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## ***Barleria prionitis* Linn.: A Review of its Traditional Uses, Phytochemistry, Pharmacology and Toxicity**

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### **ABSTRACT**

*Barleria prionitis* Linn. (Family: Acanthaceae) is a well-known perennial, Ayurvedic herb distributed in the tropical Asia, Africa and Yemen. The whole plant or its specific parts (leaf, stem, root, bark and flower) has been utilized for treatment of toothache, catarrhal affections, whooping cough, inflammations, glandular swellings, urinary infection, jaundice, fever, gastrointestinal disorders and as diuretic and tonic. A wide range of phytochemical constituents including balarenone, pipataline prionisides, barlerinoside, verbascoside, shanzhiside methyl ester, barlerin, acetylbarlerin, lupulinoside, scutellarein have been isolated from the different parts of this plant. Extracts and isolated phytochemicals from this plant have been found to possess wide range of pharmacological include antimicrobial, anthelmintic, antifertility, antioxidant, antidiabetic, anti-inflammatory, anti-arthritic, cytoprotective, hepatoprotective, diuretic, antidiarrhoeal, enzyme inhibitory and anti-nociceptive activities without any toxic effects. So, in this review attempt has been made to highlight the traditional uses, phytochemistry, pharmacology and toxicity of this plant.

**Key words:** *Barleria prionitis*, traditional uses, phytochemistry, pharmacology and toxicity

### **INTRODUCTION**

Medicinal plants are used worldwide in management of healthcare problems since time immemorial and approximately 60-80% of the world's population still depending on the traditional medicines (Dey *et al.*, 2009; Ansari and Inamdar, 2010; Shafaei *et al.*, 2011; Menghani *et al.*, 2011; Ramachandran *et al.*, 2011; Kumar and Chandrashekar, 2011). Currently, the global demand of herbal medicines is increasing rapidly because of their higher safety margin and low cost (Musyimi *et al.*, 2008). Medicinal plants are believed to be a potential source for the discovery of new drug candidates (Mohajer *et al.*, 2006; Dey *et al.*, 2010; Roy and Banerjee, 2010; Kayode and Kayode, 2011). Numbers of active compound classes like alkaloids, terpenes, flavonoids, glycosides, lignans, phenolics, saponins etc has been used in the modern system of medicines for their wide therapeutic activities (Saadabi *et al.*, 2006; Mukherjee *et al.*, 2009; Sohail *et al.*, 2011; Agrawal *et al.*, 2011; Gantait *et al.*, 2011).

Ayurveda, a traditional systems medicine in India, have major treatment globally (Mukherjee *et al.*, 2009; Bele *et al.*, 2010). *B. prionitis* Linn. (family: Acanthaceae) is well-known

medicinal plant in ayurvedic system of medicine in India. The whole plant, root, leaves and bark of the plant occupy a significant place in the indigenous system of medicine of India for the treatment of various diseases like toothache, inflammations, boils, glandular swellings, catarrhal affections etc. (Khare, 2004, 2007; Daniel, 2006; Aneja *et al.*, 2010). In India it has several vernacular names like In English-yellow nail-dye plant, porcupine flower; Sanskrit-vajradanti, kurantaka, koranta; Hindi-kala bans, katsareya, piabansa; Bengali-kantajinti, peetjhanti; Gujarati-kantashila; Kannada-karunta, mullugorante; Malayalam-chemmulhi, varelmutti; Marathi-kalsunda, kate koranti, kholeta, koranta, pivala-koranta; Odia-daskeranta; Tamil-kaattu kanagaambaram, semmulli and in Telugu-mullugorinta chettu (Shendage and Yadav, 2010; Singh and Panda, 2006). In Indian traditional systems of medicine (Ayurveda) it is known as sahadara, baana, kurantaka, kuranta, koranda, korandaka, shairiya and pita-saireyaka. In folk medicine it is known as piyaabaasaa, jhinti and katsaraiyaa (Khare, 2007). Here, the attempt has been made to highlight its traditional uses, phytoconstituents, pharmacology and toxicity.

## **DISTRIBUTION**

It is commonly found in tropical Asia include India, Malesia, Pakistan, Philippines, Sri Lanka and in tropical Africa and Yemen. This plant is distributed throughout the hotter parts of India and commonly grown in gardens as a hedge plant (Khare, 2007; Shendage and Yadav, 2010). It is commonly found in the states of India include Andaman and Nicobar Islands, Andhra Pradesh, Assam, Bihar, Chhattisgarh, Delhi, Diu and Daman, Goa, Gujarat, Jharkhand, Karnataka, Kerala, Laccadive and Maldiv Islands, Madhya Pradesh, Maharashtra, Orissa, Pudhucherry, Rajasthan, Tamil Nadu, Uttarakhand, Uttar Pradesh and West Bengal (Shendage and Yadav, 2010).

## **GENERAL BOTANICAL DESCRIPTION**

*B. prionitis* is a perennial, erect, bushy shrub grows up to 1-2 m high. They possess 2-4 sharp long axillary spines which about 11 mm long. The stems are terete, glabrous, much branched with cylindrical and tapering branchlet (Dassanayake, 1998; Kamble *et al.*, 2007). Leaves are smooth, opposite, ovate-elliptic to obovate, acuminate, tapering to base, bristle-tipped and about 6-15 cm long and 4-6 cm wide. The petioles are about 0.5-3 cm long (Shendage and Yadav, 2010). The flowers are sessile, yellow in colour and often solitary in lower axils and spicate in the upper axils. Bracts are acute, linear-lanceolate, foliaceous, about 1-1.5 cm long and 0.2-0.8 cm wide with bristle tipped (Dassanayake, 1998; Shendage and Yadav, 2010). The bracteoles are long, narrowly linear-lanceolate, spinous-tipped, about 1.4 cm long and 0.15 cm wide. The calyx is two partite. The outer calyx-lobes are mucronate, ovate-oblong and inner lobes are mucronate, linear-lanceolate. The outer lobes are 1.5 cm long and 0.4 cm wide while the inner lobes are 13 mm long and 2 mm wide (Dassanayake, 1998; Kamble *et al.*, 2007). The corolla is bright, golden yellow in colour with pubescent outside and glabrous inside and about 1.5 cm long. It is somewhat bilipped and lobes are oval-oblong, rounded and entire. The stamens include 2 fertile stamens and 2 staminoid stamens. The fertile stamens are exerted beyond the corolla tube while the staminoid stamens are very short. The filaments are hairy and about 2-2.5 cm long, glandular-pubescent and yellowish in colour. The yellow anthers are 3 mm long (Dassanayake, 1998; Kamble *et al.*, 2007; Shendage and Yadav, 2010). The ovary is ovoid and stigma is long, linear, sticky and pinkish in colour. The fruit capsule is ovoid, 2 seeded and about 1.5-2 cm long and 0.6-0.8 cm wide. The seeds are oval-oblong,

covered with silky copper-brown appressed hairs and measuring about 7.4-8.5×6-6.8 mm (Dassanayake, 1998; Kamble *et al.*, 2007; Shendage and Yadav, 2010).

### USE IN TRADITIONAL MEDICINE

In indigenous system of medicine in India, the juice of *B. prionitis* leaves is used in stomach disorders, urinary affections, ulcer and fever (Khare, 2007). The leaf juice mixed with honey given to children in catarrhal affections and fever (Khare, 2007). Leaves are chewed to relieve from toothache. Some tribal communities are used leaves for the treatment of piles and reduce irritation (Aneja *et al.*, 2010; Shukla *et al.*, 2011). The leaf juice is applied externally in lacerated soles of feet and pimples. The dried stem bark is used as an expectorant in whooping cough and diaphoretic (Khare, 2007; Aneja *et al.*, 2010). The aerial parts of this plant are also used in inflammations and gastrointestinal disorders. The root paste is externally applied to disperse boils and glandular swellings (Aneja *et al.*, 2010). The flowers are used internally for the treatment of migraine, internal abscesses, oedema, haemoptysis, urethral discharges, seminal disorders and reduce obesity (Khare, 2004). The whole plant is also used in stiffness of limbs, enlargement of scrotum and sciatica. The whole plant, specifically the roots are used as diuretic and tonic. It is also used in urinary infection, jaundice, hepatic obstruction and dropsy (Shukla *et al.*, 2011; Khadse and Kakde, 2011). Ash of the whole plant with honey is given in bronchial asthma. The crude extract of this plant in oil is recommended in arresting the greying of hair, arthritis and gout (Khare, 2004, 2007). In South India, this plant is widely used in neurological disorders like paraplegia, sciatica, also in leprosy and other skin diseases (Khare, 2004). The plant formulation, available in over the counter is prescribed in dysurea, rheumatic affections, internal abscesses, nervine disorders and in chronic sinusitis (Khare, 2004).

### PHYTOCHEMISTRY

Preliminary phytochemical analysis of hydro-methanolic extract of *B. prionitis* whole plant indicated the presence of glycosides, saponins, flavonoids, steroids and tannins (Maji *et al.*, 2011). The leaves and flowering tops were reported to rich in potassium salts (Khare, 2007). Several phytochemicals viz., balarenone (1), pipataline (2), lupeol (3), prioniside A (4), prioniside B (5) and prioniside C (6) has been isolated from the ethanolic extract of *B. prionitis* (Ata *et al.*, 2007; Kosmulalage *et al.*, 2007). Numbers of glycosides include barlerinoside (7), verbascoside (8), shanzhiside methyl ester (9), 6-O-trans-p-coumaroyl-8-O-acetylshanzhiside methyl ester (10), barlerin (11), acetylbarlerin (12), 7-methoxydiderroside (13), lupulinoside (14) has been also isolated from the aerial parts (Taneja and Tiwari, 1975; Chen *et al.*, 1998; Singh *et al.*, 2005; Ata *et al.*, 2009). Two anthraquinones derivatives has been also identified in this plant and their structures were characterized as 1,8, dihydroxy-2,7-dimethyl 3, 6-dimethoxy anthraquinone and 1,3,6,8-tetra methoxy-2,7-dimethyl anthraquinone (Ganga Raju *et al.*, 2002). The leaves were reported to contain scutellarein (15), melilotic acid (16), syringic acid (17), vanillic acid (18), p-hydroxybenzoic acid (19), 6-hydroxyflavones (20) (Daniel, 2006). Beside these phytochemicals, luteolin-7-O- $\beta$ -D-glucoside (21),  $\beta$ -sitosterol (22), scutellarein 7-neohesperidoside (23), apigenin 7-O-glucoside (24), 13, 14-seco-stigmasta-5, 14-diene-3-a-ol (25) were also reported to present in *B. prionitis* (Harborne *et al.*, 1971; Gupta and Saxena, 1984; Gupta *et al.*, 2000; Khare, 2007; Kosmulalage *et al.*, 2007). The structures of some phytochemicals are given in Fig. 1.

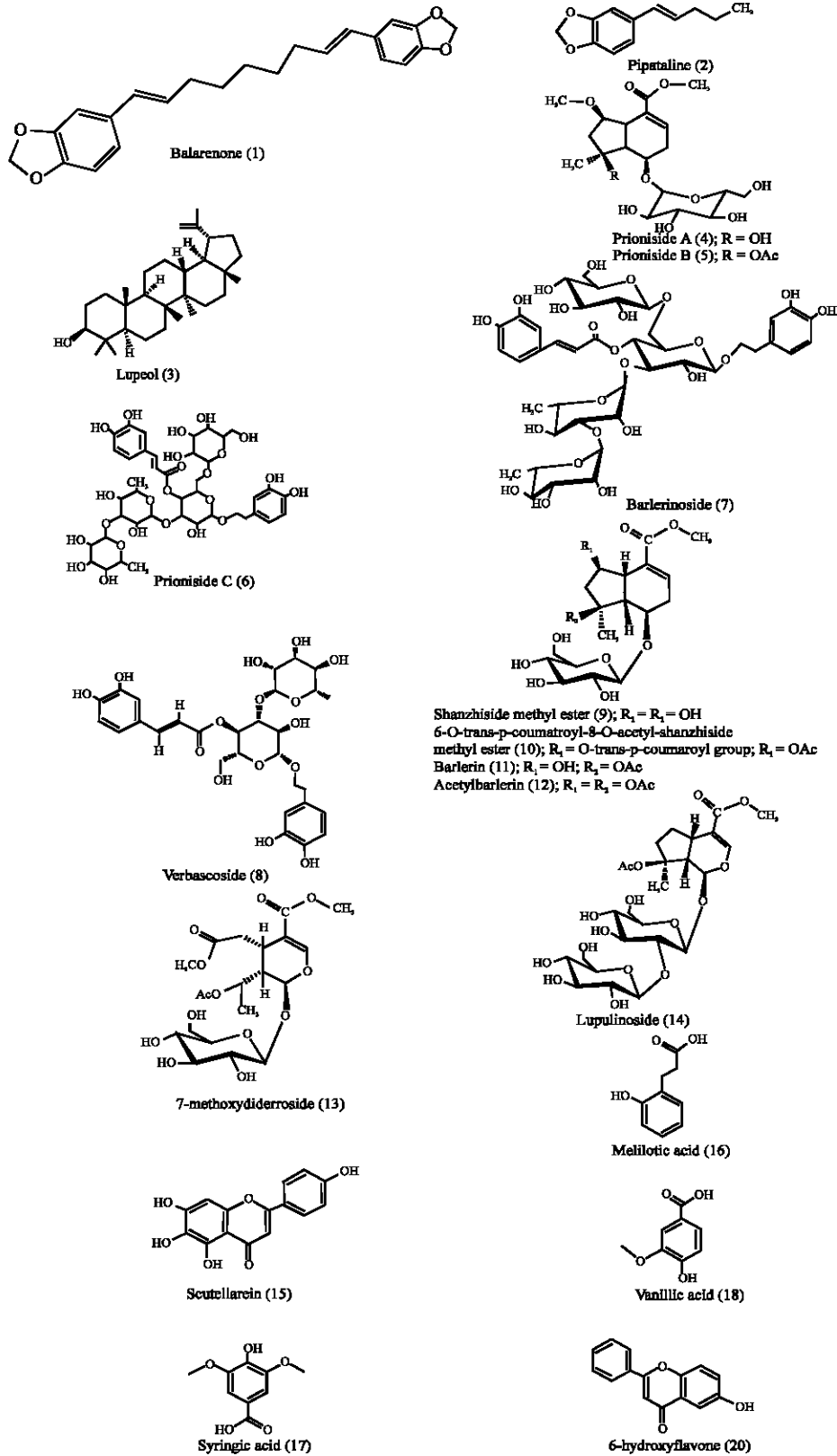


Fig. 1: Continued

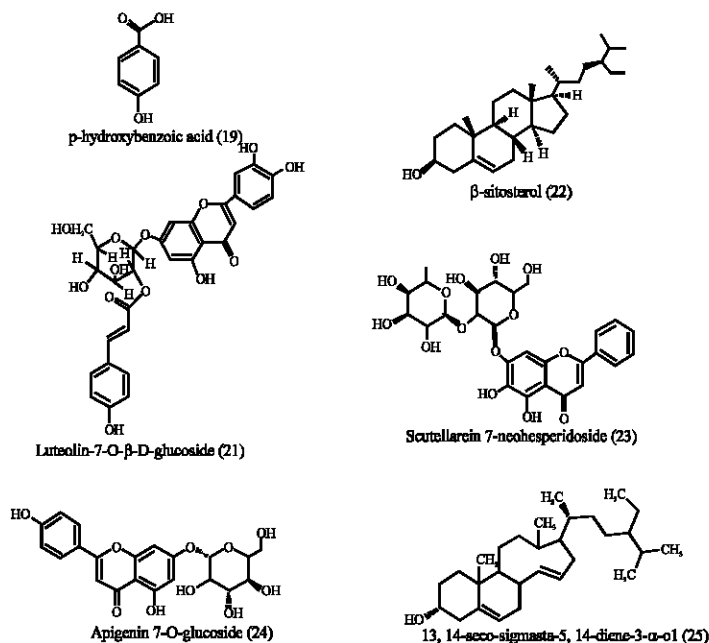


Fig. 1: Structures of some selected phytochemical isolated from *B. prionitis* Linn.

## PHARMACOLOGICAL ACTIVITY

**Antibacterial activity:** It has been reported that different solvent (ether, ethanol and chloroform) extracts of *B. prionitis* leaves and callus showed antibacterial activity against numbers of gram positive bacterial isolates while no or slight inhibitions were observed against the aqueous extracts. Among these extracts, the ether extract showed strongest antibacterial activity (Shukla *et al.*, 2011). Some antibacterial phytochemicals include balarenone, pipataline and 13, 14-seco-stigmasta-5, 14-diene-3- $\alpha$ -ol have been isolated from the ethanolic extract of *B. prionitis* and these compounds showed strong antibacterial activity against *Bacillus cereus* and *Pseudomonas aeruginosa* (Kosmulalage *et al.*, 2007). It was reported that the different solvent extracts of barks, leaves and stems showed potent antibacterial activity against oral pathogens *Streptococcus mutans*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Bacillus cereus* causing dental caries (Aneja *et al.*, 2010). Among the extracts, the methanolic bark extract showed more potent inhibitory activity against all the oral pathogenic bacteria (Aneja *et al.*, 2010). The antimicrobial activity of *B. prionitis* may be due to the presence of acetylbarlerin, barlerin, shanzhiside methyl ester, verbascoside, balarenone, pipataline, 13, 14-seco-stigmasta-5, 14-diene-3- $\alpha$ -ol and 6-O-acetyl shanzhiside methyl ester (Kosmulalage *et al.*, 2007; Aneja *et al.*, 2010).

**Antifungal activity:** The acetone, methanol and ethanol extracts of *B. prionitis* bark showed antifungal activity against oral pathogenic fungus *Saccharomyces cerevisiae* and two strains of *Candida albicans*. Among the extracts, methanolic extract was more potent against all the fungal isolates (Aneja *et al.*, 2010). Amoo *et al.* (2011) reported that the petroleum ether, dichloromethane and ethanol extract of stem and root showed fungistatic and fungicidal activities against *C. albicans*.

**Antiviral activity:** Chen *et al.* (1998) isolated two iridoid glycosides viz. 6-O-trans-p-coumaroyl-8-O-acetylshanzhiside methyl ester and its cis isomer from *B. prionitis*. *In vitro* study showed that

these two glycosides possess potent antiviral activity against Respiratory Syncytial Virus (RSV) with  $EC_{50}$  and  $IC_{50}$  values of 2.46 and 42.2  $\mu\text{g mL}^{-1}$ , respectively (Chen *et al.*, 1998).

**Anthelmintic activity:** The whole plant extract of *B. prionitis* was reported to have anthelmintic activity (Chavan *et al.*, 2010a). *In vitro* study showed that aqueous and ethanolic extracts were significantly paralyzed the *Pheretima posthuma* worms at lower doses (50, 75 and 100  $\text{mg mL}^{-1}$ ) and caused death over 100  $\text{mg mL}^{-1}$  dose concentration in compare to standard drug albendazole (Chavan *et al.*, 2010b).

**Antifertility activity:** The antifertility activity of *B. prionitis* roots was reported by Gupta *et al.* (2000). Oral administration of methanolic root extract (100  $\text{mg/rat/day}$ ) reduced the spermatogenesis in male albino rats (Gupta *et al.*, 2000; Verma *et al.*, 2005). It was observed that the root extract decreased the production of round spermatids, sperm motility, spermatogonia, preleptotene spermatocytes population and mature leydig cells. Biochemical investigation revealed that the root extract was also reduced the total protein, glycogen, sialic acid contents of the testes, testicular glycogen contents, epididymides, ventral prostate and seminal vesicle (Gupta *et al.*, 2000; Verma *et al.*, 2005). The antifertility effect of root extract may be due to the presence of iridoid glycosides barlerin and acetyl barlerin via affecting the functions of testicular somatic cells (Gupta *et al.*, 2000).

**Antioxidant activity:** The whole plant extract of *B. prionitis* was reported to show potent antioxidant activity (Chetan *et al.*, 2011). *In vitro* study showed that the ethanol and aqueous extracts of whole plant possess significant antioxidant activity against 1, 1-diphenyl-2-picrylhydrazyl (DPPH), 2, 2'-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid (ABTS), nitric oxide and hydroxyl radical scavenging assay and  $\text{Fe}^{3+}$  reduction assay (Chetan *et al.*, 2011). In compare to antioxidant potency, the ethanol extract was more potent than aqueous extract and its antioxidant potency showed sharp co-relation with the phenolic content of the extract (Chetan *et al.*, 2011). Amoo *et al.* (2011) reported that the methanolic extract of roots, leaves and stems showed significant antioxidant property. It was observed that the leaves showed higher degree antioxidant potential and high phenolic content in comparison to flower and stem (Jaiswal *et al.*, 2010a). Some glycosides have been isolated from the aerial parts of *B. prionitis* namely barlerinoside, shanzhiside methyl ester, 6-O-trans-p-coumaroyl-8-O-acetylshanzhiside methyl ester, barlerin, acetylbarlerin, 7-methoxydideroside and lupulinoside showed antioxidant activity. Among the isolated glycosides, only barlerinoside showed higher potential of antioxidant property with an  $IC_{50}$  value of 0.41  $\text{mg mL}^{-1}$  (Ata *et al.*, 2009).

**Antidiabetic activity:** Dheer and Bhatnagar (2010) revealed that the alcoholic extract of *B. prionitis* leaves showed antidiabetic activity. Oral administration of alcoholic extract at dose concentration 200  $\text{mg kg}^{-1}$  body weight significantly decreased the blood glucose, glycosylated hemoglobin level and increased serum insulin and liver glycogen level in diabetic rats. The extract also arrested the diabetes mediated weight loss (Dheer and Bhatnagar, 2010).

**Enzyme inhibitory effects:** The extracts from the different parts and isolated phytochemicals of *B. prionitis* reported to inhibit the clinically significant enzymes, Acetylcholinesterase (AChE) and

glutathione S-transferase (GST). Kosmulalage *et al.* (2007), Ata *et al.* (2007, 2009), Amoo *et al.* (2009, 2011) reported that the methanolic extracts of leaf, stem and root exhibited AChE inhibitory activities and the leaf and stem extracts exhibited higher potency of inhibition in compare the root extract. Several glycosides include barlerinoside, shanzhiside methyl ester, 6-O-trans-p-coumaroyl-8-O-acetylshanzhiside methyl ester, barlerin, acetylbarlerin, pataline, lupeol, 7-methoxydideroside, 13, 14-seco-stigmasta-5, 14-diene-3- $\alpha$ -ol and lupulinoside have been isolated from the aerial parts of *B. prionitis* and these compounds showed different levels of AChE inhibitory activity (Kosmulalage *et al.*, 2007; Ata *et al.*, 2009). All these compounds and prioniside B and prioniside C also showed GST inhibitory activity of which prioniside B and prioniside C were more potential GST inhibitors (Kosmulalage *et al.*, 2007; Ata *et al.*, 2007, 2009).

**Anti-inflammatory activity:** Several reports demonstrated the usage of *B. prionitis* in the treatment of inflammations. The anti-inflammatory activity of *B. prionitis* was evaluated through *in vitro* enzyme based cyclooxygenase (COX-1 and COX-2) assays. It was found that the dichloromethane, petroleum ether and ethanol extracts of leaves, stems and roots exhibited significant inhibition of COX-1 and COX-2 with subsequent inhibition of prostaglandin synthesis that are involved in pain sensation (Amoo *et al.*, 2009). The Aqueous Fraction (TAF) of hydromethanolic extract of *B. prionitis* whole plant reported to have significant anti-inflammatory activity against the acute inflammation induced by carrageenan, histamine and dextran in rats (Singh *et al.*, 2003). The anti-inflammatory activity of the 'TAF' may be due to the presence of iridoid glucosides, shanzhiside methyl ester, acetyl barlerin and barlein (Singh *et al.*, 2003). Another study revealed that the aqueous extract fractions (FR-III and FR-IV) of root significantly inhibited the caragennan induced rat paw edema (Khadse and Kakde, 2011). The FR-III and FR-IV at oral dose concentration of 400 mg kg<sup>-1</sup> body weight inhibited the paw edema by 50.64 and 55.76%, respectively and the results were comparable with the reference standard drug indomethacin with a 60.25% of inhibition (Khadse and Kakde, 2011). The ethanolic extract of flowers also exhibited anti-inflammatory activity in rats (Jaiswal *et al.*, 2010b). Oral administration of flower extract (200 mg kg<sup>-1</sup> body weight) showed significant dose-dependent reduction in carrageenin induced swelling and cotton pellet granuloma weight that were equivalent to 48.6 and 36.4% protection (Jaiswal *et al.*, 2010b).

**Anti-arthritic activity:** The TAF fraction was reported to have anti-arthritic property in *Mycobacterium tuberculosis* induced adjuvant arthritis rats model (Singh *et al.*, 2003). The TAF at oral dose range of 12.5-100 mg kg<sup>-1</sup> significantly inhibited leucocytes migration and lowered the Erythrocyte Sedimentation Rate (ESR) and exudate volume in pleural cavity which indicated the inhibition of vascular permeability in arthritis-induced rats (Singh *et al.*, 2003).

**Cytoprotective activity:** Mast cells play an important role in inflammatory responses and release histamine upon their degranulation to produce various allergic reactions (Manek *et al.*, 2011). Maji *et al.* (2011) reported that the hydro-methanolic extract of whole plant showed dose-dependent mast cells and erythrocyte membrane protection activity in response to the toxic chemicals. The extract inhibited the Compound 48/80 induced mast cells degranulation up to 64.91% at dose concentration 10  $\mu$ g mL<sup>-1</sup> and the result was comparable with the reference standard disodium cromoglycate (10  $\mu$ g mL<sup>-1</sup>) with 19.32% protection (Maji *et al.*, 2011). The extract (10  $\mu$ g mL<sup>-1</sup>) provided significant erythrocyte membrane protection (27.10%) against hypotonicity haemolysis



and the result was comparable with reference standard indomethacin ( $10 \mu\text{g mL}^{-1}$ ) with 61.29% protection (Maji *et al.*, 2011).

**Hepatoprotective activity:** The iridoid glycosides enriched fraction from hydroethanolic extract of leaves and stems of *B. prionitis* was reported to show significant hepatoprotection against carbon tetrachloride, galactosamine and paracetamol induced hepatotoxicity in mice and rats (Singh *et al.*, 2005). The oral administration of iridoid fraction significantly reduced the hepatotoxin induced elevated levels of serum alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), bilirubin and triglycerides in a dose dependent manner. The fraction was also increased the hepatic glutathione content and reduced the hepatic lipid peroxidation in response to the hepatotoxicity in mice and rats (Singh *et al.*, 2005).

**Diuretic effect:** The diuretic property of *B. prionitis* flower extract was performed by Musale *et al.* (2011). The oral administration of aqueous flower extract ( $200 \text{ mg kg}^{-1}$ ) was significantly increased the urination (diuresis) and sodium elimination but not potassium in rats. The diuretic effect of flower extract ( $200 \text{ mg kg}^{-1}$ ) was comparable and statistically significant with the reference drug furosemide ( $20 \text{ mg kg}^{-1}$ ) (Musale *et al.*, 2011).

**Anti-nociceptive activity:** The analgesic activity of *B. prionitis* flowers was evaluated using an Ugo Basile Analgesy meter induced artificial pain and acetic acid induced writhing models (Jaiswal *et al.*, 2010b). *In vivo* study showed that the flower extract dose dependently provided a significant increase in the analgesio-meter-induced force and exhibited significant resistance against pain in mice (Jaiswal *et al.*, 2010b). The flower extract was also provided dose dependent significant reduction in writhing characterizes by the reduction in acetic acid induced abdominal cramping and abdominal cramping. At a dose concentration of  $50 \text{ mg kg}^{-1}$  body weight, the extract provided statistically significant reduction of writhing by 5.24% (Jaiswal *et al.*, 2010b).

**Anti-diarrheal activity:** Jaiswal *et al.* (2010c) reported the anti-diarrheal potential of butanol fraction of *B. prionitis* leaves. *In vivo* study showed that the butanol fraction dose dependently inhibited the castor oil induced diarrhea and PGE2 induced enteropooling in sprague-dawley rats. The butanol fraction also reduced the gastrointestinal motility in response to charcoal-induced gut transit changes (Jaiswal *et al.*, 2010c).

## TOXICITY

The toxicity study with the alcoholic extract of roots and leaves of *B. prionitis* did not showed any toxic effects in adult albino rats (Dheer and Bhatnagar (2010). No death was observed up to the oral administration of extract dose concentration  $2.5 \text{ g kg}^{-1}$  body weight during the 14 days of study period Dheer and Bhatnagar (2010). Singh *et al.* (2005) reported that the iridoid glucosides rich aqueous fraction *B. prionitis* did not produced any signs of abnormalities or any mortality up to the single oral administration of  $3000 \text{ mg kg}^{-1}$  dose in mice during the 15 days of study period. However, the intraperitoneal  $\text{LD}_{50}$  was determined as  $2530 \text{ mg kg}^{-1}$  for the aqueous fraction in mice (Singh *et al.*, 2005).

## CONCLUSION

*B. prionitis* occupy a significant place in the Ayurvedic medicine in India. The detailed information as provided in this review on its traditional uses, phytochemistry, pharmacology and

toxicity of the extracts of different parts might be added value in the scientific evaluation of medicinal use of this plant. Extensive literature survey revealed the promising pharmacological includes antimicrobial, anthelmintic, antifertility, antioxidant, antidiabetic, anti-inflammatory, anti-arthritic, cytoprotective, hepatoprotective, anti-diarrhoeal, enzyme inhibitory, diuretic and anti-nociceptive activities of the extract and isolated molecules of this plant without any toxic effects. In future study, the conversion of these pharmacological activities in to the modern drugs, proper scientific evaluation includes isolation of responsible phytochemicals, their mechanism of actions, toxicity and proper standardization need to be explored.

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