RESEARCH PAPER

Herbal product Development Perspective of Boerhavia diffusa: Challenges in Standardization and Regulation

Nasim Sahin[1], Raj Kamal[1], Thakur Gurjeet Singh[1], Sonia Dhiman[1*], Harish Dureja[2]

[1]Chitkara College of Pharmacy, Chitkara University, Punjab, India

[2]Department of Pharmaceutical Sciences, MDU, Rohtak, Haryana

* Corresponding Author: Dr. Sonia Dhiman, Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab. Email: Sonia.dhiman@chitkara.edu.in

ABSTRACT

Boerhavia diffusa (Punarnava) is a well-known medicinal plant that is characterized by a variety of pharmacological effects and a wide range of applications in the systems of traditional medicine. The current review thoroughly discusses the phytochemical, ethnopharmacological, and therapeutic potential of B. diffusa, diuretic, hepatoprotective, anti-inflammatory, anti-oxidant, anti-fibrinolytic, anti-cancer, anti-diabetic, immunomodulatory and anti-microbial effects. These biological actions are mediated by a number of pathways including the adjustment of cellular signaling pathways, prevention of inflammatory mediates, improvement of antioxidant defenses, and control of apoptosis and angiogenesis. Besides its therapeutic importance, the review has also pointed out the new evolving surveys that have been developed in the experimental and preclinical research on its effectiveness. Moreover, the changing regulatory systems of the herbal products in the key areas of the world are reported in a specific section with the focus on the issues related to the standardization, quality control, and clinical validation. Even though its medicinal potential is promising, the problem of inconsistency in phytochemical composition and absence of regulatory measures to harmonize it are significant challenges to the global acceptance of the product. In general, B. diffusa is a promising natural resource with massive potential to develop as a source of the future drugs, and therefore, the research should be further developed, clinically validated and regulated to guarantee the safety and efficacy of its therapeutic benefits.

Keywords: Boerhavia diffusa, medicinal plant, bioactive compounds, therapeutic potential.

How to cite this article: Sahin N, Kamal R, Singh TG, Dhiman S, Dureja H. Herbal product Development Perspective of Boerhavia diffusa: Challenges in Standardization and Regulation. Int J Drug Deliv Technol. 2026;16(15s): 826-839. DOI: 10.25258/ijddt.16.15s.93

1. 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]. 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].

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
	Stomachache, anemia, cough, cold
	Snake and rat bites antidote, contraceptives
Whole plant, seeds	Nutritional use, lactation enhancement

2. Various Therapeutic Potentials of *B. Diffusa*

2.1 Diuretic

B. Diffusa has the ability to produce a lot of urine and sodium loss which is a symptom of being a diuretic agent [9]. The plant extract also increases the renal blood flow and glomerular filtration rate which increases the amount of urine produced, and prevents sodium and water reabsorption in the renal tubules, which further increases diuresis [10]. It also balances the electrolytes by stopping the excessive loss of potassium and other important electrolytes, it maintains the electrolyte balance as well [11]. In addition, B. Diffusa too displays renal protective effect, and it has antioxidant and anti-inflammatory effects that could guard the kidneys against oxidative damage and inflammation [12]. As Sahu et al. explored the therapeutic potential of phytochemicals in Boerhavia diffusa (B. diffusa) in treating mutant forms of the nephrin protein that causes nephrotic syndrome type 1, a disease that is not treated through conventional methods. They used computational tools like virtual screening and molecular dynamics simulations and identified seven bioactive compounds in B. diffusa, out of which boeravinone M and boeravinone E exhibited good binding properties in the wild type and mutant model of the Ig4 domain of the nephrin protein. Hydrate-ligand docking indicated an improved binding activity of boeravinone M and boeravinone E with the mutant model, which can be explained by a more accurate estimation of the water molecule effects. The simulations performed through the molecular dynamics hinted boeravinone E as a possible inhibitor of NPHS1 because it has the lowest short-range interaction energies and the stability and effects of the mutant nephrin protein are well modulated. The results give boeravinone E as a potential therapeutic agent in nephrotic syndrome type 1, and this provides information on the use of natural products in treating genetic mutations in chronic illnesses [13]. On the same note, the diuretic activity of alcohol extracts made of the stem and leaves of Boerhaavia diffusa were tested in normal rats. Experimental rats were orally given the extracts of 150 and 300mg/kg. A standard drug that was used was the furosemide, 20mg/kg. Urine volume, sodium and potassium content were used to assess the diuretic effects. AEBD produced a great amount of urine in comparison to the control group, as well as sodium excretion. Such effects were similar to the ones with the standard drug. Thus, the paper can be characterized as the presentation of the quantitative data which confirms the idea of the traditional use of Boerhaavia diffusa as the diuretic agent [14].

2.2 Hepatoprotective

B. Diffusa controls activity of hepatic enzymes in process of detoxification and biomolecule synthesis thus improving liver performance [15]. It also activates the regeneration and healing mechanisms of hepatocellular regeneration, hepatocytes proliferation and liver proteins synthesis [16]. Also, it contributes to the structural and functional integrity of hepatic cells, preventing the apoptosis and necrosis caused by diverse hepatotoxic agents [17, 18]. In general, hepatoprotective activity of B. Diffusa is due to its antioxidant, anti-inflammatory, enzyme-modulating, regenerative, and cytoprotective activity. Thajudeen et al. tested the hepatoprotective behavior of B. Diffusa against cytotoxicity caused by GalN on the HepG2 cell lines. The silymarin hepatoprotective activity was 78.7% and 84.34% at 100 and 200 µg/mL respectively and caffeic acid hepatoprotective activity was 46.17 and 52.34% at 100 and 200 µg/mL respectively and boeravinone B hepatoprotective activity was 40.89 and 62.21 at 100 and 200 µg It is worth noting that, boeravinone B and caffeic acid were found to be hepatoprotective effects, in comparison to standard silymarin. These findings give credence to the conventional application of B. Diffusa as a useful functional food to the human being health [19]. Another study by Dey et al. determined the hepatoprotective implication of B. Diffusa against alcohol-induced liver injuries. When HepG2 cells were exposed to 120mM ethanol (48 hours-longs) toxicity was induced (it was significant, about 42%), B. Diffusa treatment had a dose-dependent protection

against ethanol induced cell death, and its effect was stronger than single extracts. In addition to that, B. Diffusa also exhibited a strong antioxidant potential in the DPPH assay. The administration of BV-7310 (250 and 500 mg/kg body weight) as an oral dose prevented the body weight loss induced by alcohol, and markedly improved increased liver enzyme levels over the control group in a rat model of hepatitis induced by repetitive alcohol (40) and carbon tetrachloride (CCl4) dosing. The results mentioned above point to the effectiveness of B. Diffusa in avoiding alcohol-induced toxicity in in vitro and in vivo models, which indicates its possible therapeutic use in ALD and other diseases leading to liver toxicity [20].

2.3 Anti-inflammatory

B. Diffusa has bioactive compounds such as flavonoids, phenolic compounds and alkaloids, which suppress the synthesis and release of the pro-inflammatory compounds such as cytokines and prostaglandins that decrease cellular inflammation [21]. It also disrupts inflammatory signaling pathways, in particular, it suppresses the activation of nuclear factor-kappa B (NF-κB) [22]. *B. Diffusa* also suppresses the activity of the inflammatory enzymes, cyclooxygenase (COX) and lipoxygenase (LOX), which inhibits the generation of the inflammatory mediators [23]. Moreover, it regulates the immune response by balancing the immune cells and the generation of the anti-inflammatory and pro-inflammatory cytokines [24]. All these mechanisms help to increase the therapeutic potential of B. Diffusa in the treatment of inflammation-related conditions [25]. To determine the effect of B. Diffusa on different inflammatory and anti-inflammatory markers, angiogenesis, and several regulatory proteins including Nrf-2 and NF-kB, Karwasra et al. used an immunohistochemical analysis to examine the effect. Findings showed that there was a great dose-dependent decrease in biomarkers of inflammation and oxidative stress with B. Diffusa treatment. Inflammation and joint dysfunction in the 200 mg/kg dose were significantly reduced. In general, Boerhavia diffusa roots had the capacity to reduce paw edema, inflammation, and bone destruction by blocking the activity of pro-inflammatory mediators, Nrf-2, and NF-kB-mediated cytokine production [26]. Mathias et al. performed another study to determine the anti-inflammatory effect of aqueous extracts of B. Diffusa. The experimental design of the study was that, pre-incubation of cells with the extracts was followed followed by stimulating them with either TNFalpha or arachidonic acid (AA) to see the effect of the extracts on inflammatory signalling. These findings indicated that B. Diffusa stopped the TNFalpha-induced mRNA gene expression of IL- 6, IKBA and COX2, and IkB alpha protein degradation and p65 phosphorylation. Equally, these extracts also inhibited AA-induced expression of COX2, ALOX5 and IL-6 mRNAs and phosphorylation of p65. In general, the research proposed that extracts of B. Diffusa have the potential to suppress intracellular inflammatory signaling pathways proving their possible anti-inflammatory effect [27].

2.4 Anti-oxidant activity

B. Diffusa removes free radicals and reactive oxygen species and inhibits oxidative cellular damage [28]. The plant also increases the activity of endogenous antioxidant enzymes including superoxide dismutase, catalase and glutathione peroxidase that neutralize reactive oxygen species (ROS) and restore redox balance within the cell [29]. Phytochemicals within B. Diffusa chelate metal ions inhibit their catalytic action in the production of reactive oxygen species hence avoiding the damages caused by the oxidative stress [30]. The constituents of the plant prevent the lipid peroxidation by scavenging lipid peroxyl radicals [31]. In addition, B. Diffusa increases the activity and expression of phase II detoxification enzymes, such as glutathione S-transferase and quinone reductase which cells are safer to oxidative damage [32]. Altogether, the mechanisms play a role in the protective effect of the plant against oxidative stress-associated illnesses and aging. Sudheer and Nagella assayed the antioxidant properties of B. Diffusa antioxidant including radical scavenging, metal-binding, and reducing. The findings had shown the high antioxidant potential. The radical scavenging activity was recorded high at 91.1 and the metal chelating activity was recorded at 74. These results helped as a source of its possible use in antioxidant treatment [33]. Akhter et al. gave their attention to antioxidant, DNA-protective and 0 -amylase-inhibitory activity of the root extract of the plant. Methanol root extract exhibited antioxidant activity and preventive effect on oxidative DNA damages than the ethanol and aqueous extracts. It also had high alpha-amylase level of inhibition. The extract that was further processed to come up with a powerful antioxidant and a-amylase inhibitory fraction. This single compound had the same antioxidant and a-amylase inhibitory properties as the crude extract. The paper suggested possible health positive effects of B. diffusa in fighting against

oxidative DNA damage and its alpha-amylase inhibitory capacity [34].

2.5 Anti-fibrinolytic activity

B. Diffusa revents the plasminogen to plasmin conversion, which would cause fibrinolysis and aid in the stability of the clot. It also has a direct inhibition effect of plasmin and maintains the integrity of the clot and no early breakdown of the clot. It also affects numerous elements of the fibrinolytic system including tissue plasminogen activator, plasminogen activator inhibitor-1, and balances the processes of clot formation and dissolution [35]. The anti-fibrinolytic effect of B. Diffusa is an indirect effect of its antioxidant and anti-inflammatory effects in the reduction of oxidative stress and inflammation that may induce fibrinolysis [36]. All in all, these processes aid in stabilization of the blood clots and inhibition of overfibrinolysis [35]. Juneja et al. examined the wound healing capacity of Boerhavia diffusa leaf methanol extract (ME) by conducting in-vitro and in-vivo tests. The outcome of the MTT assay showed that the ME treatment improved the human keratinocyte cell viability and migration in comparison to the untreated and CE-treated cells. Moreover, topical exposure of ME to rat model wound lesions had in-vivo wound assays that showed that the wound area had decreased 91 per cent in the 14^{th} day in comparison to the control group (22 per cent) [37].

2.6 Anti-cancer activity

B. Diffusa ontains lots of bioactive compounds which result in cancer cell apoptosis and inhibition of their proliferation by arresting the cell cycle. The presence of flavonoids and phenolic compounds in the plant which lower the oxidative stress and prevent carcinogenesis makes the plant have antioxidative properties. It is also anti-inflammatory in that it prevents the formation of pro-inflammatory cytokines which may prevent the growth and metastasis of tumors. It also suppresses the angiogenesis of tumor hence preventing growth and metastasis of tumors by depriving the tumors of blood. It also removes immunomodulatory effects that enhance the immune reaction of the body in fighting cancer cells by promoting the functions of immune cells such as T cells, natural killer cells, and macrophages [38, 39]. Saraswati *et al.* examined the effects of punarnavine on the VEGF-A expression by RT-PCR, Western blot and ELISA. In vitro studies revealed that punarnavine was an important inhibitor of endothelial cell migration, invasion and capillary structure of HUVECs. Punarnavine, also, suppressed the MMP-2 and MMP-9 expression in HUVECs. Angiogenesis studies in vivo with sponge implant assay proved punarnavine to be an inhibitor of neovascularization. Moreover, punarnavine therapy in an Ehrlich ascites carcinoma tumor model resulted in the 60.94% and 86.40% reduction in the volume of ascitic fluid and tumor volume respectively. These results point to the strong anti-angiogenic property of punarnavine and give a clue of the possibility of its use in developing therapeutic regimes in the treatment of cancer [40].

2.7 Anti-diabetic activity

B. diffusa enhances the insulin sensitivity and facilitates glucose uptake by the peripheral tissues hence controlling the metabolism of glucose. It also inhibits the gluconeogenesis which is the formation of glucose out of non-carbohydrate precursors thereby lowering the sugar levels in the blood [41]. In addition, it enhances the pancreas as it enhances the secretion of insulin in the pancreatic beta cells hence, affecting the health of the pancreas positively. The use of B. diffusa with its potent antioxidant and anti-inflammatory properties protects the pancreatic beta cells against damage and enhances insulin sensitivity by reducing oxidative stress and inflammatory processes. In addition, it controls lipid metabolism through reduction of serum lipids and lipid profiling, which resolves dyslipidemia, a metabolic complication commonly seen in diabetes [42]. Alam *et al.* tested the possibility of using B. diffusa methanolic extract in the treatment of diabetes induced on male Wistar rats. The extract was highly phenolic and flavonoid which showed good free radical-scavenging ability. Extract was effective when it was applied on diabetic rats by improving different health parameters like blood glucose, plasma enzyme level, weight loss, total protein, serum insulin, and liver glycogen. Also, it reinstated antioxidant enzyme activity [43]. Jayachitra and Janani used B. diffusa to determine the anti-breast cancer activity on the HepG2 cells lines. According to the MTT test of study outcome, the treatment of B. diffusa revealed that the level of cell viability of the percentage dropped by 5 times as compared to the control. The extract has also caused apoptosis and DNA fragmentation in the cancer cells. In general, the research established that B. diffusa methanolic extract exhibits a strong anticancer property against human breast cancer cells [44].

2.8 Immuno-modulatory activity

B. diffusa has immuno-modulatory activity in a number of ways. It regulates synthesis of cytokines, inhibits pro-inflammatory cytokine, including

interleukin-6 and tumor necrosis factor-alpha, and induces production of anti-inflammatory cytokines, including interleukin-10, helping the body control the immune responses and inflammation The extracts of this plant stimulate the activity of various immune cells including the macrophages and T lymphocytes thereby enhancing their ability to recognize and destroy the pathogens and cancerous cells. B. diffusa also alters the immune signaling pathway through suppression of nuclear factor-kappa B pathway, and subsequently, the inflammatory reactions. Also, it enhances phagocytic ability of the macrophage and other phagocytic cells which helps to eliminate pathogens and protect the immune system [45]. Aher *et al.* studied the immunostimulatory properties of punarnavine alkaloid (PA) that is isolated in the root of Boerhaavia diffusa Linn. The use of PA treatment actually resulted in the thickening of the foot pads in Delayed Type Hypersensitivity (DTH) experiments that detected the influx of mononuclear cells. Also, PA increased phagocytic activity, humoral immune response as shown through Plaque Forming Assay (PFA) and it has increased the number of α-esterase positive cells and bone marrow cellularity. The PCR expression studies revealed the enhanced IL-7, IL-10, IL-12a, and IL-12b mRNA gene expression following PA treatment. These results indicate that PA may be a powerful immunomodulatory agent without any toxicity side effects [46, 47].

2.9 Immuno-suppressive activity

It regulates the role and performance of different immune cells, such as T lymphocytes, B lymphocytes, natural killer (NK) cells, and dendritic cells, suppressing their growth and activation. Thirdly, B. diffusa alters the cellular signaling pathways of immune system, especially the NF-2 pathway, which inhibits the activation of the immune cells and cytokine generation. In addition, it facilitates the apoptosis of stimulated immune cells and has anti-oxidant effects, scavenging free radicals and reducing oxidative stress that collectively results in its immunosuppressive effect [2].

3.10 Anti-lymphoproliferative activity

B. diffusa inhibits the lymphocyte deficiency that is a form of white blood cell in various ways. Secondly, it prevents the proliferation of T cells and B cells without it. The other mechanism is that it induces the process of apoptosis, or self-destruction of pathologically abnormal or cancer cells. It also disaggregates cell division to cause a slow replication of white blood cells. It also reduces inflammation as well as oxidative stress of cells that promote the growth of tumors. In most cases, B. diffusa regulates the proliferation of lymphocytes by supporting the immune system whereby abnormal cells are killed and the extent of cell division is reduced [48].

3.11 Anti-bacterial activity

B. diffusa has bioactive compounds, which are able to interfere with cell membranes of bacteria. The compounds react with the lipid bi-layer of the bacterial cell membrane resulting to destabilization and cellular contents leakage that eventually causes cell death in bacteria. Certain parts of B. diffusa inhibit the synthesis of bacterial cell walls by attacking enzymes that are involved in the synthesis of peptidoglycan or by disrupting the formation of cell wall components and thus inhibiting bacterial growth and cell wall integrity. In addition, it also disrupts the bacterial protein synthesis by attaching to the ribosomes or other part of the protein synthesis apparatus thus inhibiting bacterial growth and replication [49]. *B. diffusa* interferes with a number of metabolic pathways that support survival in bacteria. It disrupts processes like the energy production nucleic acid synthesis or metabolism of amino acids causing metabolic dysfunction and eventual death of bacteria cells. Also, it also triggers the formation of ROS in bacterial cells that may cause oxidative stress on bacterial DNA, proteins, and lipids causing dysfunction and death of bacterial cells. Finally, there are a handful of constituents of B. diffusa that disrupt bacterial virulence factors, including toxins or adhesion molecules. The prevention of these virulence factors expression or activity of B. diffusa makes the bacteria less pathogenic and allows the host to better anti-infective strategies. All these mechanisms, in general, lead to the broad-spectrum antibacterial action of Boerhavia diffusa against different 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. 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 silver nanoparticles (AgNPs). The 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].

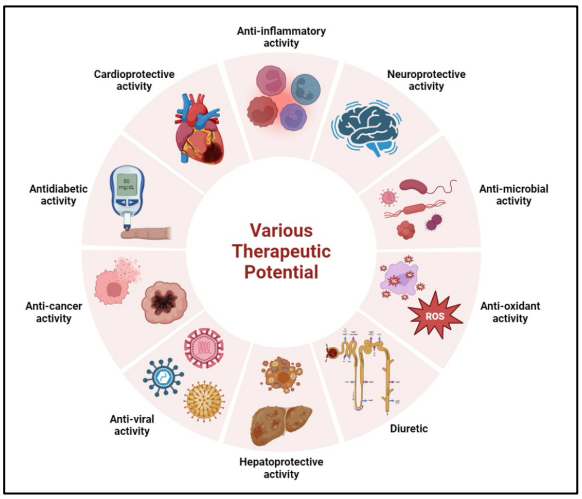

Figure 1: Various therapeutic potentials of *B. diffusa*

3. Nanotechnology-Based Applications of *Boerhavia diffusa*

Recent advancements in green nanotechnology have highlighted the potential of *B. diffusa* as a versatile biological source for the synthesis of diverse nanomaterials with significant biomedical, environmental, and industrial applications [53, 54]. The plant's rich phytochemical profile, including flavonoids, phenolics, and glycosides, plays a crucial role in the reduction and stabilization of nanoparticles [55]. Various studies have explored the synthesis of metallic (Ag, Au, ZnO, Se), bimetallic (Co–Ni), and hybrid nanocomposites derived from *B. diffusa*, demonstrating a wide spectrum of functional properties such as antimicrobial, antioxidant, anticancer, anti-inflammatory, wound healing, photocatalytic, and bioenergy-enhancing activities [56]. The diversity in nanoparticle types, synthesis approaches (plant extract vs callus-mediated), particle size, and applications reflects the adaptability of this plant in nanotechnology-driven research. The table 2 summarizes key studies, synthesis methods, characterization features, and major applications of *B. diffusa*-mediated nanomaterials.

Table 2: Comparative summary of *B. diffusa*-mediated nanomaterials highlighting synthesis methods, physicochemical characteristics, and diverse applications.

Author (Year)	Nanomaterial / System	Synthesis Method	Particle Size	Key Characterization	Major Findings / Applications	Ref
Renu et al. (2024)	$CoFe_2O_4$-CDs@Boehmite nanocomposite	Hydrothermal (biomass-derived carbon dots)	Not reported	Structural & optical analysis	Fluorescent sensing (MP, UO_2^{2+}), photocatalysis (92% TC degradation)	[57]
Vijay Kumar et al. (2013)	Silver nanoparticles (AgNPs)	Plant extract-mediated green synthesis	~25	UV–Vis, XRD, SEM, TEM, FTIR	Antibacterial activity against fish pathogens	[58]
James et al. (2025)	Silver nanoparticles (AgNPs)	Green synthesis (plant extract)	30–40	UV–Vis, XRD, FESEM, EDAX	Antioxidant (78.57%), anticancer (HeLa cells)	[59]
Bibi et al. (2026)	Gold nanoparticles	Phyto synthesis (aque	~53	UV–Vis, FTIR, XRD,	Antibacterial, antifu	[60]

	(AuNPs)	ous extract)		SEM, DLS	ngal, antioxidant (~80 %), anticancer	
Sushma et al.	Selenium nanoparticles (SeNPs)	Plant extract-mediated synthesis	Not reported	UV–Vis	Antioxidant, anti-inflammatory	[61]
Sudheer et al. (2025)	Silver nanoparticles (AgNPs)	Callus-mediated green synthesis	~9	UV–Vis, SEM, FTIR, XRD, EDX	Dye degradation, antimicrobial activity	[62]
Patil et al. (2023)	GRP-loaded AgNPs nanogel	Chemical reduction + bioactive loading	<50	SPR, FTIR, Zeta potential	Enhanced wound healing (in vivo)	[63]
Kodhaiyolii et al. (2019)	Bimetallic Co–Ni nanoparticles	Plant extract-mediated synthesis	<10	FTIR, GC–MS, HR-TEM	Biohydrogen & bioethanol production	[64]
Jalan et al.	Zinc oxide nanoparticles (ZnO NPs)	Plant-mediated synthesis	Not reported	Spectrophotometric assay	Anti-inflammatory activity (protein denaturation inhibition)	[65]

4. Regulatory Framework of Herbal Products Across Major Global Regions

The use of herbal medicine has been widely accepted all around the world because of their varied therapeutic capability, safety image and the substantial ground in the domain of traditional medicine systems [66]. Nevertheless, the regulatory framework used in herbal products is quite different across various nations irrespective of their high usage. Such differences are due to the cultural practices, health care priorities, and the extent of scientific validation [67]. Lack of a globally harmonized regulatory framework has resulted in inconsistency of quality, safety and efficacy thus rendering global acceptance and commercialization of herbal products challenging [68, 69]. Herbal products in the United States are mostly regulated as dietary supplements through Dietary Supplement Health and Education Act (DSHEA) of 1994 [70]. In this model, manufacturers have the duty to provide their products with the correct safety and labeling and pre-market approval is not normally necessary. This provides the possibility of quick market penetration but also creates an issue of inconsistency in quality and insufficient clinical proof. Nevertheless, where the herbal products are meant to have therapeutic usage, then it can be developed under the botanical drug pathway which entails stringent regulatory review i.e. clinical trials [71, 72]. Such a two-sided regulation indicates flexibility as well as constriction in the American regime. Conversely, the European Union has a more organized and scientific method of regulating the herbal medicinal products. The Traditional Herbal Medicinal Products Directive (THMPD) offers a streamlined registration route to products that have a long history of traditional use [73, 74]. Herbal products should have a history of safe use of 30 years or more and have adequate quality and safety data. Evaluation and standardization of these products are major roles played by the European Medicines Agency (EMA) via its Herbal Medicinal Products Committee (HMPC). This system will guarantee quality control and will encourage evidence-based application of herbal medicines [75].

India has a rich tradition of traditional systems of medicine like Ayurveda, Siddha and Unani, which are controlled by the ministry of AYUSH [76]. The herbal products are divided into classical formulations, patent and proprietary medicines [77]. The classical formulations rest on ancient sources and are usually unchallenged due to lack of much clinical verification but the proprietary products are expected to be

supported by evidence on safety and efficacy. Despite the multi-strides that India has undertaken to enhance the traditional medicine, issues like failure in standardization, inconsistency in raw materials, inadequate pharmacovigilance mechanisms, among others, still emerge to challenge regulatory strength [78, 79]. China has already developed a highly integrated framework of herbal medicine, within the Traditional Chinese Medicine (TCM), and is controlled by the National Medical Products Administration (NMPA) [80, 81]. Herbal medicines are considered to be a part of the health care system and are backed up with the traditional knowledge and recent scientific research. The Chinese Pharmacopoeia has explicit standards of the herbal drugs, which is of consistency and quality [82]. Over the last few years China has been working on modernizing the TCM by subjecting it to advanced methods of analytical practices and clinical validation thereby increasing its acceptance across the world [83]. On the same note, Japan approves herbal medicines in the form of Kampo formulations through the ministry of health labour and welfare (MHLW) [84]. Kampo medicines are formalized formulations of herbs that have a long-standing traditional usage [85]. These formulae are validated on historical grounds and are commonly incorporated in practice. These products are consistent, safe and reliable in all their therapeutic uses through strict compliance to quality control and Good Manufacturing Practices [86]. The table 3 presents a comparative analysis of regulatory approaches for herbal products and synthetic drugs across key global regions. It highlights differences in regulatory authorities, classification systems, approval pathways, and evidence requirements. Herbal products are generally regulated under simplified frameworks based on traditional use and historical evidence, whereas synthetic drugs undergo rigorous evaluation involving preclinical studies, phased clinical trials, and strict quality assessments. This comparison emphasizes the variability in global regulatory standards and underscores the fundamental distinction between tradition-based and evidence-based approval systems.

Table 3: Comparative overview of regulatory frameworks for herbal products and synthetic drugs across major global regions (USA, EU, India, China, and Japan).

Region	Regulatory Authority	Herbal Product Classification	Herbal Approval Pathway	Synthetic Drug Approval Pathway	Key Differences (Herbal vs Synthetic)
USA	FDA	Dietary Supplements / Botanical Drugs	No pre-market approval (DSHEA); post-market surveillance; Botanical drugs require IND → NDA	Strict: Preclinical studies + Phase I–III clinical trials + NDA approval	Herbal products (supplements) have minimal regulation; synthetic drugs require full safety & efficacy data [87]
EU	EMA (HMPC)	Traditional Herbal Medicinal Products (THMP)	Simplified registration (30 years traditional use); limited clinical data required	Full marketing authorization with extensive preclinical & clinical data	Herbal drugs rely on traditional evidence; synthetic drugs need strong scientific proof [88]
India	Ministry of AYUSH, CDSCO	Classical & Patent/Proprietary Ayurvedic drugs	Classical drugs: no clinical trials if per texts; Proprietary: limited evidence required	CDSCO approval: Preclinical + clinical trials + quality validation	Herbal drugs based on traditional systems; synthetic drugs strictly evidence-based [89]
China	NMPA	Traditional Chinese Medicine (TCM)	Based on pharmacopoeia + traditional use + some clinical support	Full drug approval with clinical trials and quality contro	Herbal medicines integrated with tradition; synthetic drugs follow

				l	global scientific standards [90]
Japan	MHLW	Kampo Medicines	Standardized formulations; approved based on historical use	Strict approval with clinical trials, GMP, pharmacokinetics & safety data	Herbal (Kampo) relies on fixed traditional formulas; synthetic drugs require complete scientific validation [91]

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.

REFERENCES

1. Senthilkumar, A., A. Saravanan, and V.L. Divyaa, *Boerhavia diffusa: A traditional herb in homoeopathy.*
2. Nayak, P. and M. Thirunavoukkarasu, *A review of the plant Boerhaavia diffusa: its chemistry, pharmacology and therapeutical potential.* J. Phytopharmacol, 2016. **5**(2): p. 83-92.
3. Chaudhry, S., N.K. Sharma, and N. Singh, *A Field Guide to Flowering Plants of The Mekal Hills, Central India*. 2019: Scientific Publishers.
4. Némethy, S., et al., *Collection, cultivation and processing of medical plants, herbs and spices in the Balaton Ecomuseum–herbal medicine as intangible cultural heritage.* Ecocycles, 2020. **6**(1): p. 52-87.
5. De, L. and T. De, *Indigenous Horticultural Crops of India for Immunity Development.* Int. J. Curr. Microbiol. App. Sci, 2020. **9**(6): p. 3068-3089.
6. Unnisa, A., et al., *The discovery of the natural compound Boeravinone-C as a potential antiobesity drug candidate targeting pancreatic lipase using chemo-informatics-based approaches.* Cellular and Molecular Biology, 2023. **69**(7): p. 57-65.
7. Kumar, R., et al., *Pharmacological properties of Boerhavia diffusa: A review.* International Journal of Chemical Studies. SP4, 2018: p. 72-80.
8. Kaur, H., *Boerhaavia diffusa: bioactive compounds and pharmacological activities.* Biomedical and Pharmacology Journal, 2019. **12**(4): p. 1675-1682.
9. Khan, M.I., et al., *Role of plant bioactive as diuretics: General considerations and mechanism of diuresis.* Current Hypertension Reviews, 2023. **19**(2): p. 79-92.
10. Patel, V. and R. Gour, *EVALUATION OF DIURETIC AND NATRIURETIC ACTIVITY OF ETHANOLIC EXTRACT OF BOERHAVIA DIFFUSA LINN ROOT IN ALBINO WISTAR RATS.* European Journal of Biomedical, 2020. **7**(2): p. 252-256.
11. Konan, B.A., et al., *Diuretic activities of root bark aqueous and ethanolic extracts of Parquetina nigrescens: I-effects on urinary*

excretion in wistar rat. Journal of Drug Delivery and Therapeutics, 2022. **12**(3): p. 57-61.

12. Kalaivani, M., et al., *Therapeutic potential of Boerhavia diffusa L. against cyclosporine A-Induced mitochondrial dysfunction and apoptosis in madin–Darby canine kidney cells.* Pharmacognosy Magazine, 2018. **14**(Suppl 1): p. S132-S140.
13. Sahu, S.N., et al., *Boerhavia diffusa plant extract can be a new potent therapeutics against mutant nephrin protein responsible for type1 nephrotic syndrome: Insight into hydrate-ligand docking interactions and molecular dynamics simulation study.* Journal of the Indian Chemical Society, 2022. **99**(10): p. 100669.
14. Venkatesh, P., A. Dinakar, and N. Senthilkumar, *Evaluation of diuretic activity of an alcoholic extracts of Boerhaavia diffusa and Anisochilus carnosus in rats.* Int J Drug Dev Res, 2012. **4**: p. 239-42.
15. Motwani, H., et al., *Hepatoprotective plants role in human health: A cross-kingdom review.* Journal of Medicinal Plants, 2021. **9**(3): p. 41-51.
16. Dwivedi, S., et al., *Environmental toxicants, oxidative stress and health adversities: interventions of phytochemicals.* Journal of Pharmacy and Pharmacology, 2022. **74**(4): p. 516-536.
17. Stanković, V., et al., *Protective and therapeutic possibility of medical herbs for liver cirrhosis.* Rom J Morphol Embryol, 2017. **58**(3): p. 723-9.
18. Aladejana, E.B. and A.E. Aladejana, *Hepatoprotective activities of polyherbal formulations: A systematic review.* Journal of Medicinal Plants for Economic Development, 2023. **7**(1): p. 206.
19. Thajudeen, K.Y., et al., *Validation, Optimization and Hepatoprotective Effects of Boeravinone B and Caffeic Acid Compounds from Boerhavia diffusa Linn.* Separations, 2022. **9**(7): p. 177.
20. Dey, D., et al., *Hepatoprotective Activity of BV-7310, a Proprietary Herbal Formulation of Phyllanthus niruri, Tephrosia purpurea, Boerhavia diffusa, and Andrographis paniculata, in Alcohol-Induced HepG2 Cells and Alcohol plus a Haloalkane, CCl₄, Induced Liver Damage in Rats.* Evidence-Based Complementary and Alternative Medicine, 2020. **2020**: p. 6428906.
21. Kishore, N., et al., *Human disorders associated with inflammation and the evolving role of natural products to overcome.* European journal of medicinal chemistry, 2019. **179**: p. 272-309.
22. Gurjar, V.K. and D. Pal, *Natural compounds extracted from medicinal plants and their immunomodulatory activities.* Bioactive Natural Products for Pharmaceutical Applications, 2021: p. 197-261.
23. Ambati, G.G. and S.M. Jachak, *Natural product inhibitors of cyclooxygenase (COX) enzyme: A review on current status and future perspectives.* Current Medicinal Chemistry, 2021. **28**(10): p. 1877-1905.
24. Ju, Z., et al., *Recent development on COX-2 inhibitors as promising anti-inflammatory agents: The past 10 years.* Acta Pharmaceutica Sinica B, 2022. **12**(6): p. 2790-2807.
25. Gaur, P.K., S. Rastogi, and K. Lata, *Correlation between phytocompounds and pharmacological activities of Boerhavia diffusa Linn with traditional-ethnopharmacological insights.* Phytomedicine Plus, 2022. **2**(2): p. 100260.
26. Karwasra, R., et al., *Protective Effect of Boerhavia diffusa in Attenuating Pro-inflammatory Cytokines and Inhibition of Activated NF-κB-TNF-α-Nrf2 in Freund's Adjuvant-induced Rheumatoid Arthritis.* Indian Journal of Pharmaceutical Education and Research, 2021. **55**: p. s563-s571.
27. Mathias, G.P., et al., *Combination of Aqueous Extracts of Phyllanthus niruri, Boerhavia diffusa,and Picrorhiza kurroaor Zingiber officinalealone Inhibit Intracellular Inflammatory Signaling Cascade.* Journal of Herbal Medicine, 2020. **23**: p. 100378.
28. Shameela, S., et al., *Studies on Antigenotoxic and In-vitro Antioxidant Activity of Ethanolic Extract of Boerhaavia diffusa L.(Nyctaginaceae).* 2018.
29. Fatima, N., *Association of Peroxisomes, Reactive Oxygen Species (ROS) and Antioxidants: Insights from Preclinical and Clinical Evaluations.* The Metabolic Role of Peroxisome in Health and Disease, 2022.

30. Giresha, A.S., et al., *Neutralization of Inflammation by Inhibiting In vitro and In vivo Secretory Phospholipase A2 by Ethanol Extract of Boerhaavia diffusa L.* Pharmacognosy Research, 2017. **9**(2): p. 174.
31. Shanmugapriya, A., et al., *A Combinative Evaluation Of Antioxidant Potential In Tridax procumbens and Boerha-via diffusa.* International Journal of Pharmaceutics and Drug Analysis, 2018: p. 197-202.
32. Bhalodiya, M., et al., *Determination of Polyphenolic content and Antioxidant Activity from Various Extracts of Boerhaavia diffusa Linn Root: An in vitro Approach for Selection of Appropriate Extracting Solvent.* Pharmacognosy Journal, 2020. **12**(6s).
33. Sudheer, W.N. and P. Nagella, *Production of Boeravinone-B, total phenolic, flavonoid content and antioxidant activity from callus cultures of Punarnava (Boerhavia diffusa L.).* Plant Science Today, 2023. **10**(2): p. 354-365.
34. Akhter, F., et al., *Antioxidant, α-amylase inhibitory and oxidative DNA damage protective property of Boerhaavia diffusa (Linn.) root.* South African Journal of Botany, 2013. **88**: p. 265-272.
35. Bahiram, D.N., et al., *BOERHAAVIA DIFFUSA LINN (PUNARNAVA)-PHYTOCHEMISTRY & PHARMACOLOGICAL EFFECTS ON VARIOUS DISEASES IN CONDITION.*
36. Ghosh, S., *Multi-functional therapeutic effect of Boerhaavia diffusa: A contemporary review.* GSC Biological and Pharmaceutical Sciences, 2022. **20**(3): p. 299-306.
37. Juneja, K., et al., *Metabolite profiling and wound-healing activity of Boerhavia diffusa leaf extracts using in vitro and in vivo models.* Journal of Traditional and Complementary Medicine, 2020. **10**(1): p. 52-59.
38. Ahmad, I., et al., *An Overview on the Anticancer Potential of Punarnavine: Prediction of Drug-Like Properties.* Oncologie, 2021. **23**(3).
39. Khan, M.S., et al., *Chemotherapeutic potential of Boerhaavia diffusa Linn: A review.* Journal of Applied Pharmaceutical Science, 2013. **3**(1): p. 133-139.
40. Saraswati, S., A.A. Alhaider, and S.S. Agrawal, *Punarnavine, an alkaloid from Boerhaavia diffusa exhibits anti-angiogenic activity via downregulation of VEGF in vitro and in vivo.* Chemico-Biological Interactions, 2013. **206**(2): p. 204-213.
41. Rahman, M.M., et al., *Exploring the plant-derived bioactive substances as antidiabetic agent: an extensive review.* Biomedicine & Pharmacotherapy, 2022. **152**: p. 113217.
42. Murti, K., et al., *Antidiabetic and antihyperlipidemic activity of roots of Boerhaavia diffusa on streptozotocin induced diabetic rats.* Pharmacologyonline, 2011. **1**(1): p. 15-21.
43. Alam, P., et al., *Anti-diabetic Effect of Boerhavia diffusa L. Root Extract via Free Radical Scavenging and Antioxidant Mechanism.* Toxicology and Environmental Health Sciences, 2018. **10**(3): p. 220-227.
44. Jayachitra, J. and B. Janani, *Anticancer activity of methanolic extract of Boerhavia diffusa L.* Thematics Journal of Geography, 2019. **8**(12): p. 80-90.
45. Niraj, S. and S. Varsha, *A review on scope of immuno-modulatory drugs in Ayurveda for prevention and treatment of Covid-19.* Plant Science Today, 2020. **7**(3): p. 417-423.
46. Aher, D.V., P. Chattopadhyay, and A. Patra, *Immunomodulatory Activity of Punarnavine Alkaloid from Boerhaavia diffusa.* Current Bioactive Compounds, 2020. **16**(4): p. 460-468.
47. Manu, K.A. and G. Kuttan, *Immunomodulatory activities of Punarnavine, an alkaloid from Boerhaavia diffusa.* Immunopharmacology and Immunotoxicology, 2009. **31**(3): p. 377-387.
48. Kumari, M., P. Sharma, and N. Sharma, *Evaluation of anti-anxiety effects of the hydromethanolic extract of Boerhaavia diffusa L. roots in mice exposed to unpredictable chronic mild stress.* Indian Journal of Natural Products and Resources (IJNPR)[Formerly Natural Product Radiance (NPR)], 2023. **14**(2): p. 249-254.
49. Das, S., et al., *Ethnomedicinal values of Boerhaavia diffusa L. as a panacea against multiple human ailments: a state of art review.* Frontiers in Chemistry, 2023. **11**.
50. Kaviya, M., et al., *Evaluation of Nutritional Substances and Investigation of Antioxidant and Antimicrobial Potentials of Boerhavia*

diffusa with in Silico Molecular Docking. Molecules, 2022. **27**(4): p. 1280.
51. Adefokun, D.I., et al., *The Antimalarial Effect and Mechanism of Action of Methanolic Root Extract of Boerhaavia diffusa in Mice.* Journal of Pharmaceutical Research International, 2015. **8**(2): p. 1-14.
52. Sobi, M.A., et al., *Size dependent antimicrobial activity of Boerhaavia diffusa leaf mediated silver nanoparticles.* Journal of King Saud University - Science, 2022. **34**(5): p. 102096.
53. Kirubakaran, D., et al., *A Comprehensive Review on the Green Synthesis of Nanoparticles: Advancements in Biomedical and Environmental Applications.* Biomedical Materials & Devices, 2026. **4**(1): p. 388-413.
54. Gunasena, M.D.K.M., et al. *Advancements in Bio-Nanotechnology: Green Synthesis and Emerging Applications of Bio-Nanoparticles*. Nanomaterials, 2025. **15**, 528 DOI: 10.3390/nano15070528.
55. Sudhakar, C., et al., *Catalytic degradation of methyl orange and biomedical efficacy of sustainable silver nanoparticles from Boerhaavia diffusa leaf extract.* Journal of Molecular Structure, 2025. **1344**: p. 142973.
56. Prabhu, M.S.A., et al., *Green synthesis of ZnO, Fe3O4, and TiO2 nanoparticles: exploring enhanced bacterial inhibition, catalysis, and photocatalysis for sustainable environmental applications.* International Journal of Environmental Analytical Chemistry, 2025. **105**(17): p. 5793-5817.
57. Renu, et al., *Rational design of Boerhavia diffusa derived CoFe2O4-Carbon dots@Boehmite platform for photocatalysis and ultra trace monitoring of hazardous pesticide and UO22+ ions.* Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 2025. **325**: p. 125111.
58. Vijay Kumar, P.P.N., et al., *Green synthesis and characterization of silver nanoparticles using Boerhaavia diffusa plant extract and their anti bacterial activity.* Industrial Crops and Products, 2014. **52**: p. 562-566.
59. James, J.M., et al., *Green synthesis of silver nanoparticles using Boerhavia diffusa plant and the potential of its antioxidant and anticancer efficacy.* Pharmacological Research - Natural Products, 2025. **6**: p. 100142.
60. Bibi, Y., et al., *Phytosynthesis of gold nanoparticles from Boerhavia diffusa L. and their antibacterial, antifungal, antioxidant, and anticancer activities.* Discover Nano, 2026. **21**(1): p. 7.
61. Sushma, B., R.V. Geetha, and S.R. Kumar, *Boerhavia diffusa Mediated Selenium Nanoparticles and their Antioxidant and Anti-Inflammatory Activity.* Journal of Pharmaceutical Research International, 2021. **33**(64A): p. 343-350.
62. Sudheer, W.N., et al., *Photocatalytic and antimicrobial properties of Boerhavia diffusa bio-callus synthesized Silver nanoparticles.* Plant Nano Biology, 2025. **12**: p. 100153.
63. Patil, S., et al., *Small size silver nanoparticles loaded with glycoside rich portion of Boerhavia Diffusa Linn. promotes wound healing: in-silico and in-vivo studies.* Colloids and Surfaces B: Biointerfaces, 2023. **230**: p. 113483.
64. Kodhaiyolii, S., et al., *Phytofabrication of bimetallic Co–Ni nanoparticles using Boerhavia diffusa leaf extract: analysis of phytocompounds and application for simultaneous production of biohydrogen and bioethanol.* Materials Research Express, 2019. **6**(9): p. 095051.
65. Jalan, R.S., et al., *Anti-Inflammatory Activity of Boerhavia diffusa Zinc Oxide Nanoparticle.* Journal of Pharmaceutical Research International, 2021. **33**(61B): p. 343-353.
66. Moreira, D.d.L., et al., *Traditional use and safety of herbal medicines1*. Revista Brasileira de Farmacognosia, 2014. **24**(2): p. 248-257.
67. Mir, P., et al., *Traditional and Herbal Medicines: Opportunities and Challenges.* Pharmacognosy Communications, 2022. **14**: p. 107-114.
68. Prabhakar, P. and M. Banerjee, *Technical Problems, Regulatory and Market Challenges in Bringing Herbal Drug into Mainstream of Modern Medicinal Practices.* Research Journal of Biotechnology, 2021. **16**: p. 212-222.
69. Rahman, S.U., et al., *Regulatory considerations for herbal products*, in *Herbal pharmacopeia*. 2025, CRC Press. p. 440-457.
70. Wallace, T.C. and I. Koturbash, *DSHEA 1994 – Celebrating 30 Years of Dietary*

Supplement Regulation in the United States. Journal of Dietary Supplements, 2025. **22**(1): p. 1-8.
71. Farooq, S. and V.A. Master, *Chapter 69 - Food and dietary supplements*, in *Translational Urology*, A.E.M. Eltorai, et al., Editors. 2025, Academic Press. p. 365-368.
72. Rider, C.V., *Chapter 8 - Dietary supplements*, in *History of Food and Nutrition Toxicology*, E. Haugabrooks and A.W. Hayes, Editors. 2023, Academic Press. p. 157-182.
73. Mihailović, A., N. Vuksanović, and D.B. Popović, *20 - Regulatory security and legal framework of herbal medicinal products in the European Union*, in *Therapeutic Potential of Medicinal Plants*, V.M. Popović and M. Emerald, Editors. 2026, Academic Press. p. 543-566.
74. Qu, L., et al., *Opportunities and hurdles to European market access for multi-herbal traditional Chinese medicine products: An analysis of EU regulations for combination herbal medicinal products.* Pharmacological Research, 2022. **186**: p. 106528.
75. Jain, T., et al., *Regulatory status of traditional medicines in different countries: An overview.* Research Journal of Pharmacy and Technology, 2011. **4**: p. 1007-1015.
76. Muthappan, S., et al., *AYUSH digital initiatives: Harnessing the power of digital technology for India's traditional medical systems.* Journal of Ayurveda and Integrative Medicine, 2022. **13**(2): p. 100498.
77. Kaushik, R., K. Upadhyaya, and T. Dixit, *Regulation of Ayurveda, Siddha and Unani (ASU) drugs: An overview of current framework, challenges and way forward.* Journal of Drug Research in Ayurvedic Sciences, 2025. **10**(2).
78. Kaundal, R. and D. Kumar, *Current demands for standardization of Indian medicinal plants: A critical review.* Medicine in Drug Discovery, 2025. **27**: p. 100211.
79. Wal, P., et al., *Pharmacovigilance of herbal products in India.* J Young Pharm, 2011. **3**(3): p. 256-8.
80. Hua, H., et al., *From traditional medicine to modern medicine: the importance of TCM regulatory science (TCMRS) as an emerging discipline.* Chinese Medicine, 2025. **20**(1): p. 92.
81. Xia, M., et al., *Advancing human-use experience for real-world evidence for the registration of traditional Chinese medicine products in China.* BMC Complementary Medicine and Therapies, 2025. **25**(1): p. 174.
82. Leong, F., et al., *Quality standard of traditional Chinese medicines: comparison between European Pharmacopoeia and Chinese Pharmacopoeia and recent advances.* Chinese Medicine, 2020. **15**(1): p. 76.
83. Chan, K., *The Evolutional Development of Traditional Chinese Medicine (TCM) Outside the Chinese Mainland: Challenges, Training, Practice, Research, and Future Development.* World Journal of Traditional Chinese Medicine, 2016. **2**(4).
84. Arai, I., J.S. Yongue, and K. Tsutani, *The development of the Kampo medicines industry:"Good Practices" and health policy making in Japan*, in *Asian Medical Industries*. 2022, Routledge. p. 81-109.
85. Togo, T. and T. Makino, *History, Present and Prospect of Kampo Medicine*, in *History, Present and Prospect of World Traditional Medicine*. 2023, WORLD SCIENTIFIC. p. 395-446.
86. Teng, L., *Pharmacovigilance for Herbal and Traditional Medicines in Japan*, in *Pharmacovigilance for Herbal and Traditional Medicines: Advances, Challenges and International Perspectives*, J. Barnes, Editor. 2022, Springer International Publishing: Cham. p. 371-383.
87. Thakkar, S., et al., *Regulatory landscape of dietary supplements and herbal medicines from a global perspective.* Regulatory Toxicology and Pharmacology, 2020. **114**: p. 104647.
88. Mihai, M., et al. *European Consumer and Regulatory Trends in Medicinal Plant Food Supplements and Their Functional Properties: The Road from Farm to Fork*. Applied Sciences, 2025. **15**, 11605 DOI: 10.3390/app152111605.
89. Jadhav, R., et al., *Regulations, current development, and future prospects of phytopharmaceuticals, a new class of herbal medicines in India.* Discover Pharmaceutical Sciences, 2025. **1**(1): p. 6.
90. Marshall, A.C., *Traditional Chinese Medicine and Clinical Pharmacology*, in

Drug Discovery and Evaluation: Methods in Clinical Pharmacology, F.J. Hock and M.R. Gralinski, Editors. 2020, Springer International Publishing: Cham. p. 455-482.

91. Arai, I. and N. Kawahara, *Kampo pharmaceutical products in the Japanese health-care system: Legal status and quality assurance: Current status of Kampo medicines.* Traditional & Kampo Medicine, 2018. **6**.