Journal of Applied Pharmaceutical Science Vol. 3 (01), pp. 133-139, January, 2013
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2013.30126
ISSN 2231-3354

Chemotherapeutic potential of *Boerhaavia diffusa* Linn: A review

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ARTICLE INFO

Article history:
Received on: 13/12/2012
Revised on: 04/01/2013
Accepted on: 18/01/2013
Available online: 29/01/2012

Key words:
B. diffusa, antidiabetic, antiglycating, antioxidant, anticarcinogenic, immunomodulatory.

ABSTRACT

Boerhaavia diffusa Linn. has been shown to exhibit a wide range of medicinal properties for the treatment of diabetes, inflammation, stress, hepatotoxicity, jaundice and heart failure. The extraordinary antioxidant, hepatoprotective, antibiotic, antidiabetic and anticarcinogenic properties of *B. diffusa* have attracted pioneers in the field of science and medicine. Moreover, the therapeutic importance of this plant, which is due to presence of polyphenols and flavanoids, makes this plant medically more important to be exploited by clinicians and scientists to gain more insight into its biological and medicinal properties. The present review on *B. diffusa* focuses over the chemical compositions and its ethno-medicinal uses, linked from ancient times to the present with a scope of development in future. Furthermore, a recent update on mechanistic approaches of *B. diffusa* has also been discussed, which could be helpful for the researchers working in this field. Eventually, based on its antioxidant and antidiabetic characteristics, it is hypothesized that *B. diffusa* might exhibit antiglycating properties as well.

INTRODUCTION

Boerhaavia diffusa Linn., a herbaceous member of family *Nyctaginaceae*, is also known as Punarnava, Raktapunarnava, Shothaghni, Kathillaka, Kshudra, Varshabhu, Raktapushpa, Varshaketu amd Shilatika in India (Yelne *et al*., 2000). There are several species of genus *Boerhaavia* which are distributed in the tropical, subtropical and temperate regions throughout the world like Australia, Asia, U.S.A., and Africa. *B. diffusa* is indigenous to India and found throughout the warmer parts of the country up to an altitude of 2000 m in the Himalayan region (Dhar *et al*., 2011). Out of the 40 species of this genus, six are found in India e.g. *B. diffusa*, *B. chinensis*, *B. erecta*, *B. repens*, *B. rependa*, and *B. rubicunda*. The preliminary screening of the *B. diffusa* plant revealed the presence of sugars, sterols (Singh and Udupa, 1972), β-sitosterol (Srivastava *et al*., 1972) and alkaloids (Garg *et al*., 1980; Shukla, 1982). Surange and Pendse (1972) also reported the presence of alkaloids (0.04%) known as punarnavine and punarnavoside. Misra and Tiwari (1971) isolated hentriacontane, β-sitosterol and ursolic acid along with glucose, fructose and sucrose from the roots of *B. diffusa*. Ahmed and Yu (1992) isolated a new dihydroisofuranoxanthone from the benzene extract of the roots of *B. diffusa* and its structure was elucidated as methyl 3,10-dihydro-11-hydroxy-1-methoxy-4,6-dimethyl-10-oxo-1*H*-furo [3,4-*b*]xanthene-3-carboxylate and designated as borhavine (Ahmed and Yu, 1992). A C-methyl flavone characterized as 5,7-dihydroxy-6-8-dimethoxy flavones was also reported from root (Gupta and Ahmad, 1984).

The most interesting metabolites from the therapeutic point of view are the rotenoids which are known as boeravinones (boeravinone A-F) and have been isolated from the roots of *B. diffusa* plant (Misra and Tewari, 1971; Jain and Khanna, 1989; Kadota et al., 1989; Lami *et al*., 1992) (Figure 1). Two lignans, liriodendrin and syringaresinol mono-beta-D-glucoside, have been isolated from the methanol extract of the roots of *B. diffusa* and the former compound was found to exhibit a significant calcium ($Ca2^{+}$) channel antagonistic effect in frog heart single cells (Lami *et al*., 1991). Gupta and Ali (1998) isolated four new compounds from the root namely boerhavisterol, boerhadiffusene, diffusarotenoid, boerhavilanastenyl benzoate and a rotenoid, boerhavinone A and their structures were elucidated as 9,10-seco-stigmast-5,8 (9)- dien-3β-ol; 1-(2',6',6'-trimethylcyclohex-1'-enyl) -11-(3"-3"-dimethyl cyclohexyl) -4,8-dimethy l–undiec-1-ene; 4,9- dihydroxy- 10-methyl- 6a-dehydrorotenoid-6-pentanoate; 27-*O*- (4'-benzoyl-β-D-glucopyranosyl) 9β-lanost-5-en-3-one and 6-methoxy-9,11-dihydroxy- 10-methyl-6-a, 12a-dihydrorotenoid, respectively .

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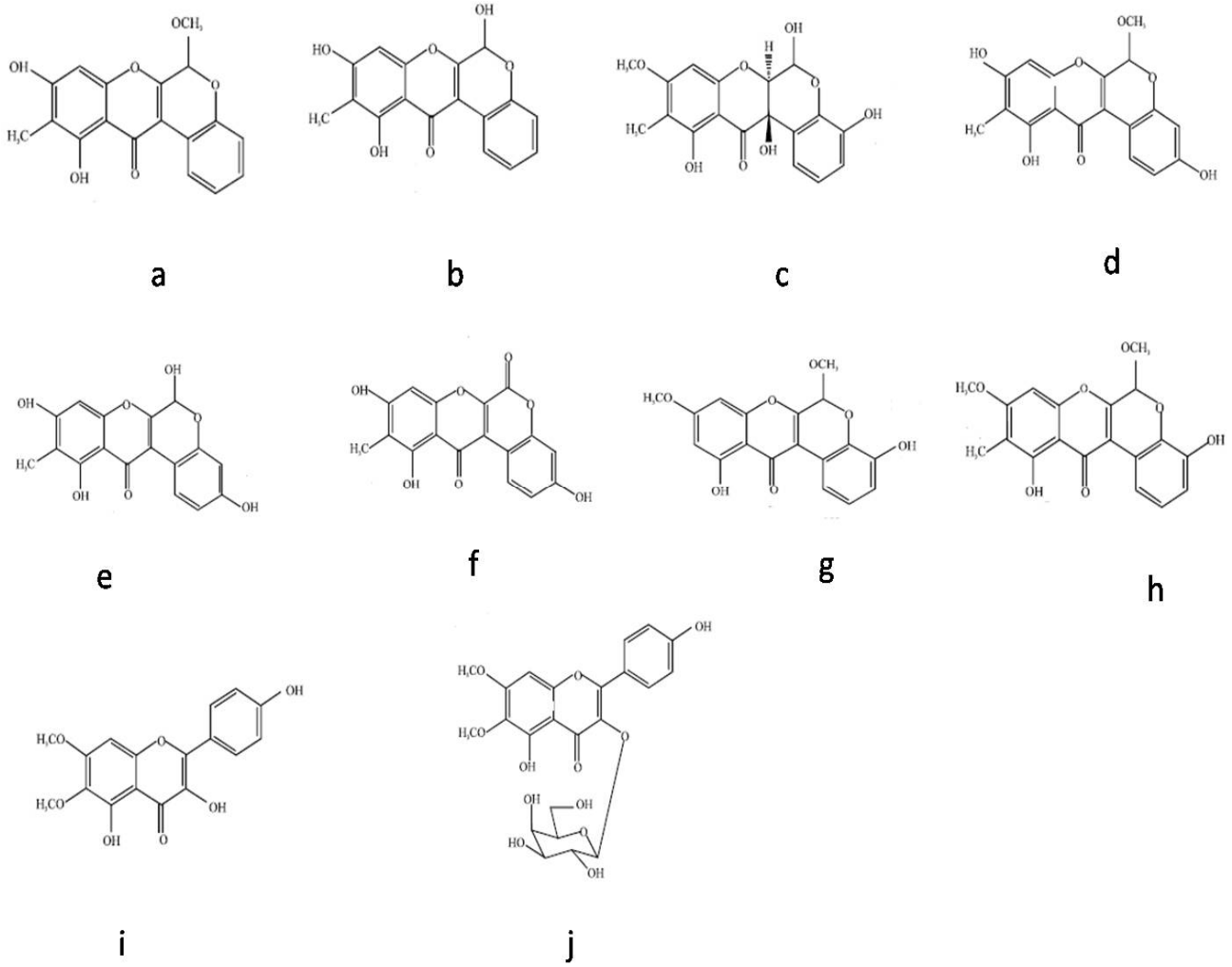

Fig. 1: Chemical structures of bioactive constituents isolated from *Boerhaavia diffusa*. Boeravinone A (a), Boeravinone B (b), Boeravinone C (c), Boeravinone D (d), Boeravinone E (e), Boeravinone F (f), Boeravinone G (g), Boeravinone H (h), Eupalitin (i) and Eupalitin 3-O-galactoside (j).

(Gupta and Ali, 1998). Punarnavoside, a phenolic glycoside is reportedly present in roots (Seth *et al*., 1986). Punarnavoside was later characterized as 2-glucopyrano-4-hydroxy-5-(p-hydroxy phenyl) propionyldiphenylmethane (Jain and Khanna, 1989). Maurya *et al*. (2007) isolated four new compounds from *B. diffusa* namely eupalitin 3-*O*-β-D-galactopyranosyl-(1‴→2″)-*O*-β-D-galactopyranoside, 3,3′,5-trihydroxy-7-methoxyflavone, 4′,7-dihydroxy-3′-methylflavone and 3,4-dimethoxyphenyl-1-*O*-β-D-apiofuranosyl-(1″→3′)-*O*-β-D-glucopyranoside (Maurya *et al*., 2007).

Pharmacological and Clinical properties of *B. diffusa*

Various parts of *B. diffusa* are used for the treatment of numerous disorders in different parts of India. The root, leaves, aerial parts or the whole plant of *B. diffusa* have been employed for the treatment of various disorders in the Ayurvedic herbal medicine. The pharmacological studies have demonstrated that the roots of *B. diffusa* exhibit a wide range of properties such as anti-inflammatory (Bhalla *et al*., 1971), diuretic (Gaitonde *et al*., 1974), laxative (Chopra *et al*., 1956), antiurethritis (Nadkarni, 1976), anticonvulsant (Adesina, 1979), antinematodal (Vijayalakshmi *et al*., 1979), antifibrinolytic (Jain and Khanna, 1989), antibacterial (Olukoya *et al*., 1993), antihepatotoxic (Mishra, 1980; Chandan *et al*., 1991; Rawat *et al*., 1997), anthelmintic, antileprotic, antiasthmatic, antiscabby and antistress activities (Figure 2). The flowers and seeds are used as a contraceptive (Chopra *et al*., 1956).

The leaf extracts from *B. diffusa* has been shown to have hepatoprotective, antioxidant, antinociceptive, antibacterial and antidiabetic properties (Dhar *et al*., 2011). Toxicological studies conducted on *B. diffusa* demonstrated the absence of teratogenic and mutagenic effects (Singh *et al*., 1991). Some of the therapeutically important properties of *B. diffusa* are described below:

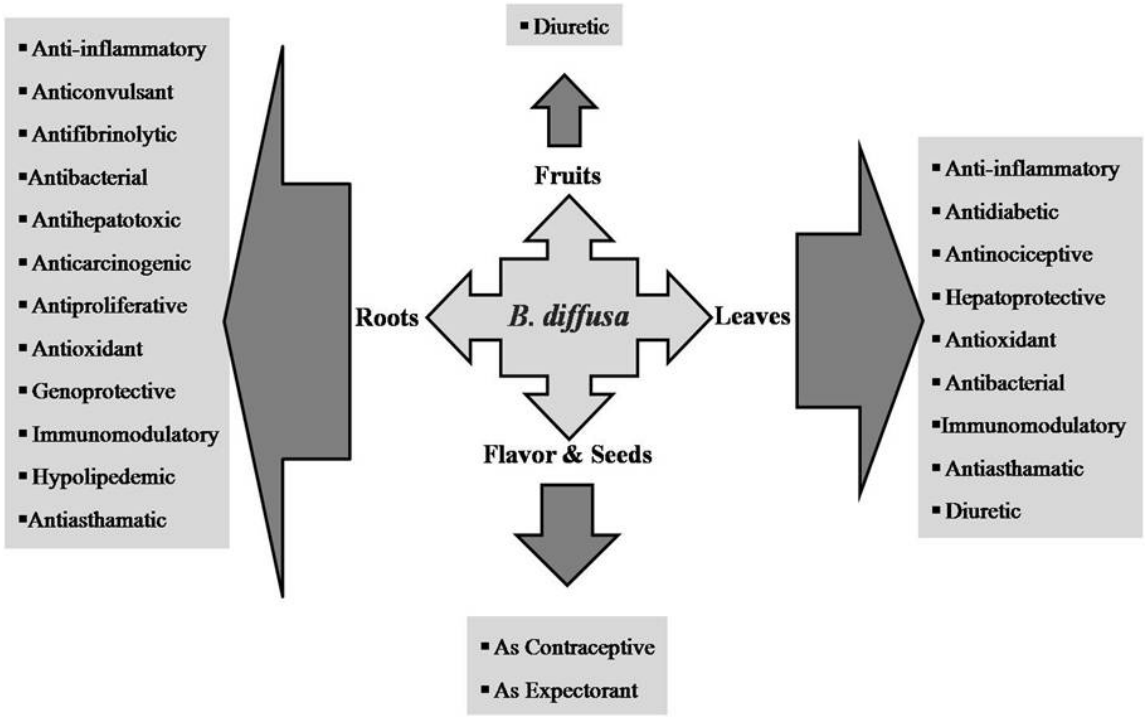

Fig. 2: Chemotherapeutic properties of *Boerhaavia diffusa*

Antioxidant and Genoprotective properties

Excessive generation of free radicals, known as oxidative stress, is one of the major causes of various diseases like diabetes, cancer, cardiovascular diseases etc. There are several antioxidants or plant phytochemicals which are known to ameliorate the various damages caused by oxidative stress (Khan *et al.*, 2011a; Khan *et al*., 2011b). *B. diffusa* possess a rotenoid named boeravinone G, which has been shown to be a very powerful antioxidant and genoprotective agent (Yelne *et al*., 2000; Aviello *et al*., 2011). These effects of rotenoids help in the prevention against the diseases caused by free radicals, cancer and aging which cause damages to DNA macromolecules. The extraordinary antioxidant property of boeravinone G could possibly be used in the near future in order to develop drugs against different pathological conditions and those related to reactive oxygen species (ROS)-mediated injuries.

Antiproliferative and Anticarcinogenic properties

There are only few reports which have strongly shown the antiproliferative and anticarcinogenic potential of *B. diffusa* (Mehrotra *et al*., 2002; Srivastava *et al*., 2009). Mehrotra *et al*. (2002) evaluated the antiproliferative activity of ethanolic extract of *B. diffusa* in several cell lines of different origin and anatomical locations and observed that *B. diffusa* extract inhibited T-cell mitogen phytohemagglutinin and concanavalin A-stimulated proliferation of human peripheral blood mononuclear cells (PBMC). In addition, *B. diffusa* extract also inhibited the growth of several cell lines of mouse and human origin, such as mouse macrophage cells (RAW 264.7), human macrophage cells (U937), human monocytic cells (THP-1), mouse fibroblast cells (L929), human embryonic kidney cells (HEK293), mouse liver cells (BNLCL.2), African green monkey kidney cells (COS-1), mouse lymphoma cells (EL-4), human erythroleukemic cells (K562), and human T cells (Jurkat) (Mehrotra *et al*., 2002).

A previous study has established that a methanol: chloroform fraction of *B. diffusa* (BDF 5) could inhibit the proliferation of human cervical cancer HeLa cell line (Srivastava *et al*., 2009). The S-phase inhibition of the cell cycle and apoptosis played important roles in *B. diffusa*-induced antiproliferative activity against HeLa cells. Moreover, the alcoholic and water extracts of *B. diffusa* is known to contain several bioactive molecules such as reducing sugars, starch and lignans, liriodendrin, syrigaresinol and several boeravinones (boeravinone A–J.) The activity shown by the BDF 5 has been attributed to these diverse compounds. In another study, two rotenoids isolated from *B. diffusa*, boeravinones G and H, have been found to potently inhibit the drug efflux activity of breast cancer resistance protein (BCRP/ABCG2), a multidrug transporter responsible for cancer cell resistance to chemotherapy (Ahmed-Belkacem *et al*., 2007). Thus, these studies provided enough evidences to further explore the potential of this plant in the chemoprevention and management of cancer.

Immunomodulatory properties

Immunoregulation is a complex balance between regulatory and effector cells and any imbalance in the immunological mechanism may lead to pathogenesis of several diseases. Modulation of the immune system is an emerging trend in chemotherapeutic research. Immunomodulators are materials which can modify the body's defense mechanism either by

enhancing or controlling immune responses. They can regulate 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.

There are many reports which have demonstrated the immunomodulatory properties of *B. diffusa*. Pandey *et al*. (2005) evaluated the effect of hexane, chloroform and ethanol extracts of *B. diffusa* and two pure compounds Bd-I (eupalitin-3-O-beta-D-galactopyranoside) and Bd-II (eupalitin) on T cell mitogen (phytohemagglutinin; PHA) stimulated proliferation of human peripheral blood mononuclear cell (PBMC), mixed lymphocyte culture, lipopolysaccharide (LPS) stimulated nitric oxide production by RAW 264.7, PHA and LPS induced IL-2 and TNF-α production, in human PBMCs, superoxide production in neutrophils, human natural killer (NK) cell cytotoxicity and nuclear translocation of nuclear factor-kappa B and AP-1 in PHA stimulated PBMCs. The results showed that chloroform and ethanol extracts inhibited PHA stimulated proliferation of peripheral blood mononuclear cells, NK cell cytotoxicity as well as LPS induced NO production by RAW 264.7; the hexane extract showed no activity. Bd-I inhibited PHA-stimulated proliferation of peripheral blood mononuclear cells, NK cell cytotoxicity as well as LPS induced NO production by RAW 264.7 equally or more effectively than the parent ethanolic extract. Bd-I inhibited production of PHA stimulated IL-2 at the protein and mRNA transcript levels and LPS stimulated TNF-α production in human PBMCs; it also blocked the activation of DNA binding of nuclear factor-kappa B and AP-1, two major transcription factors centrally involved in expression of the IL-2 and IL-2R gene, which are necessary for T cell activation and proliferation (Pandey *et al*., 2005).

Mehrotra *et al*. (2002) evaluated the immunomodulatory properties of this plant extract on various *in vitro* tests such as human natural killer (NK) cell cytotoxicity, production of nitric oxide (NO) in mouse macrophage cells, RAW 264.7, IL-2, tumor necrosis factor-α (TNF-α), intracytoplasmic interferon-γ (IFN-γ) and expression of various cell surface markers on human peripheral blood mononuclear cells (PBMCs). This study established that ethanolic extracts of *B. diffusa* roots inhibited human NK cell cytotoxicity *in vitro*, production of NO in mouse macrophage cells, IL-2 and TNF-α in human PBMCs. Intracytoplasmic IFN-γ and cell surface markers such as CD16, CD25, and HLA-DR did not get affected on treatment with *B. diffusa* extract (Mehrotra *et al*., 2002).

Manu and Kuttan (2008) studied the effect of *B. diffusa* extract on the cell mediated immune (CMI) response against metastatic progression of B16F-10 melanoma cells in C57BL/6 mice model and observed that administration of *B. diffusa* extract enhanced natural killer (NK) cell activity, antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent complement mediated cytotoxicity (ACC). Production of the cytokine IL-2 was significantly enhanced by the administration of *B. diffusa* compared to the untreated metastatic tumor bearing control. Levels of GM-CSF and pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α were significantly lowered by *B. diffusa* administration compared to metastatic control (Manu and Kuttan, 2008). The gene expression level of IL-2, IL-1β, IL-6, TNF-α and GM-CSF in B16F-10 cells also correlated the above result. In another study, Manu and Kuttan (2009) studied the effect of punarnavine, an alkaloid from *B. diffusa*, on the immune system using Balb/c mice and observed that intraperitoneal administration of punarnavine enhanced the proliferation of splenocytes, thymocytes and bone marrow cells both in the presence and absence of specific mitogens *in vitro* and *in vivo*. More over administration of punarnavine significantly reduced the lipopolysaccharide (LPS) induced elevated levels of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 in mice (Manu and Kuttan, 2009).

Antiinflammatory properties

Ethanol extract of *B. diffusa* leaves exhibited anti-inflammatory effect with carrageen, serotonin, histamine and dextran induced rat paw edema models, respectively (Bhalla *et al*., 1971).

Hepatoprotective properties

The roots of *B. diffusa* are used by a large number of tribes in India for the treatment of various hepatic disorders and for internal inflammation Clinical data has reported effectiveness of *B. diffusa* in cases of oedema and ascites resulting from early cirrhosis of the liver and chronic peritonitis. An aqueous extract of thinner roots of *B. diffusa* exhibited the remarkable protection of various enzymes such as serum glutamic-oxaloacetic transaminase and glutamic-pyruvic transaminase against thioacetamide induced hepatic injury in rats (Rawat *et al*., 1997). The aqueous root extract of *B. diffusa* also showed the hepatoprotective activity against the toxic effects generated by carbon tetrachloride in the liver (Chandan *et al*., 1991). Surange and Pendse (1972) studied the effect of ethanol root extract of *B. diffusa* on country made liquor induced hepatotoxicity in albino rats and observed that *B. diffusa* extract protected the rats from hepatotoxic action of liquor by ameliorating the alanine aminotransferase (ALT), triglyceride, cholesterol and total lipid levels in both serum and tissues (Surange and Pendse, 1972). Histopathological studies also showed marked reduction in fat deposits in animals receiving *B. diffusa* along with country made liquor. The aerial parts of *B. diffusa* have also been reported to exhibit the hepatoprotective activity (Chakraborti and Handa, 1989). The hepatoprotective properties of *B. diffusa* have been attributed to ursolic acid. Olaleye *et al*. (2010) also evaluated the antioxidant and hepatoprotective properties of leaf extract of *B. diffusa* in the acetaminophen-induced liver damage model and found that pretreatment with aqueous and ethanolic extracts decreased the activities of alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, and the level of bilirubin in the serum that were elevated by acetaminophen. The extracts also protected against acetaminophen induced lipid peroxidation (Olaleye *et al*., 2010).

Antibacterial properties

The leaves of *B. diffusa* have been shown to exhibit potent antibacterial activity against various Gram-negative and Gram-positive bacteria which might be due to various phytochemicals present in the leaves (Olukoya *et al*., 1993; Awasthi and Verma, 2006). The ethanol extract of the plant showed an inhibitory effect on Gram-positive bacteria like *Staphylococcus aureus, Bacillus subtilis, Streptococcus faecalis, Micrococcus luteus* and all Gram-negative bacteria. In addition, methanol extract demonstrated an inhibitory effect against all Gram-positive bacteria, however, *Micrococcus luteus* and Gram-negative bacteria like *Klebsiella pneumoniae, Proteus vulgaris, Serratia marcescens* and *Shigella flexneri* showed no inhibitory effect (Awasthi and Verma, 2006).

Anticonvulsant properties

Kaur and Goel (2011) investigated the possible anticonvulsant properties of the methanol root extract of *B. diffusa* and its different fractions including a calcium channel antagonist, liriodendrin-rich fraction in pentylenetetrazol (PTZ)-induced seizures in mice and observed that the crude methanol extract of *B. diffusa* and only its liriodendrin-rich fraction showed a dose-dependent protection against PTZ-induced convulsions. The liriodendrin-rich fraction also showed significant protection against seizures induced by BAY k-8644, a calcium channel agonist. These findings reiterated the anticonvulsant activity of methanol extract of *B. diffusa* roots (Kaur and Goel, 2011).

Hypolipidemic properties

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). Recent investigations have revealed the efficacy of *B. diffusa* as an antioxidant and hypolipidemic agent by analyzing all the parameters in plasma 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. In a recent study, all the plasma lipid parameters were found to be significantly increased in hyperlipidemic control rats and administration *of B. diffusa* extract significantly reduced the overall oxidative burden and effectively ameliorated the above altered parameters (Khan *et al*., 2011).

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 (Bhatia *et al*., 2011). Both the extracts from *B. diffusa* have also been shown improve the condition of diabetes as indicated by parameters like body weight along with serum cholesterol and triglyceride levels. The extracts of *B. diffusa* showed significant increase in glucose tolerance, but methanol extract exhibited more activity (Bhatia *et al*., 2011). 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). In another study, the chloroform extract of *B. diffusa* leaves produced dose-dependent reduction in blood glucose in STZ-induced non insulin dependent diabetes mellitus (NIDDM) rats comparable to that of glibenclamide, an antidiabetic drug (Nalamolu *et al*., 2004).

Pari and Amarnath Satheesh (2004) investigated the effects of oral administration of aqueous solution of *B. diffusa* L. leaf extract on blood glucose concentration and hepatic enzymes in normal and alloxan-induced diabetic rats and observed a significant decrease in blood glucose and increase in plasma insulin levels in normal and diabetic rats. Treatment with *B. diffusa* L. leaf extract resulted in a significant reduction of glycosylated haemoglobin and an increase in total haemoglobin level. The activities of the hepatic enzymes such as hexokinase was significantly increased and glucose-6-phosphatase, fructose-1,6-bisphosphatase were significantly decreased by the administration of extract in normal and diabetic rats. A comparison was made between the action of leaf extract and glibenclamide and the effect of extract was found more prominent when compared to glibenclamide (Pari and Amarnath Satheesh, 2004).

Antiglycating properties of *B. diffusa*: a future perspective

B. diffusa has been traditionally used in treating different ailments due to its multiple pharmacological activities viz., immunomodulatory, antidiabetic, analgesic, hepatoprotective, antiviral and anti-fibrinolytic activity etc. The therapeutic importance of plants is mainly due to polyphenols and their antioxidant properties. As discussed earlier, *B. diffusa* ethanol extract (BDE) showed significant scavenging activity against hydroxyl and superoxide radical. It also significantly inhibited the lipid peroxidation in linoleic acid emulsion system. Antioxidant activity of BDE was also evident from its significant reducing power and ferrous ion chelating potency. Thus, the data obtained from *in vitro* models clearly established the antioxidant potency of BDE (Aftab *et al*., 1996). Furthermore, our previous study has shown that DNA and proteins undergo glycation reaction in the hyperglycemic conditions and these reaction produces highly reactive free radical species i.e., hydroxyl radical and superoxide anions which cause damage to the DNA and protein macromolecule (Ahmad *et al*., 2011; Mustafa *et al*., 2011; Ahmad *et al*., 2011). Since, it is well established that BDE 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. In the light of the above explanation, we hypothesize that the ethanol extract of *B. diffusa* might be useful as antiglycating agent apart from antidiabetic and antioxidant properties.

CONCLUSION

In recent year major thrust by whole of the pharmaceutical industry is focused towards design and development of new innovative/indigenous plant based drugs through investigation of leads from traditional system of medicine. Ethno-botanical and traditional uses of natural compounds, especially of plant origin received much attention as they are well tested for their efficacy and generally believed to be safe for human use. Numerous investigations on *B. diffusa* have now established that it is an important medicinal plant having a plethora of chemical constituents effective against a large number of ailments. However, further extensive biochemical and molecular investigations are needed in order to identify the active components involved in various pharmacological activities. Furthermore, our novel hypothesis of antiglycating properties of the plant extract could help in better understanding and prevention of bio-macromolecule (DNA and protein) damage in hyperglycemic condition which in turn could help in prevention of onset of several diseases linked to the glycation reaction like, diabetes, arthritis and ageing.

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How to cite this article:

M. Salman Khan, Irfan A. Ansari, Saheem Ahmad, Firoz Akhter, Arshya Hashim, A. K. Srivastava., Chemotherapeutic potential of *Boerhaavia diffusa* Linn: A review. J App Pharm Sci. 2013; 3 (01): 133-139.