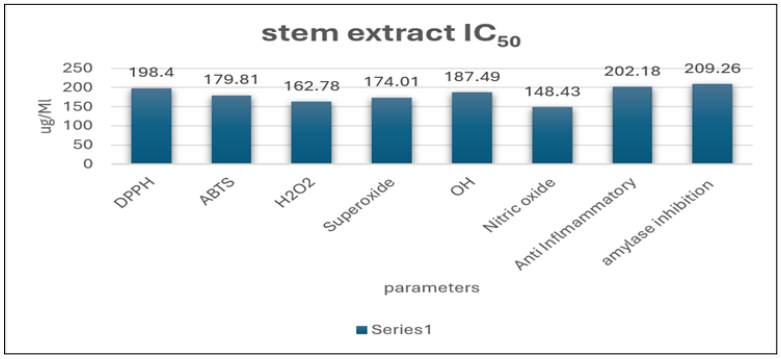

Fig 3: The bar graph presents the IC_{50} values (µg/mL) of various biological and antioxidant assays for the stem extract of Boerhavia *diffusa*

Anti-inflammatory activity

The anti-inflammatory potential of Boerhavia *diffusa.* Leaf and stem extracts was evaluated by measuring their inhibition percentage at different concentrations (50 and 300 µg/mL) in comparison with the standard drug (ascorbic acid or diclofenac sodium). The results (Table 2) indicate a dose-dependent increase in anti-inflammatory activity for both extracts. At 50 µg/mL, the leaf extract exhibited 17.20 ± 0.45% inhibition, while the stem extract showed 13.52 ± 0.33%, both lower than the standard (34.12 ± 0.75%). However, at 300 µg/mL, the leaf extract demonstrated a marked increase (79.90 ± 1.59%), surpassing the stem extract (72.68 ± 1.33%) and showing activity comparable to the standard (97.19 ± 1.77%). The calculated IC_{50} values further confirm this trend: the leaf extract (178.30 µg/mL) displayed stronger inhibitory potential than the stem extract (202.18 µg/ mL), indicating higher anti-inflammatory efficacy. The standard exhibited an IC_{50} of 98.01 µg/mL, reflecting its potent reference activity. The higher activity of the leaf extract suggests a greater concentration of these compounds, Consistent with earlier reports on Boerhavia *diffusa*. which showed comparable *in vitro* and *in vivo* anti-inflammatory effects. Ozay and Keleş (2024) reported that Boerhavia *diffusa* extracts significantly suppressed nitric oxide production and reactive oxygen species in LPS-induced macrophages, validating the genus's anti-inflammatory potential

Table 4: Percentage of anti-inflammatory activity of Boerhavia *diffusa*

Concentration µg	Leaf extract	Stem extract	Standard
50	17.20±0.45	13.52±0.33	34.12±0.75
300	79.90±1.59	72.68±1.33	97.19±1.77
IC_{50}Value µg/Ml	178.30	202.18	98.01

In Vivo Studies:

Induction of Apoptosis

Boerhavia diffusa (Punarnava) exhibits significant anticancer activity by inducing programmed cell death (apoptosis), a crucial mechanism for eliminating damaged or malignant cells. Unlike necrosis, apoptosis is a controlled and energy-dependent process that prevents inflammation and limits tumour progression.

The apoptotic effect of *Boerhavia diffusa* is primarily mediated through the intrinsic (mitochondrial) pathway. Bioactive compounds such as flavonoids and retinoid modulate the balance between pro-apoptotic and anti-apoptotic proteins, particularly increasing the Bax/Bcl-2 ratio. This shift leads to mitochondrial membrane permeabilization and subsequent release of cytochrome c into the cytosol.

Following this, cytochrome c forms the apoptosome complex, which activates caspase-9, subsequently triggering caspase-3, the key executioner enzyme responsible for DNA fragmentation and cell death. Additionally, *Boerhavia diffusa* has been reported to influence tumour suppressor proteins such as p53, further promoting apoptosis in cancer cells.

Furthermore, its antioxidant properties help regulate oxidative stress, which plays a dual role in apoptosis signalling. By modulating reactive oxygen species (ROS), the plant enhances apoptotic signalling while protecting normal cells from excessive damage.

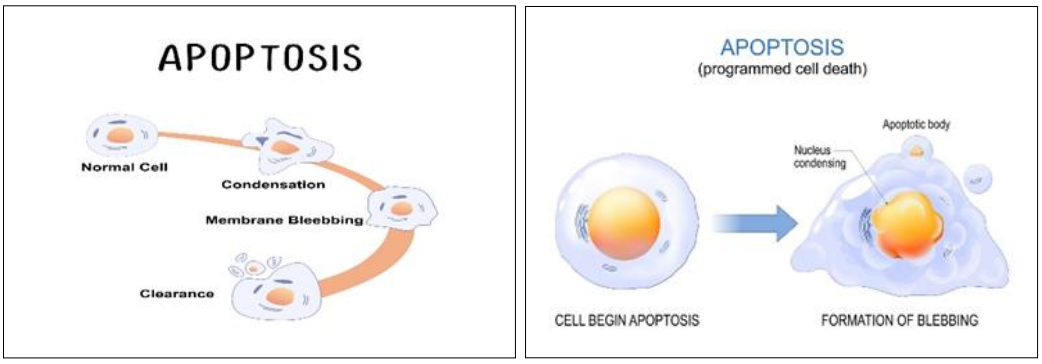

Fig 4: Induction of Apoptosis by *Boerhavia diffuse*

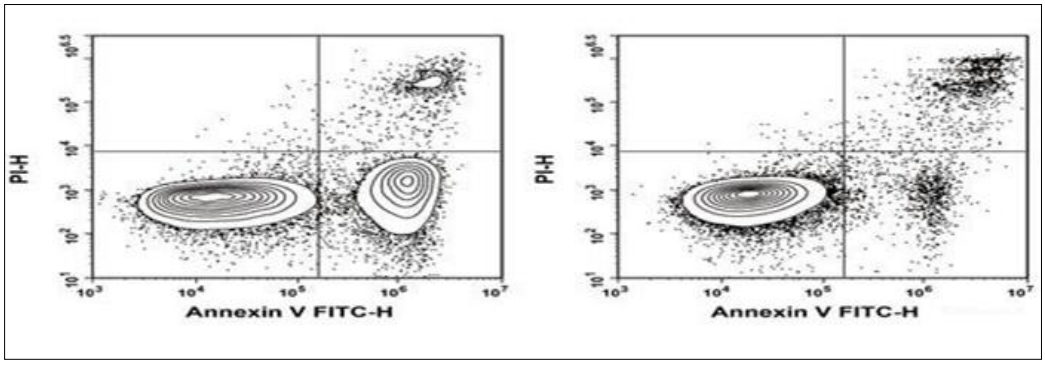

Fig 5: Apoptosis Assays used to Evaluated *Boerhavia diffusa*

Mechanistic Summary

- ↑ Bax / ↓ Bcl-2 expression
- Mitochondrial membrane disruption
- Cytochrome c release
- Activation of caspase-9 and caspase-3
- DNA fragmentation and cancer cell death

Significance in Cancer Therapy

The ability of *Boerhavia diffusa* to induce apoptosis highlights its potential as a targeted anticancer agent, as many cancer cells evade apoptosis. By restoring this pathway, Punarnava contributes to:

- Selective elimination of tumour cells
- Reduction in tumour growth
- Enhancement of therapeutic efficacy

Inhibition of Tumour Growth and Metastasis

Boerhavia diffusa (Punarnava) demonstrates significant potential in suppressing tumour growth and preventing metastasis through multiple molecular mechanisms. Tumour progression involves uncontrolled proliferation, angiogenesis, and the ability of cancer cells to invade surrounding tissues and spread to distant organs.

The bioactive constituents of *Boerhavia diffusa*, particularly flavonoids and retinoid, target these processes at different levels. One of the key mechanisms involves the inhibition of angiogenesis, the formation of new blood vessels required for tumour nourishment. *Boerhavia diffusa* has been reported to down regulate vascular endothelial growth factor (VEGF) and related signalling pathways, thereby restricting blood supply to tumours and limiting their growth.

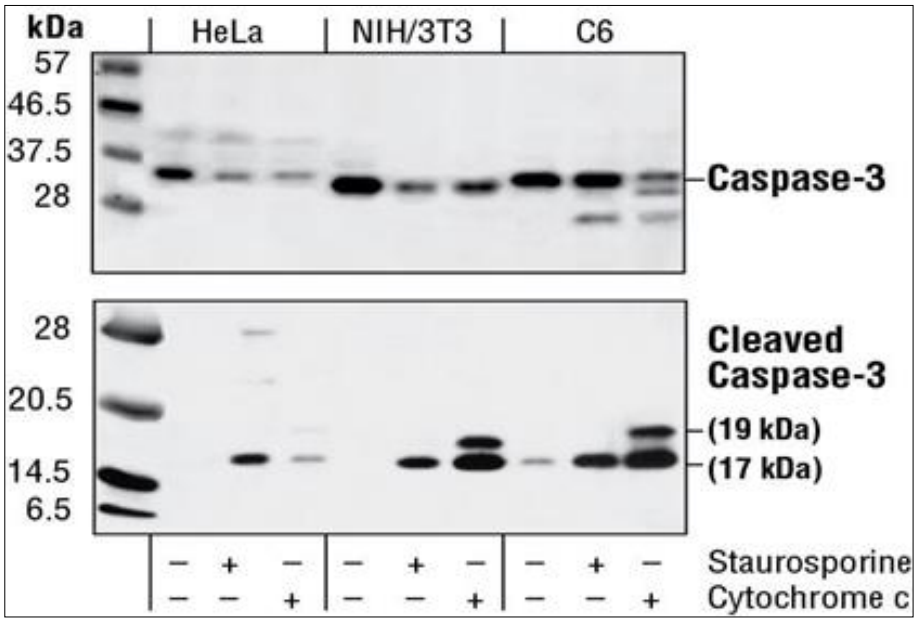

Fig 6: Early apoptosis (Annexing V positive)

Additionally, the plant inhibits tumour invasion and metastasis by suppressing matrix metalloproteinase (MMPs), particularly MMP-2 and MMP-9, which are responsible for degradation of the extracellular matrix. By preventing this degradation, *Boerhavia diffusa* reduces cancer cell migration and invasion.

The extract also interferes with key signalling pathways such as PI3K/Akt and NF-κB, which are involved in cell survival, proliferation, and metastatic potential. Modulation of these pathways results in reduced tumour cell proliferation and increased susceptibility to apoptosis. Furthermore, its anti-inflammatory and antioxidant properties contribute to altering the tumour microenvironment, making it less conducive for cancer progression and spread.

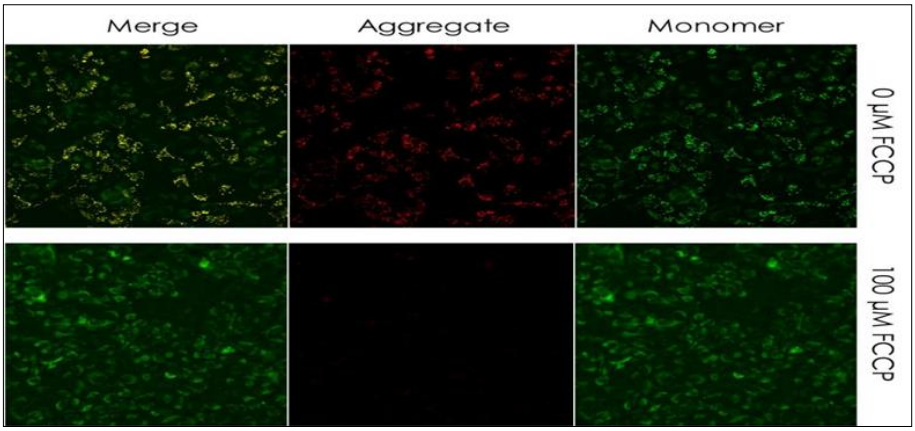

Fig 7: Late apoptosis → Annexing V + PI positive

- **Mechanistic Summary**
- ↓ VEGF expression → inhibition of angiogenesis
- ↓ MMP-2 and MMP-9 activity → reduced invasion and metastasis
- Modulation of PI3K/Akt and NF-κB pathways
- Suppression of tumour cell proliferation
- Alteration of tumour microenvironment
-
- **Significance in Cancer Therapy**
- The ability of *Boerhavia diffusa* to target both tumour growth and metastatic spread highlights its importance as a multi-target anticancer agent. By interfering with key processes involved in cancer progression, it may:
- Limit tumour expansion
- Prevent secondary tumour formation
- Enhance the effectiveness of conventional therapies

Role in Siddha Medicine

Traditional Concepts of Cancer (Neoplasms)

In Siddha Medicine, diseases resembling cancer are described under conditions such as "Kuttam," "Putru," or abnormal growths, which are understood as the result of internal imbalance and long-term pathological changes in the body. These conditions are not viewed as a single disease entity but rather as complex disorders arising from disturbances in the three fundamental humours—Vali (Vatham), Azhal (Pitham), and Iyyam (Kapham).

According to Siddha principles, neoplastic conditions develop when these humors become severely imbalanced, leading to improper tissue growth, accumulation of toxins (referred to as "Kazhichal" or "Ama"), and disruption of normal cellular function. Poor diet, environmental factors, chronic inflammation, and weakened immunity are considered major causes.

In Siddha Medicine, cancer-like conditions are described as abnormal growths caused by imbalance of the three humours—Vali, Azhal, and Iyyam. These imbalances lead to toxin accumulation and uncontrolled tissue development. Treatment focuses on restoring balance, detoxification, and strengthening the body using herbal remedies such as *Boerhavia diffusa* attributing causes.

Therapeutic Applications of *Boerhavia diffusa*

In Siddha Medicine, *Boerhavia diffusa* is used for its rejuvenating, detoxifying, and anti-inflammatory properties. It helps in reducing abnormal tissue growth, improving metabolism, and enhancing immunity. The plant is also used to support liver and kidney function, which aids in overall disease management and recovery.

Integration with Modern Oncology-Complementary and Alternative Approaches

The use of *Boerhavia diffusa* in modern oncology is increasingly viewed within an integrative framework, where traditional remedies are combined with standard cancer treatments to enhance overall care. In systems such as Siddha Medicine, this plant has long been valued for restoring balance and supporting the body during chronic illness.

As a complementary therapy, *Boerhavia diffusa* may help manage side effects associated with chemotherapy and radiotherapy, such as oxidative stress, inflammation, and weakened immunity. Its bioactive compounds are believed to support immune function and improve general health, which can be beneficial during cancer treatment.

In an alternative context, laboratory studies suggest that the plant possesses properties that may slow tumour growth and limit the spread of cancer cells. However, these findings are largely based on preclinical research, and there is not enough clinical evidence to recommend it as a replacement for established cancer therapies.

Therefore, the integration of *Boerhavia diffusa* into cancer care should be approached cautiously and under medical supervision. Its most appropriate role is as a supportive agent within evidence-based oncology, where it may complement conventional treatments while further research continues to confirm its efficacy and safety in humans.

Synergistic Effects with Conventional Therapies

The combined use of *Boerhavia diffusa* with standard cancer treatments is being explored for its potential to improve therapeutic outcomes. In this context, synergy refers to the ability of the plant's bioactive compounds to work alongside conventional therapies such as chemotherapy and radiotherapy, enhancing their effectiveness while reducing unwanted side effects.

Research at the experimental level indicates that compounds present in *Boerhavia diffusa* may help increase the responsiveness of cancer cells to anticancer drugs. This may support better control of tumour growth by promoting programmed cell death and limiting the Multiplication of malignant cells. At the same time, its antioxidant and anti-inflammatory actions may help protect healthy tissues from treatment-related damage.

Another possible advantage is its role in addressing drug resistance, a common challenge in cancer therapy. Certain plant constituents may influence cellular pathways involved in resistance, thereby improving the efficiency of standard treatments. In addition, its immunomodulatory properties may strengthen the body's defence mechanisms, supporting overall treatment response.

However, these effects are mainly supported by preclinical findings, and strong clinical evidence in humans is still lacking. Therefore, *Boerhavia diffusa* should be considered only as a supportive therapy under medical supervision. Further research is needed to confirm its synergistic benefits, establish proper dosing, and ensure safety in combination with conventional cancer treatments.

Safety, Toxicity, and Dosage Considerations of *Boerhavia diffusa*

- **Safety**

  Boerhavia diffusa (Punarnava) is generally considered safe when used in recommended amounts. It has a long history of use in traditional systems such as Siddha Medicine, where it is valued for treating various chronic conditions. Most experimental studies report no serious side effects at normal therapeutic doses.

- **Toxicity**

  Available research indicates that the plant has low toxicity. Animal studies have shown that even moderate to high doses do not produce significant harmful effects. However, excessive intake or prolonged use without medical guidance may lead to mild issues such as stomach discomfort or Dosage balance in body fluids. Human toxicity data are still limited, so careful use is advised.

The dose depends on the form of the preparation:

- **Powder (Churna):** about 3–6 grams per day
- **Decoction (Kashayam):** around 20–50 ml per day
- **Extracts:** dosage varies based on strength and formulation

It is best to use this herb under the supervision of a qualified practitioner, especially in long-term use or for serious conditions like cancer.

Precautions

- Avoid use during pregnancy and breastfeeding unless advised by a doctor
- Patients with kidney or liver problems should consult a healthcare professional
- May interact with diuretic drugs or other medications

Long-term use should be monitored *Boerhavia diffusa* has a good safety profile and low toxicity when used correctly. However, proper dosage, medical supervision, and further clinical studies are important for its safe and effective use in modern therapy.

Discussion and Critical Analysis

The present review highlights the therapeutic potential of *Boerhavia diffusa* (Punarnava) as an integrative agent in cancer management by bridging Siddha medicine and modern biomedical science. The convergence of traditional knowledge and contemporary molecular research underscores the relevance of multi-targeted phototherapy in addressing the complex pathophysiology of cancer.

From a Siddha perspective, cancer (*Putru Noi*) is not merely a localized disease but a systemic disorder arising from the imbalance of *Vatham, Pitham,* and *Kapham*, along with the accumulation of metabolic toxins (*Ama*) and impaired digestive/metabolic function (*Agni*). This holistic framework aligns conceptually with modern understandings of cancer as a multifactorial disease involving chronic inflammation, oxidative stress, immune dysfunction, and metabolic deregulation. The traditional use of Punarnava as a Kayakalpa (rejuvenate) drug reflects its role in restoring systemic balance, which is increasingly recognized in modern oncology as supportive care and immune restoration.

At the molecular level, *Boerhavia diffusa* demonstrates significant anticancer activity through modulation of multiple signalling pathways, including NF-κB, PI3K/Akt, and mitochondrial apoptosis pathways. This multi-target approach is particularly relevant given that cancer progression involves redundant and overlapping pathways. Unlike single-target chemotherapeutic agents, phytochemicals such as punarnavine, boeravinones, and flavonoids exert pleiotropic effects, simultaneously influencing inflammation, proliferation, apoptosis, and metastasis. Such broad-spectrum activity supports the rationale for integrating herbal medicine into cancer therapy.

However, despite promising preclinical findings, several critical limitations must be acknowledged. First, the majority of evidence supporting the anticancer effects of *Boerhavia diffusa* is derived from *in vitro* and animal studies, with limited clinical validation in human subjects. This raises concerns regarding the translatability of results, particularly in terms of bioavailability, pharmacokinetics, and effective dosing. Second, variability in phytochemical composition due to geographical, environmental, and processing factors presents challenges in standardization and reproducibility. Without standardized extracts, it becomes difficult to ensure consistent therapeutic outcomes.

Another important consideration is the lack of rigorous clinical trials evaluating its efficacy as an adjunct to conventional therapies. While preliminary evidence suggests that *Boerhavia diffusa* may reduce chemotherapy-induced toxicity and enhance immune function, well-designed randomized controlled trials are necessary to establish its safety, efficacy, and potential herb-drug interactions. The possibility of interactions with chemotherapeutic agents, particularly those metabolized through hepatic pathways, must be carefully evaluated to avoid adverse effects.

From a pharmacological standpoint, the synergistic action of multiple phytochemicals represents both an advantage and a challenge. While synergy enhances therapeutic efficacy, it complicates the identification of specific active compounds and mechanisms. Advanced techniques such as metabolomics, systems biology, and network pharmacology are needed to better understand these interactions and optimize therapeutic formulations.

In the context of integrative oncology, *Boerhavia diffusa* holds significant promise as a complementary agent rather than a standalone treatment. Its role may be particularly valuable in:

- Enhancing immune response
- Reducing inflammation and oxidative stress
- Mitigating side effects of chemotherapy
- Improving patient quality of life

Importantly, the integration of Siddha medicine into modern healthcare requires a scientifically validated and evidence-based approach. Bridging traditional knowledge with clinical research can facilitate the development of standardized, safe, and effective herbal interventions.

Conclusion of Discussion

In summary, *Boerhavia diffusa* represents a compelling example of how traditional medicinal knowledge can inform modern therapeutic strategies. While preclinical studies provide strong evidence supporting its anticancer potential, the translation of these findings into clinical practice necessitates rigorous scientific validation, standardization of extracts, and well-designed clinical trials. Furthermore, interdisciplinary collaboration between pharmacologists, clinicians, and traditional medicine experts is essential to fully realize its therapeutic value. The future of *Boerhavia diffusa* lies in evidence-based integrative oncology, where the convergence of traditional wisdom and modern scientific approaches can contribute to more effective and holistic cancer care outcomes.

Future Perspectives

- Conducting well-designed clinical trials to establish the safety and effectiveness of *Boerhavia diffusa* in human subjects.
- Identifying, isolating, and thoroughly characterizing the bioactive constituents responsible for its therapeutic effects.
- Developing standardized and quality-controlled formulations to ensure consistency, reliability, and reproducibility in treatment outcomes.

- Investigating advanced delivery approaches, including Nano-based drug delivery systems, to enhance bioavailability and targeted action.
- Promoting its incorporation into evidence-based oncology through integrative research that bridges traditional knowledge with modern medical science.

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