Boerhavia diffusa: A Medicinal Goldmine of Therapeutic Potentials

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Abstract

Boerhavia diffusa is a medicinal plant with a wide range of therapeutic potentials. The plant's bioactive compounds and pharmacological properties are explored in depth, including its diuretic, hepatoprotective, anti-inflammatory, antioxidant, anti-fibrinolytic, anti-cancer, anti-diabetic, immunomodulatory, immunosuppressive, anti-lymphoproliferative, and antibacterial effects. In this review, mechanisms of action of these properties are discussed, highlighting their impact on cellular signaling pathways, enzyme activity, cytokine production, antioxidant and detoxification systems, apoptosis, angiogenesis, and bacterial cell disruption. The review further delves into the plant's traditional and ethnopharmacological uses, demonstrating its versatility in treating a variety of health conditions.

Keywords

Boerhavia diffusa, medicinal plant, bioactive compounds, therapeutic potential

Introduction

Boerhavia diffusa (*B. Diffusa*) also known as punarnava or red spiderling, is a perennial herb from the Nyctaginaceae family [1]. This plant has a creeping habit with much-branched stems that are purplish and thickened at the nodes and stout fusiform roots [2]. Its purplish stems are thickened at the nodes, and its leaves are opposite, oblique, and ovate or suborbicular in shape.

The plant produces small flowers about 5 mm in diameter and its fruit is a rounded 6-ribbed achene. The seed is minute, albuminous with endosperm, and the embryo is curved [3]. The different parts of plants exhibit different therapeutic potential which has been described in Table 1 [2]. This plant thrives in sunny, dry locations and can tolerate a wide range of soil conditions [4].

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It is often found in disturbed soils, such as along roadsides and in abandoned fields and is widely dispersed throughout India, the Pacific, and southern United States [5]. *B. Diffusa* is a medicinal plant rich in various chemical compounds. It contains flavonoids such as C-methylflavone and borhavone, alkaloids like punarnavine, glycosides including punarnavoside, and rotenoids such as boeravinone A-H [6]. Additionally, it has steroids, triterpenoids, lipids, lignans, carbohydrates, proteins, glycoproteins, phenolic glycoside, terpenoids, organic acids, flavone, isoflavone, flavonol, flavonoid glycoside, xanthone, lignin, purine nucleoside, sterol, sterol ester, ecdysteroid, fatty acid, and hydrocarbons [7].

These diverse compounds give the plant its numerous pharmacological properties, such as diuretic, hepatoprotective, anti-inflammatory, anti-fibrinolytic, anti-cancer, anti-diabetic, immuno-modulatory, immuno-suppressive, anti-lymphoproliferative, and analgesic properties (Figure 1) [8]. *B. Diffusa* can significantly increase urine output and sodium excretion indicating its potential as a diuretic agent [9]. The plant extract enhances renal blood flow and glomerular filtration rate, leading to increased urine formation, and inhibits the reabsorption of sodium and water in the renal tubules, further promoting diuresis [10].

Table 1: *Different parts of plants indicating various therapeutic uses*

Part of Plant Used	Therapeutic Uses
Root, leaves, aerial parts, whole plant	Liver and kidney complaints, rheumatism
Whole plant, leaves	Inflammation, strangury, jaundice, dyspepsia, constipation
Leaves	Hypotension, skin diseases, night blindness
Roots	Gonorrhoea, dropsy, bronchial asthma
Decoction, powder	Post-delivery complaints, menstrual issues, cold
Root decoction	Fever, internal inflammation, abdominal pain
Root, leaf juice	Eye diseases, virility restoration, childbirth facilitation
Various parts	Renal ailments, seminal weakness, blood pressure
Various parts	Stomach ache, anemia, cough, cold
Various parts	Snake and rat bites antidote, contraceptives
Whole plant, seeds	Nutritional use, lactation enhancement

Various Therapeutic Potentials of *B. Diffusa*

1. Diuretic

Additionally, it also maintains electrolyte balance by preventing excessive loss of potassium and other essential electrolytes [11]. Furthermore, *B. Diffusa* also exhibits renal protective effects, possessing antioxidant and anti-inflammatory properties that may protect the kidneys from oxidative stress and inflammation [12]. Sahu *et al.* investigated the therapeutic potential of phytochemicals from Boerhavia diffusa (B. diffusa) in addressing mutant forms of the nephrin protein associated with nephrotic syndrome type 1, a condition resistant to conventional treatments. Utilizing computational methods such as virtual screening and molecular dynamics simulations, they identified seven bioactive compounds from B. diffusa, with boeravinone M and boeravinone E showing promising binding properties against both wild type and mutant models of the Ig4 domain of the nephrin protein. Hydrate-ligand docking revealed enhanced binding performance of boeravinone M and boeravinone E with the mutant model, attributed to a more precise estimation of water molecule contributions. Molecular dynamics simulations suggested boeravinone E as a potential inhibitor against NPHS1, exhibiting the lowest short-range interaction energies and modulating stability and function of the mutant nephrin protein effectively. These findings highlight boeravinone E as a prospective therapeutic agent for nephrotic syndrome type 1, offering insights into natural product-based approaches for addressing genetic mutations in chronic diseases [13]. Similarly, diuretic effects of alcoholic extracts derived from the stems and leaves of *B. diffusa* were evaluated in normal rats. The extracts were orally administered to experimental rats at doses of 150 and 300mg/kg. Furosemide was employed as a standard drug at a dose of 20mg/kg. Diuretic effects were evaluated by measuring urine volume, sodium, and potassium content. AEBD significantly increased urine volume compared to the control group, along with increased sodium excretion. These effects were comparable to those observed with the standard drug. Therefore, this study provides quantitative evidence supporting the traditional use of *B. diffusa* as a diuretic agent [14].

2. Hepatoprotective

B. Diffusa regulates the activity of hepatic enzymes involved in detoxification and synthesis of biomolecules, thereby enhancing liver function [15]. It also stimulates hepatocellular regeneration and

repair mechanisms, promoting the proliferation of hepatocytes and enhancing the synthesis of liver proteins [16]. Furthermore, it helps maintain the structural and functional integrity of hepatic cells, protecting against apoptosis and necrosis induced by various hepatotoxic agents [17,18]. Overall, the hepatoprotective effects of *B. Diffusa* are a result of its antioxidant, anti-inflammatory, enzyme-modulating, regenerative, and cytoprotective actions. Thajudeen et al. evaluated the hepatoprotective effects of *B. Diffusa* against GalN-induced cytotoxicity on HepG2 cell lines. The hepatoprotective efficacy of silymarin ranged from 78.7% at 100 µg/mL to 84.34% at 200 µg/mL, while caffeic acid exhibited protection ranging from 46.17% at 100 µg/mL to 52.34% at 200 µg/mL, and boeravinone B showed protection ranging from 40.89% at 100 µg/mL to 62.21% at 200 µg/mL. Notably, boeravinone B and caffeic acid demonstrated superior hepatoprotective activity compared to standard silymarin. These results lend support to the traditional usage of *B. Diffusa* as a beneficial functional food for human health [19]. In another study, Dey *et al.* examined hepatoprotective effects of *B. Diffusa* against alcohol-induced liver damage. In HepG2 cells, ethanol exposure (120 mM for 48 hours) induced significant toxicity (approximately 42%), treatment with *B. Diffusa* exhibited a dose-dependent prevention of ethanol-induced cell death, demonstrating synergistic activity surpassing individual extracts. Additionally, *B. Diffusa* demonstrated potent antioxidant activity in the DPPH assay. In a rat model of hepatitis induced by repeated alcohol (40%) and carbon tetrachloride (CCl4) dosing, oral administration of BV-7310 (at 250 and 500 mg/kg body weight) mitigated alcohol-induced body weight loss and significantly improved elevated liver enzyme levels compared to the vehicle-treated group. These findings highlight *B. Diffusa's* efficacy in preventing alcohol-induced toxicity in both in vitro and in vivo models, suggesting its potential therapeutic utility for ALD and other conditions associated with liver toxicity [20].

3. Anti-inflammatory

B. Diffusa contains bioactive compounds like flavonoids, phenolic compounds, and alkaloids that inhibit the production and release of pro-inflammatory mediators, including cytokines and prostaglandins, reducing cellular inflammation [21]. It also interferes with inflammatory signaling pathways, notably by inhibiting the activation of nuclear factor-kappa B (NF-κB) [22]. *B. Diffusa* also inhibits the activity of inflammatory enzymes such as

cyclooxygenase (COX) and lipoxygenase (LOX), blocking the production of inflammatory mediators [23]. Furthermore, it modulates the immune response by regulating immune cells and balancing the production of anti-inflammatory and pro-inflammatory cytokines [24]. Collectively, these mechanisms contribute to *B. Diffusa's* therapeutic potential in alleviating inflammation-related conditions [25]. Karwasra *et al*. conducted an immunohistochemical analysis to evaluate the impact of *B. Diffusa* on various inflammatory and anti-inflammatory markers, angiogenesis, and key regulatory proteins such as Nrf-2 and NF-κB. Results indicated a significant dose-dependent reduction in inflammation and oxidative stress markers with *B. Diffusa* treatment. The 200 mg/kg dose showed notable reductions in inflammation and joint dysfunction. Overall, *B. Diffusa* roots demonstrated the ability to attenuate paw edema, inflammation, and bone damage by inhibiting pro-inflammatory mediators, Nrf-2, and NF-κB-mediated cytokine production [26]. In another study, Mathias *et al.* evaluated the anti-inflammatory properties of aqueous extracts of *B. Diffusa.* The study involved pre-incubating cells with the extracts before stimulating them with TNFα or arachidonic acid (AA) to observe their effects on inflammatory signaling. The results showed that *B. Diffusa* inhibited TNFα-induced mRNA expression of IL-6, IKBA, and COX2, as well as IκBα protein degradation and p65 phosphorylation. Similarly, AA-induced mRNA expression of COX2, ALOX5, and IL-6, and p65 phosphorylation were also inhibited by these extracts. Overall, the study suggested that *B. Diffusa* extracts have potential to inhibit intracellular inflammatory signaling pathways demonstrating their potential as anti-inflammatory agents [27].

4. Anti-oxidant activity

B. Diffusa scavenges free radicals and neutralizes reactive oxygen species, preventing oxidative damage to cellular components [28]. The plant also enhances the activity of endogenous antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, which detoxify reactive oxygen species (ROS) and maintain cellular redox balance [29]. Some phytochemicals in *B. Diffusa* chelate metal ions inhibit their catalytic activity in generating reactive oxygen species thereby preventing oxidative stress-induced damage [30]. The plant's constituents inhibit lipid peroxidation by scavenging lipid peroxyl radicals [31]. Furthermore, *B. Diffusa* enhances the expression and activity of phase II detoxification enzymes like glutathione S-transferase and quinone reductase,

protecting cells from oxidative damage [32]. Overall, these mechanisms contribute to the plant's protective effects against oxidative stress-related diseases and aging processes. Sudheer and Nagella evaluated the antioxidant activities such as radical scavenging, metal chelating, and reducing power of *B. Diffusa.* The results indicated the superior antioxidant potential. Radical scavenging activity was high at 91.1%, while metal chelating activity was recorded at 74%. These findings provided a basis for its potential application in antioxidant therapy [33]. Akhter *et al.* focused on the antioxidant, DNA-protective, and α-amylase inhibitory properties of the plant's root extract. The methanol root extract showed antioxidant power and protective activity against oxidative DNA damage compared to ethanol and aqueous extracts. It also exhibited strong α-amylase inhibitory properties. The methanol extract further processed to isolate a potent antioxidant and α-amylase inhibitory fraction. This isolated compound demonstrated similar antioxidant and α-amylase inhibitory activities as the crude extract. The study indicated potential health benefits of *B. diffusa* in combating oxidative DNA damage and its α-amylase inhibitory activity [34].

5. Anti-fibrinolytic activity

B. Diffusa inhibits the conversion of plasminogen to plasmin, reducing fibrinolysis and helping maintain clot stability. It also directly inhibits the activity of plasmin, preserving clot integrity and preventing premature clot breakdown. Additionally, it influences various components of the fibrinolytic system, such as tissue plasminogen activator and plasminogen activator inhibitor-1, regulating the balance between clot formation and dissolution [35]. The antioxidant and anti-inflammatory properties of *B. Diffusa* indirectly contribute to its anti-fibrinolytic activity by reducing oxidative stress and inflammation, which can promote fibrinolysis [36]. Overall, these mechanisms contribute to the stabilization of blood clots and prevention of excessive fibrinolysis [35]. Juneja *et al.* investigated the wound healing potential of *B. Diffusa* leaf methanol extract (ME) through *in-vitro* and *in-vivo* assays. The MTT assay result indicated that ME treatment enhanced human keratinocyte cell viability and migration compared to untreated and CE-treated groups. Further, *in-vivo* wound assays in rat models demonstrated that topical application of ME reduced wound area by 91% on the 14th day as compared to the control group (22%) [37].

6. Anti-cancer activity

B. Diffusa is rich in bioactive compounds that cause apoptosis of cancer cells and block their proliferation through cell cycle arrest. Antioxidative properties of the plant are because of the flavonoids and phenolic compounds present in the plant that reduce oxidative stress and stop carcinogenesis. It is also anti-inflammatory by inhibiting the production of pro-inflammatory cytokines which potentially suppresses tumor growth and metastasis. It also represses tumor angiogenesis, thus hindering tumor growth and metastasis by starving tumors of blood. Additionally, it pulls out immunomodulatory properties that strengthen the body's immune response against cancer cells by activating immune cells like T cells, natural killer cells, and macrophages [38,39]. Saraswati *et al.* investigated the effects of punarnavine on VEGF-A expression using RT-PCR, Western blotting, and ELISA. *In-vitro* experiments showed that punarnavine significantly inhibited endothelial cell migration, invasion, and capillary structure formation of HUVECs. Additionally, punarnavine inhibited MMP-2 and MMP-9 expression in HUVECs. *In-vivo* studies using sponge implant angiogenesis assay demonstrated punarnavine's ability to inhibit neovascularization. Furthermore, in an Ehrlich ascites carcinoma tumor model, punarnavine treatment led to a dose-dependent decrease in ascitic fluid volume by 60.94% and tumor volume by 86.40%. These findings highlight the potent anti-angiogenic activity of punarnavine and suggest its potential for developing therapeutic protocols for cancer treatment [40].

7. Anti-diabetic activity

B. diffusa increases insulin sensitivity and promotes glucose uptake by peripheral tissues thus regulating glucose metabolism. It also suppresses gluconeogenesis, the process of glucose synthesis from non-carbohydrate precursors, thus reducing blood sugar levels [41]. Moreover, it improves pancreatic activity by intensifying insulin secretion by pancreatic beta cells, thus, influencing pancreatic health positively. *B. diffusa's* strong antioxidant and anti-inflammatory capabilities shield pancreatic beta cells from damage and improve insulin sensitivity by lowering oxidative stress and inflammation. Moreover, it regulates lipid metabolism by decreasing serum lipids and improving lipid profiles, solving dyslipidemia, a metabolic problem frequently observed in diabetes [42]. Alam *et al.* evaluated the potential of *B. diffusa* methanolic extract as a treatment for diabetes induced in male Wistar rats. The extract was rich in phenolic and flavonoid content that demonstrated significant free radical-scavenging activity. When

administered to diabetic rats, extract improved various health parameters such as blood glucose levels, plasma enzyme levels, weight loss, total protein, serum insulin, and liver glycogen levels. Additionally, it restored the activity of antioxidant enzymes [43]. In another study, Jayachitra and Janani evaluated the anti-breast cancer activity of *B. diffusa* on $HepG_2$ cell lines. The MTT assay of result of the study indicated that *B. diffusa* treatment showed decrease in % cell viability by 5-fold as that of untreated group. The extract also induced DNA fragmentation and apoptosis in the cancer cells. Overall, study concluded that methanolic extract of *B. diffusa* has potent anticancer activity against human breast cancer cells [44].

8. Immuno-modulatory activity

B. diffusa possesses immuno-modulatory activity in several ways. It controls the synthesis of cytokines, inhibiting pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-alpha, while stimulating the secretion of anti-inflammatory cytokines like interleukin-10, assisting in regulating the immune responses and inflammation The extracts of this plant stimulate the activity of different immune cells such as macrophages and T lymphocytes thereby improving their ability to identify and destroy pathogens and cancerous cells. *B. diffusa* further modulates the immune signaling pathways by inhibiting the nuclear factor-kappa B pathway and consequently reducing the inflammatory responses. Also, it increases phagocytic activity in macrophages and other phagocytic cells, facilitating pathogen clearance and immune defence [45]. Aher *et al.* explored the immunostimulatory effects of punarnavine alkaloid (PA) isolated from the root of *B. Diffusa* Linn. PA treatment led to an increase in foot pad thickness in Delayed Type Hypersensitivity (DTH) studies indicating influx of mononuclear cells. Additionally, PA enhanced phagocytic activity, elevated humoral immune response confirmed by Plaque Forming Assay (PFA) and increased the number of α-esterase positive cells and bone marrow cellularity. Real-time PCR studies showed increased expression of IL-7, IL-10, IL-12a, and IL-12b mRNA genes with PA treatment. These findings suggest that PA could be a potent immunomodulatory agent without toxic effects [46,47].

9. Immuno-suppressive activity

It modulates the function and activity of various immune cells, including T lymphocytes, B lymphocytes, natural killer (NK) cells, and dendritic cells, downregulating their proliferation and

activation. Secondly, it controls cytokine production reducing pro-inflammatory cytokines such as interleukin-2 (IL-2), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha) while increasing anti-inflammatory cytokines, for instance, interleukin- The thirdly, *B. diffusa* interferes with cellular signaling pathways of the immune system, particularly the NF-κB pathway, preventing activation of the immune cells and production of cytokines. Furthermore, it promotes apoptosis in activated immune cells and shows anti-oxidant properties, scavenging free radicals and lowering oxidative stress which in sum leads to its immunosuppressive effect [2].

10. Anti-lymphoproliferative activity

B. diffusa hinders the deficiency of lymphocytes which is a type of white blood cell in different ways. Secondly, it keeps T cells and B cells from proliferating without it. Another way is that it triggers a process named apoptosis, or the self-destruction of pathologically abnormal or cancer cells. Additionally, it breaks down cell division to make white blood cells slow to reproduce. Also, it lowers inflammation and oxidative stress of the cells which are catalysts of tumor growth. Generally, *B. diffusa* moderates the growth of lymphocytes by assisting the immune function, leading to the death of abnormal cells and slowing down the amount of cell multiplication [48].

11. Anti-bacterial activity

B. diffusa contains bioactive compounds that can disrupt the integrity of bacterial cell membranes. These compounds interact with the lipid bilayer of the bacterial cell membrane causing destabilization and leakage of cellular contents which ultimately leads to bacterial cell death. Some constituents of *B. diffusa* interfere with the synthesis of bacterial cell walls by targeting enzymes involved in peptidoglycan synthesis or disrupting the assembly of cell wall components thereby inhibiting bacterial growth and impairing cell wall integrity. Furthermore, it also interferes with bacterial protein synthesis by binding to ribosomes or other components of the protein synthesis machinery thereby hindering bacterial growth and replication [49]. *B. diffusa* disrupts various metabolic pathways essential for bacterial survival. It interferes with processes such as energy production nucleic acid synthesis, or amino acid metabolism, leading to metabolic dysfunction and ultimately bacterial cell death. Additionally, it also induces the production of ROS within bacterial cells which can cause oxidative damage to bacterial DNA, proteins, and lipids leading to cellular dysfunction and death. Lastly,

some constituents of *B. diffusa* interfere with bacterial virulence factors, such as toxins or adhesion molecules. By inhibiting the expression or activity of these virulence factors *B. diffusa* reduces the pathogenicity of bacteria and enhances the host's ability to combat infections. Overall, these diverse mechanisms contribute to the broad-spectrum antibacterial effects of Boerhavia diffusa against various bacterial pathogens [50]. Adefokun *et al.* evaluated the *in-vivo* anti-plasmodial activity of the crude methanolic root extract of *B. diffusa* against *Plasmodium berghei* NK 65, a chloroquine-resistant strain, using suppressive, curative, and prophylactic tests.

Albino mice were randomly assigned to different groups and administered varying doses of the extract, chloroquine, or nifedipine. Results demonstrated significant antimalarial activity across all dose levels and models, with the optimal activity observed at the lowest dose (125 mg/kg) in suppressive and prophylactic models, and at day 10 in the curative model. Additionally, the extract exhibited antipyretic effects, particularly notable at the 125 mg/kg dose. Furthermore, at 500 mg/kg, the extract displayed superior efficacy in lowering plasma calcium levels compared to the positive control, nifedipine.

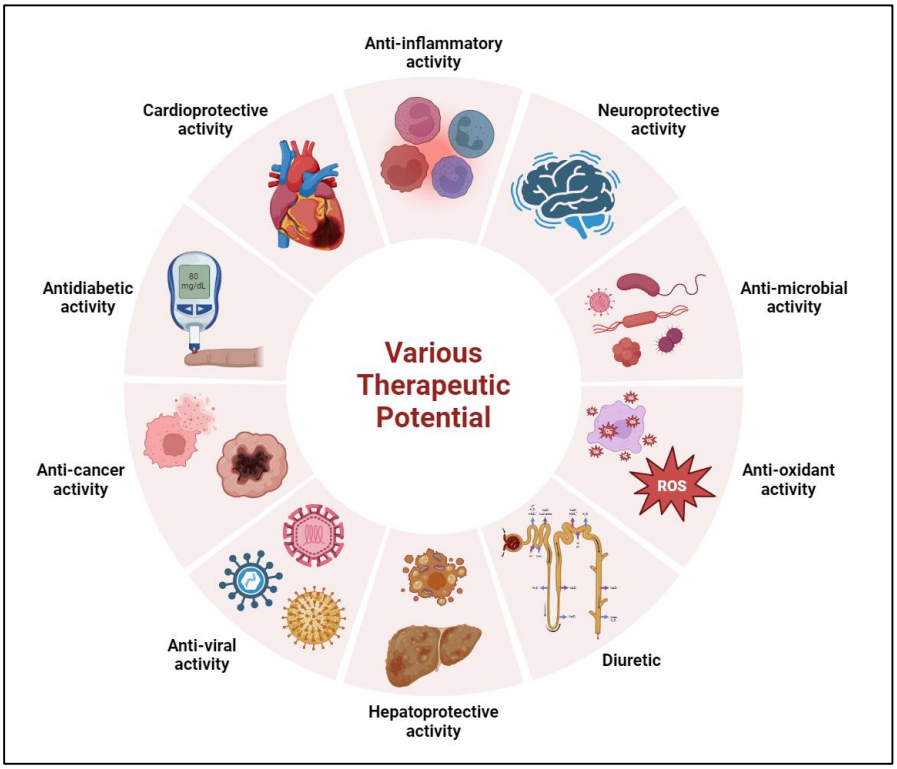

Figure 1: Various therapeutic potential of *B. diffusa*

These findings support the traditional use of *B. diffusa* in malaria and fever treatment, underscoring its potential therapeutic value [51]. In another study, Sobi et al. examined antibacterial properties of *B. diffusa* leaf (BDL) loaded formulated AgNPs exhibited antibacterial activity against Gram-negative pathogen *Salmonella typhi*, with a higher zone of inhibition (23 mm) compared to *Staphylococcus aureus* (21 mm) at higher concentrations of BDL extract. The biosynthesis method offers advantages over chemical reduction synthesis, including biosafety, eco-friendliness, and non-toxicity to the environment [52].

Future Perspective

The future of *B. diffusa* in medicine looks promising. Future research will concentrate on investigating its therapeutic effects, experimental clinical trials for it efficacy and safety, and establishment of the standardized formulations with quality control. New systems like nano-formulations and targeted delivery systems are being developed to increase bioavailability and efficacy. Moreover, different herbs, drugs and therapies in combination are likewise being examined. Various attempts are being made to identify and isolate the bioactive components of Punarnava, and its vast potential in new drug therapy is being harnessed comprehensive safety testing is conducted for its safe long-term use. Collaboration with traditional healers and indigenous communities to maintain the traditional knowledge about Punarnava is continuously carried out.

Conclusion

B. diffusa is a medicinal plant known for its wide range of bioactive compounds and pharmacological properties. It has diuretic, hepatoprotective, anti-inflammatory, antioxidant, anti-fibrinolytic, anti-cancer, anti-diabetic, immunomodulatory, immunosuppressive, anti-lymphoproliferative, and antibacterial effects. These effects are achieved through various mechanisms of action, including modulating cellular signaling pathways, regulating enzyme activity, influencing cytokine production, enhancing antioxidant and detoxification systems, inducing apoptosis, inhibiting angiogenesis, and disrupting bacterial cell membranes and metabolism. The plant's therapeutic potential has been demonstrated in various in vitro and in vivo models of diseases such as nephrotic syndrome, liver damage, rheumatoid arthritis, oxidative DNA damage, malaria, and cancer.

Conflict of Interest

None

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