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**Pharmacological properties of *Boerhavia diffusa*:
A review**

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Abstract


Now a day due to various side effects of allopathic medicine, scientists of pharmaceutical industries and research centers have been engaged to explore the pharmacological properties of herbal plants. The present review explains the pharmacological properties of *Boerhavia diffusa* plant. This plant commonly known as punarnava, is herb of family Nyctaginaceae. *B. diffusa* known to have medicinal properties and used as Ayurvedic medicine in India. Battery of phytochemicals like alkaloids, flavonoids, rotenoids and phytosterols has been found in the plant which are responsible for its various pharmacological properties such as analgesic, anti-inflammatory, diuretic, hepatoprotective, immunomodulator and nephroprotective, antiulcer and antihistaminic etc. Moreover, several new phytochemicals are discovered which again validate its medicinal importance. This review presents the evidence-based pharmacological properties of *B. diffusa*. In conclusion *B. diffusa* contain many bioactive phytochemicals that may be use as prophylactic as well as for cure of various ailments of human and animals.

Keywords: *Boerhavia diffusa*, bioactive phytochemicals, pharmacological properties, hepatoprotective and Immunomodulator

Introduction

Boerhavia diffusa, a perennial herb with stout root stock and many procumbent branches, flowers pale rose coloured, small, short-stalked; fruits highly viscid and one-seeded with many vernacular names viz. Punarnava, Raktapunarnava, Shothaghni, Kathillaka, Kshudra, Varshabhu, Raktapushpa, Varshaketu and Shilatika in India. The genus *Boerhavia* (often spelled as Boerhaavia) was named in honor of Hermann Boerhaave (1668–1738), an eighteenth century Dutch botanist, humanist and physician at the University of Leiden, while the species got the name from typical diffuse branching. The botanical name of the plant is often written in the literature as *Boerhaavia diffusa* (Hiruma-Lima *et al.*, 2000) [33], but Linnaeus Latinized Boerhaave's name to Boerhavius and adopted the spelling *Boerhavia diffusa*, which is the correct spelling to be used (Spellenberg, 2004) [75].

Punarnava is a very important medicinal herb of Ayurveda. Its name is derived from two words, *Punar* (= once again /regaining/restoring) and *Nava* (=new, renew or young), so the literal meaning of the name is, one which becomes new or young again. This name signifies the rejuvenating property of Punarnava. It is a Rasayan herb of Ayurveda which renews the body or restores youth.

<i>Boerhavia diffusa</i> (Punarnava)		
Kingdom	Plantae	
Division	Angiosperm	
Class	Eudicots	
Order	Caryophyllales	
Family	Nyctaginaceae	
Genus	<i>Boerhavia</i>	
Species	<i>diffusa</i>	

The major active principle present in *B. diffusa* is alkaloidal in nature and known as boeravinone. Battery of bioactive phytochemicals are present in the various parts of the plant, which is responsible for number of pharmacological properties such as anti-inflammatory (Babita *et al.*, 2011) [9], antidiabetic (Pari *et al.*, 2004) [57], antioxidant (Juna Beegum *et al.*, 2016) [36], antistress (Shirwaiar *et al.*, 2007) [72], antimicrobial (Gordon *et al.* 1990) [29], or antibacterial (Olukoya *et al.*, 1993) or antiviral (Awasthi *et al.*, 2006), antifungal (Agrawal *et al.*, 2003) [4], antinematodal (Vijayalakshmi *et al.*, 1979) [83], antifibrinolytic (Sengul *et al.*, 2009) [69], antiurethritis (Pereira *et al.*, 2009) [58], anticonvulsant (Adesina *et al.*, 1979) [2], antihepatotoxic (Mishra *et al.*, 1980) [50], diuretic (Desai *et al.*, 2008) [20], immunomodulatory (Mungantiwar *et al.*, 1999), hepatoprotective (Duh *et al.*, 1999) [23], renoprotective or nephroprotective (Shikha *et al.*, 2014) [71], laxative (Chopera *et al.*, 1956), adaptogenic (Mungantiwar *et al.*, 1997), antimetastatic (Manu *et al.*, 2009) [46] and antihistaminic (Irie –N Guessan *et al.*, 2011). Among many more, the important pharmacological properties are as follows:

1. Analgesic or anti-nociceptive and anti-inflammatory property

The analgesic and anti-inflammatory properties obtained from whole plant in general, leaf juice in particular (Babita *et al.*, 2011) [9]. The antinociceptive effect of the plant probably due to morphinimetric central analgesic property (Hiruma-Lima *et al.*, 2000) [33]. Moreover, ethanol extract of stem bark exhibited COX-1, a mediator of inflammation (Laxmi Banjare *et al.*, 2012) [41]. In 'Martinican folk' medicine *Boerhavia diffusa* is used for its analgesic and anti-inflammatory properties (CNayak and M. thirunavoukkrasu, 2016). Anti-inflammatory effect of water insoluble alcoholic extract of root, stem, leaves and flowers were effective against carageenan-induced oedema in rats and was highest during rainy season (Mudgal, 1974) [51]. Aqueous and acetone extract of root has significant efficacy against formaldehyde induced arthritis and carageenan induced oedema in albino rats. Like hydrocortisone, the same extract also reduces the elevated level of serum amino transferase. Moreover, the aqueous as well as acetone extract also elevate the liver ATP phosphohydrolase activity (Bhalla *et al.*, 1971) [10]. The root extract reduce bacterial count in urine sample as well as reduce the inflammatory changes and abscess formation in kidney of *Escherichia coli* induced acute pyelonephritis in rats (Singh *et al.*, 1988).

2. Anti-hepatotoxic Activity or Hepatoprotective and Cholerectic activity

Liver, a important vital organ of the body and first line of defence against xenobiotic attack. Hence, it is targeted by harmful and toxic effect of chemicals. It helps to combat the body for any onslaught. A good health is mirrored by good liver. Many workers evaluated and justify hepatoprotective potential of *Boerhaavia diffusa* against different hepatic disorders and hepatotoxins (Shikha Mishra *et al.*, 2014) [71]. Ethanol extract of root of *Boerhaavia diffusa* have hepatoprotective effect against country made liquor induced liver toxicity in albino rats, the protective effect of same is evidenced by reduction of elevated alanine aminotransferase (ALT), triglyceride, cholesterol and total lipids in both serum and tissues (Surange and Pendse, 1972) [80]. Petroleum, chloroform and methanol extracts of root and aerial parts have anti-hepatotoxic activity; as evidenced by reduction in

elevated serum glutamate oxaloacetate (SGOT), serum pyruvate transaminase (SGPT) and serum alkaline phosphate (SALP) in carbon tetra chloride induced hepatotoxicity in rats (Chakraborti and Handa, 1989) [14]. An alkaloid, rotenoid (6,11-dihydroxy-9-10-dimethyl-4-methoxyrotenoid); a steroid, androst-5-ene analogou and a flavones, 6, 5'-dimethoxy-5,7,3' trihydroxyflavone are attributed to anti-hepatotoxic property of the plant. Alcoholic extract of whole plant (Chandan *et al.*, 1991) [15] and roots (Rajkumari *et al.*, 1991) [62] have hepatoprotective effect in carbon tetra chloride induced hepatotoxicity in rats; the aforesaid property is evidenced by modulation in titer of serum alanine aminotransferase (ALT), triglycerides (TG), cholesterol and total lipid. *Boerhavia diffusa* also reduce increase in prothombin time induced by carbon tetra chloride and doubles the rate of bile flow (Chandan *et al.*, 1991) [15]. The appropriate size (1-3cm diameter), time (season of year, summer is best) of collection of roots and form of dose (compared to powder, aqueous form is more effective due to better absorption) is critical for optimum hepatoprotective activity against thiocet-amide induced liver toxicity in rats (Rawat *et al.*, 1997) [64]. Moreover, histopathology of liver in question showed minimal fatty cyst in treated group (Gulati *et al.*, 1991) [31]. *Boerhavia diffusa* has restorative effect against hepatotoxicity induce by paracetamol (Venkatalakshmi *et al.*, 2011) [82] and ethanol (Devaki *et al.*, 2005) [22] in rats.

3. Diuertic and Nephroprotective Activity

Many research workers studied the effect of *Boerhaavia diffusa* extract on kidney and are in agreement that it has diuretic effect. The diuretic activity was attributed to increased sodium excretion rate, presence of potassium, glucosides, ecdysone in various parts of plant. However, the maximum diuretic effect observed if roots are taken and as for as collection of season is concerned, maximum activity obtained in plants of rainy season (Rawat *et al.*, 1997) [64] Rawat. Moreover, the extract modulates succinic dehydrogenase level (dose dependent manner i.e. stimulatory at low dose and inhibitory at high dose), stimulatory for d-amino acid oxidase; however has no effect on phosphatase of kidney (Chawdhury and Sen, 1955).

Extract of *Boerhaavia diffusa* has definite bearing on renal therapeutics in various renal pathology viz. *E.coli* induced pyelonephritis, polycystic end stage renal diseases, urolithiasis due to deposition of ammonium magnesium phosphate hexahydrate, calcium oxalate and oedema, ascites and nephritic syndrome developing at the early onset of liver cirrhosis and chronic peritonitis.

Diuretics are the first line of therapy in renal inflammatory disorders as it almost always involve derangement in fluid dynamics of the body, in this regard hepatoprotective property of the plant has an added benefit (Shikha Mishra *et al.*, 2014) [71].

4. Adaptogenic and Antistress Activity

The adaptogen refer to substances which increase "nonspecific" resistance to adverse influence to organism and stress. The adaptogenic substances restore, strengthen the normal body function compromised by stress as well as have a protective effect on health against varied environmental assaults and emotional conditions, in other words adaptogens useful during adrenal hyper stress and adrenal hypofatigue (Pranati Nayak and M Thirunavoukkrasu, 2016) [59].

The adaptogenic activity of *Boerhavia diffusa* extract is due to flavonoids, alkaloids, glycosides and sterols, causes

significant increase in carbon clearance which is suggestive of reticuloendothelial system stimulation (Sumanth and Mustafa, 2007) [78], significant leucocytosis, restorative effect on elevated glucose, cholesterol, SGPT, triglyceride level. Moreover, normalize plasma and adrenal cortisol level as well as augment antibody production (Mungantiwar *et al.*, 1997) [52].

5. Immunomodulatory Activity

Modulation of the immune system is an emerging trend in chemotherapeutic research. Immune modulation as a part of immune therapy, in which immune response are induced, amplified, attenuated, or prevented according to therapeutic goal. In other words, immunomodulators can alter body's defense mechanism, by regulating the cytokine production such as tumor necrosis factor (TNF), interleukins (ILs) and interferons (IFNs) and these cytokines may, in turn, activate different cells of immune system such as T-cells or natural killer (NK) cells (Salman Khan *et al.*, 2013) [65].

Extract of *Boerhavia diffusa* has ability immunomodulatory properties and improve cortisol level with end stage renal exhaustion (Mungantiwar *et al.* 1997) [52]. Oral administration of 25-100 mg/kg of the alkaloid fraction for 10 days around immunization delayed hypersensitivity and increase in antibody titre in mice immunized intraperitoneally with sheep RBC. Ethanolic plant extract (100 and 500 µg/ml) inhibited human NK cell cytotoxicity, lipopolysaccharide induced nitric oxide production in mouse macrophage cells RAW 264.7 (Mehrotra *et al.*, 2002a) [48]. At a concentration as low as 10 µg/ml, it inhibited phytohaemagglutinin stimulated IL-2 as well as lipopolysaccharide stimulated TNF- α production in human PBMCs culture and inhibited cytokine production. Chloroform (50 µg/ml) and ethanol extracts (50 µg/ml) and the pure compound eupalitin-3-O- β -D-galactopyranoside (500 µg/ml) inhibited PHA stimulated proliferation of PBMCs, two way MLR, NK cell cytotoxicity as well as LPS induced nitric oxide production by RAW 264.7 (Pandey *et al.*, 2005) [9]. Purified alkaloid punarnavine (40 mg/kg) modulate the immune system and increase WBC count, bone marrow cellularity and number of alpha-esterase positive cells, enhanced proliferation of splenocytes, thymocytes and bone marrow cells both in the presence and absence of specific mitogens *in vitro* and *in vivo* and reduction in LPS induced elevated levels of proinflammatory cytokines (Manu and Kuttan, 2009) [45].

The immunosuppressive property of eupalitin-3-O- β -D-galactopyranoside could be linked with antiosteoporotic activity shown by *Boerhavia diffusa* extract in various cell cultures and *in vitro* studies. *Boerhavia diffusa* considered as one of the core ingredient in traditional and ethnopharmacological medicine; in treatment of rheumatism, a nonspecific term used for joints and connective tissues affections. The evidence for presence of compounds with antiosteoporotic, immunosuppressive, and anti-inflammatory activities approves the use of *Boerhavia diffusa* in rheumatic disorders for which it has been known since ancient times (Shikha Mishra, *et al.*, 2014) [71].

6. Antidiabetic activity

The rapidly increasing diabetes mellitus and its associate complications is becoming a serious threat to human health (Pranati Nayak and M Thirunavoukkrasu, 2016) [59]. Various biochemical and chemical agents used for control and treatment of the same. *Boerhavia diffusa* exhibit potent antidiabetic activity and its leaf extracts with various solvents

have shown hypoglycemic activity in normal animals and antihyperglycemic activity in alloxan, streptozotocin or dexamethasone induced models of diabetes.

Aqueous solution of *B. diffusa* leaf extracts at a daily oral dose of 200 mg/kg for 4 weeks, has significant change on blood glucose concentration and activity of hepatic gluconeogenic enzymes (increase in hexokinase activity and decrease in glucose-6-phosphate and fructose-1, 6-phosphate activity) in both normal and alloxan induced rats (Pari L. and Satheesh M.A., 2004) [57]. Chloroform extracts of *B. diffusa* leaves produced dose dependent reduction in blood glucose in streptozotocin induced non-insulin dependent diabetes mellitus in rats (Nalamolu *et al.*, 2004) [54]. This was probably through rejuvenation of pancreatic β -cells or through extra pancreatic action. In spite of chloroform extracts of *B. diffusa*, methanolic extract and also comparably regenerate beta cells (Bhatai *et al.*, 2001). The root extracts of *B. diffusa* at a daily dose of 150 mg/kg in dexamethasone induced hypoglycemic rats has antiperoxidative, hypoglycemic and cortisol lowering activities (Golap and Kar, 2004). Thus, the *Boerhavia diffusa* has a significant bearing on phytotherapy of diabetes mellitus and its associated complications.

7. Radioprotective activity

Reports are scanty regarding radioprotective property of *Boerhavia diffusa*. *Boerhavia diffusa* in radiation induced haemopoietic injury increase haemoglobin and total RBC count in albino mice (Thali *et al.*, 1998) [81]. The hydro-alcoholic extract of *Boerhavia diffusa* has a radioprotective effect against gamma radiation induced damage in mice (Manu *et al.*, 2007) [46].

8. Anticarcinogenic and Antiproliferative Activity

Boerhavia diffusa have shown cytotoxic and antiproliferative effect on various cell lines, like human cervical cancer HeLa cell line (Srivastava *et al.*, 2009), mouse macrophage cells (RAW 264.7), human macrophage cells (U937), human monocytic cells (THP-1), mouse fibroblast cells (L929), human embryonic kidney cells (HeLa293), mouse liver cells (BNCLC.2), African green monkey kidney cell (COS-1), mouse lymphoma cells (EL-4), human erythroleukemia cells (K562), and human T cells (Mehrotra *et al.*, 2002) [49], B16F-10 melanoma cells, pulmonary metastasis (Leyon *et al.*, 2005) [42] in mice; antiproliferative and antiestrogenic action in MCF-7 breast cancer cell line (Sreeja and Sreeja, 2009) [76]. Moreover, the plant have chemopreventive action against 7, 12-dimethyl ben(z)anthracene (DMBA) induced skin papillomagenesis in male Swiss albino mice (Goyal *et al.*, 2010) [30] and radioprotective activity against gamma radiation induced damage (Sreeja and Sreeja, 2009) [76]. Boeravinones G and H, a type of rotenoids isolated from roots of *Boerhavia diffusa* which is potential efflux inhibitors for breast cancer resistance protein (ABCG2) (Ahmed- Belkacem *et al.*, 2007) and causes 30 per cent cell death in HeLa cell line (Chopra *et al.*, 2011) [16].

Radiotherapy and chemotherapy are important weapons in the armoury against cancer combat along with its potential side effect such as myelosuppression or immunosuppression, which make the subject more prone for infection during course of the treatment. In order to maintain immunity level at optimum and keep the infection at bay phytotherapy with *Boerhavia diffusa*, along with anticancer property, offers many additional advantages like immunomodulation, hepatoprotection, radioprotection, nephroprotection and many

more. So, *Boerhavia diffusa* could be a suitable phytotherapeutic agent for management of cancer.

9. Antioxidant activity

Oxygen free radicals produced as a result of metabolic processes in our body, induce damage to biomembranes and genetic materials leading to many chronic degenerative diseases and aging (Juna Beegum *et al.*, 2016) [36]. Oxidative stress, an unbalance between pro-oxidants and antioxidant mechanisms, directed the use of dietary or medicinal supplements particularly during disease attack. Natural antioxidants act as effective free radical scavengers, by donating hydrogen to highly reactive radicals, inhibiting oxidation, and activating enzymes of the antioxidant defense systems.

Boerhavia diffusa play preventive and productive role to maintain cell survival, cellular interaction and maintenance of cell membrane architecture (Premkumar *et al.*, 2010) [60]. The antioxidant activity of different part of *Boerhavia diffusa* is different and it has been reported that leaves revealed stronger antioxidant activity than roots. Aqueous extract of the leaves of *B. diffusa* has stronger antioxidant activity than roots (Pereira *et al.*, 2009) [58]. However, antioxidant activity of ethanol extract of *Boerhavia diffusa* has been found better as compared to methanol extract (Rachh *et al.*, 2009) [61].

Administration of *B. diffusa* leaf extract (200 mg/kg, p.o.) for 4 weeks resulted in a significant reduction in thiobarbituric acid reactive substances and hydroperoxides, with a significant increase in reduced glutathione, superoxide dismutase, catalase, glutathione peroxidase and glutathione S-transferase in liver and kidney of alloxan induced diabetic rats. It can be concluded that *B. diffusa* leaf extract can remarkably improve antioxidant status in alloxan induced diabetic rats (Satheesh and Pari, 2004) [57]. The volatile compounds are described to have several biological functions like antioxidant, antiseptic and anti-atherosclerotic (Edris A.E., 2007) [24]. The aqueous extract of *Boerhavia diffusa* has anti-oxidative activity against DPPH radical, one reactive oxygen species (O_2) and one reactive nitrogen species (NO) and anti-acetylcholinesterase activity. DPPH radical and nitric oxide radical scavenging activity of leaves has been found stronger than roots. However, roots revealed stronger superoxide radical scavenging activity than leaves. Thus, it can be suggested that *B. diffusa* can be a natural source of economic and efficacious antioxidant.

10. Antiviral activity against plant viruses

Reports on antiviral activity of *Boerhavia diffusa* is scanty but some workers have suggested its antiviral activity against phytopathogenic viruses (Lohani *et al.*, 2007) [44]. The antiviral agent was found to be a glycoprotein with molecular weight of 16-20 kDa (Babita *et al.*, 2011) [9].

11. Antimicrobial activity

The rationale for studying the effects on selected microorganisms lies in their potential for causing human diseases. Human pathogenic bacteria cause different types of diseases with varying degree of morbidity and mortality; for example, *Klebsiella* infections have a high mortality rate of approximately 50% even with antimicrobial therapy. The diseases of skin, itching or eczema, conjunctivitis, diarrhoea, dysentery, and urinary troubles are caused by the microorganisms (Shikha Mishra *et al.*, 2014) [71]. The bioactive phytochemicals present in the *B. diffusa* leaves

exhibits antibacterial activity against a number of human pathogenic bacteria such as *Bacillus cereus*, *Bacillus subtilis*, *Escherichia coli*, *Klebsiella sp.*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Shigella sp.*, *Staphylococcus aureus* and *Yersinia enterocolitica* at 50µl concentration (Girish H.V. and Satish S., 2008) [26].

Ethanol extract of *Boerhavia diffusa* leaves showed inhibitory an effect on grampositive bacteria like *S. aureus*, *B. subtilis*, *S. faecalis*, *M. luteus* and all gram-negative bacteria. Methanol extract showed inhibitory effect against all gram-positive bacteria selected for the present study except *M. luteus* and gram-negative bacteria like *K. pneumoniae*, *P. vulgaris*, *S. marcescens* and *S. flexneri* (Sharma *et al.*, 2008) [15]. The active principles contained in aqueous and ethanolic extracts of *B. diffusa* leaves had activity on *E. coli*, *S. aureus* and *P. aeruginosa*. *E. coli* displayed the highest susceptibility in ethanolic extract, followed by *S. aureus* and the least susceptible was *P. aeruginosa*. In aqueous extract, *P. aeruginosa* showed the highest susceptibility, followed by *S. aureus* and *E. coli* exhibited the least susceptibility. The antimicrobial activity of the different extracts increased with increase in concentration. Results from this study showed that the aqueous and ethanolic extracts of *B. diffusa* had antibacterial activity on *E. coli*, *S. aureus* and *P. aeruginosa* (Sandhay K. Desai *et al.*, 2011) [66].

The aqueous and ethanolic extracts of *Boerhavia diffusa* (whole plant) have been found active against *Streptococcus* group, *Neisseria gonorrhoeae*, *Salmonella typhimurium*, *Shigella dysenteriae*, *Corynebacterium diphtheriae*, and *Clostridium tetani* (Olukoya *et al.*, 1993). Ethanolic and aqueous extracts also possess antibacterial activity against *Bacillus subtilis* and *Escherichia coli*. The minimum inhibitory concentration of ethanolic extract was found to be 125 and 250 µg/mL for *B. subtilis* and *E. coli*, while the aqueous extract showed 250 µg/mL for *B. subtilis* and *E. coli*, respectively (Sangameswaran *et al.*, 2008) [67]. The antibacterial activity of methanol crude extract of aerial part of plant has been found more than petroleum ether extract and chloroform extract (Ramchandra *et al.*, 2012) [63]. *Boerhavia diffusa* was effective as an adjuvant to chemotherapy in pulmonary tuberculosis. At the end of 4 weeks of experimental period, the clinical recovery rate was faster on supplementation of *Boerhavia diffusa* and 80% of the patients were relieved of cough compared to only 52% in the control group. Similarly, 88% of the patients in were afebrile in 4 weeks compared to 60% of control (Kant *et al.*, 2001) [37].

Various extracts (petroleum ether, chloroform, ethyl acetate, ethyl alcohol and aqueous) of root parts of *B. diffusa* antifungal has activity against dermatophytic fungi *Microsporum gypseum*, *M. fulvum* and *M. canis* (Aggarwal *et al.*, 2004). Ethyl acetate extract of roots of the plant was found to be most effective against target fungal species. The maximum inhibition of mycelial growth was observed for *M. gypseum* (78.83%) followed by *M. fulvum* (62.33%) and *M. canis* (42.30%) of ethyl acetate in the test concentration of 1000 µg/ml 24 hours of incubation. The hot water extract of leaves of *B. diffusa* showed inhibitory effect against the powdery mildew fungus, *Uncinula tectonae* infecting *Tectona grandis* (Sankar and Sreeramula, 2008) [68].

12. Effect on pulmonary metastasis

The hydro-alcoholic extract of *B. diffusa* has inhibitory effect on experimental pulmonary metastases formation by B16F10 melanoma cells in male C57BL/6 mice. Prophylactic (0.5 mg/dose, i.p.) and simultaneous administration of the extract

inhibited metastases formation by about 95% and 87% respectively as compared to untreated control animals. It also reduced the biochemical parameters such as lung collagen hydroxylproline, hexosamine and uronic acid levels compared to the normal levels along with reduction in levels of serum sialic acid and serum γ -glutamyltranspeptidase activity that are markers of neoplastic proliferation. The survival rate of the treated animals increased (more than double) with reduced fibrosis and smooth alveolar function (Leyon *et al.*, 2005) [42]. Administration of the alkaloid punarnavine, enhanced immune response against metastatic progression of B16F-10 melanoma cells in mice (Manu and Kuttan, 2007) [46]. This was evident from the enhanced Natural Killer (NK) cell activity, antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent complement mediated cytotoxicity (ACC), enhanced production of the cytokine IL-2 and lowered levels of GM-CSF and pro-inflammatory cytokines such as IL-1beta, IL-6 and TNF- α .

When a non-toxic concentration of the extract was treated directly to the B16F10 cells *in vitro*, it inhibited the cell proliferation as estimated by the 3H-thymidine uptake assay. From the zymogram analysis using culture supernatant from the extract treated cells it became evident that the components of the extracts inhibited the expression or activity of gelatinases A and B (MMP-2 and MMP-9). As MMPs are closely associated with cell invasion and angiogenesis, inhibition of these functions along with anti-proliferative activity might be attributed to the antimetastatic property of *B. diffusa*.

13. Chemopreventive activity against skin carcinogenesis

On the two-stage mechanism of 7, 12-dimethyl benz(a)anthracene (DMBA) induced skin papillomagenesis in male swiss albino mice (6-7 wk old), the *B. diffusa* exhibit chemopreventive activity. Topical application of *B. diffusa* extract at 3 different stage of tumor genesis i.e. peri-initial phase (7 days before and 7 days after the application of DMBA), promotional stage (from the day of start of croton oil treatment and continued till the end of experiment) and peri as well as post-initial phase (7 days prior to DMBA application and continued till the end of experiment) reduce the number of tumor incidence, average number of tumors per tumor bearing mouse and papillomas per papilloma bearing mouse (Bharali *et al.*, 2003) [11]. The inhibitory activity of the plant extract may be either by preventing the formation of active carcinogens from their precursors or by augmenting detoxification process, preventing promotional events in the mouse skin through free radical scavenging mechanism.

14. Cytotoxic activity

The *B. diffusa* plant appeared to be cytotoxic against tumor cells. The extract of *B. diffusa* root and leaves has promising cytotoxic activity in the comparison of standard anticancer drug, methotrexate. Methotrexate showed almost 40% cell death at a concentration of 200nM, whereas crude ethanolic extract of root showed almost 30% cell death at concentration of 200 μ g/ml; alkaloid fraction and leaf extract each showed 40% cell death at 300 μ g/ml (Srivastava *et al.*, 2005) [77].

15. Non-teratogenic activity

Administration of extract of *B. diffusa* daily in an oral dose of 250 mg/kg of body weight to pregnant albino female rats during the entire period of gestation and found that it was

devoid of any teratogenic effect as litter size, survival rate of fetuses and foetal anomaly (Singh *et al.*, 1991) [73].

16. Anti-convulsant activity

B. diffusa was found to be widely used in epilepsy in Nigerian folk medicine (Akah *et al.*, 1993) [7]. The compound 'liriodendrin' isolated from the methanolic root extract of this plant was reported to show a calcium channel antagonistic activity (Lami *et al.*, 1991) [40]. Based on these facts Kaur and Goel (2011) [11] verified the anti-convulsant activity of various root extracts of *B. diffusa* in male swiss albino mice. They took the methanolic extract (1000, 15000 and 2000 mg/kg), the liriodendrin rich fraction (10, 20 and 40 mg/kg) of this extract, chloroform fraction (20 mg/kg) and phenolic compound fraction (1 mg/kg) for the and showed anticonvulsant activity in pentylenetetrazol (PTZ) induced seizures in mice and concluded that the calcium antagonist activity is responsible for this since the activity was maintained only by liodendrin-rich fraction, additionally established by anticonvulsant activity in BAY k8644-induced seizures (Lami and Kaur, 2011) [40].

17. Anthelmintic activity

The oral administration of dried root powder of *Boerhavia diffusa* has curative effect in children or adults suffering from helminth infection became worm-free within five days (Singh and Udupa, 1972) [74].

18. Insecticidal activity

Ecdysone, an insect moulting hormone isolated from roots of *Boerhavia diffusa* (Babita *et al.*, 2011) [9]. The hexane and acetone extract of twigs have insecticidal activity against *Culex p.fatigans* and *Musca domestica* nebulo (Deshmukh *et al.*, 1982) [21].

19. Antispasmodic/spasmolytic activity

Involuntary muscle spasm is the symptom of various muscle disorders. Common examples include colic, tremors, neck rigidity or torticollis, pain in female genital tract, threatened miscarriages, palsy or glossal palsy and paraplegia. Antispasmodics or spasmolytics offer a symptomatic relief in such conditions.

Boeravinone E is the most potent spasmolytic compound present in the extract and that nonprenylated rotenoids are the spasmolytic agents in *Boerhavia diffusa* root extracts. The methanolic root extract on exogenous (i.e., acetylcholine, histamine, and barium chloride) as well as electrically stimulated contractions in the isolated ileum was effective in spasms. The spasmolytic activity might involve extracellular calcium, whereas intracellular calcium provides negative modulation for intestinal motility (Borrelli, 2006) [6].

20. Hypoglycemic properties

The methanol and ethanol extracts of *B. diffusa* exhibited significant anti-hyperglycemic activities in alloxan as well as in streptozotocin-induced hyperglycemic rats. In alloxan-induced diabetic rats, the maximum percentage reduction in blood glucose level was found in the rats treated with methanol extract of *B. diffusa*. Animals, which received streptozotocin (STZ), also showed a significant reduction in body weight, and increase in water and food intake as compared to vehicle control, which was significantly reversed by methanol extracts of *B. diffusa* after few weeks of treatment (Bhatia *et al.*, 2011) [12]. The chloroform extract of *B. diffusa* leaves produced dose-dependent reduction in blood

glucose in STZ induced non-insulin dependent diabetes mellitus (NIDDM) in rats comparable to that of glibenclamide, an antidiabetic drug (Nalamolu *et al.*, 2004) [54].

The oral administration of aqueous solution of *B. diffusa* L. leaf extract significantly decreased the blood glucose and increased the plasma insulin levels in normal and diabetic rats. The activities of the hepatic enzymes such as hexokinase was significantly increased and glucose-6-phosphatase, fructose 1, 6-bisphosphatase were significantly decreased (Pari and Amarnath Satheesh, 2004) [57]. The effect of leaf extract was found more prominent when compared to glibenclamide (Pari and Amarnath Satheesh, 2004) [57].

21. Hypolipidemic activity

High blood cholesterol results in atherosclerosis, which is characterized by presence of atheromas. There are several reports illustrating the role of natural products like vitamin E, in combating cardiovascular diseases (Khan *et al.*, 2011c; Iqbal *et al.*, 2012) [39, 34]. *Boerhavia diffusa* on administration in hyperlipidemic rats reduced the overall oxidative effect and burden and ameliorated the altered parameters in plasma viz; lipoprotein lipids, total cholesterol (TC), triglyceride (TG), very low-density lipoprotein cholesterol (VLDL-C), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), malondialdehyde (MDA) and in-vitro oxidizability of LDL.

22. Antiglycating properties

Antiglycating properties of *B. diffusa* has been used in treating different ailments due to its multiple pharmacological activities viz., immunomodulatory, antidiabetic, analgesic, hepatoprotective, antiviral and anti-fibrinolytic activity etc. The medicinal importance of plants is mainly due to polyphenols and their antioxidant properties. Ethanol extract of *B. diffusa* has scavenging activity against hydroxyl and superoxide radical moreover, also inhibit the lipid peroxidation in linoleic acid emulsion system. Antioxidant activity of *B. diffusa* was also evident from its significant reducing power and ferrous ion chelating potency (Aftab *et al.*, 1996) [22]. Since, it is well established that *B. diffusa* has potent scavengers of these free radicals; it may also protect biological macromolecules to get damaged further, which in turn reverses or stops the glycation reaction. The ethanol extract of *B. diffusa* might be useful as antiglycating agent apart from antidiabetic and antioxidant properties.

23. Anti-Plasmodial activity

The crude methanolic root extract of *B. diffusa* exhibited anti-plasmodial activity against *Plasmodium berghei* NK 65 (chloroquine resistant strain). It has suppressive, curative and prophylactic potential against malaria (Adefokun *et al.*, 2015) [1].

24. Antiulcer activity

The plant extract of *B. diffusa* possessed antacid activity (Gharate M and Kasture V., 2013) [25]. The aqueous extract significantly reduced the ulcer index and enhanced the percentage protection in a dose dependent manner (Gharate M and Kasture V, 2013) [25]. It might be useful in management of gastric ulcers.

25. Anti-Histaminic activity

Ethanol extract of *Boerhavia diffusa* Linn. Roots inhibited dose-dependent contraction of goat tracheal chain produced

by histamine and also showed significant protection by prolonging preconvulsion dyspnoea time (PCD) in guinea pigs. Thus, plant showed anti-histaminic and broncho-dilating activity against histamine and hence possesses a potential role in the treatment of asthma (Suralkar *et al.*, 2012).

26. Anti-Osteoporotic activity

Osteoporosis, a disorder with an inflammation-aging component; Moreover, there is increasing evidence that immune component is also involve in pathogenesis of osteoporosis. Cytokines secreted following immune response, play a role in development and activation of osteoclasts, additionally being critical for the immunity (Martinis *et al.*, 2006) [19]. Eupalitin-3-O- β -D-galactopyranoside isolated from *Boerhavia diffusa* reported for immunosuppressive property (Pandey *et al.*, 2005) [9]. Moreover, the molecule also possess antiosteoporotic activity (Li *et al.*, 1996). Thus, the evidence for presence of compounds with antiosteoporotic, immunosuppressive, and antiinflammatory activities approves the use of *Boerhavia diffusa* in rheumatic disorders.

Conclusion

On the basis of available reports it can be concluded that the pharmacological properties of *B. diffusa* can be used in therapeutic of management of many ailments. Furthermore, extensive phytochemical characterization is needed to explore various therapeutic potential of *Boerhavia diffusa*. In sphere of versatile nature of plant, to develop it as a drug for future use in human and animals more research studies still a necessity.

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