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Threat status, conservation and pharmacological activity of *Arnebia benthamii*: A review

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Abstract
Arnebia benthamii (Wall. ex G. Don) I. M. Johnston is an Endangered Plant of Northwestern Himalaya. It has immense medicinal importance and is used under the local name of '*Gul-e- Kahzaban'* or '*Gaozaban'*. Plant is the source of various important phytochemicals which have high efficacy against various ailments. The present study presents an exhaustive review of the plant with reference to its threat status, conservation strategies and pharmacological activity.

Keywords: *Arnebia*, threat, conservation, pharmacological activity

1. Introduction
Arnebia benthamii (Wall. ex G. Don) I. M. Johnston has been declared by IUCN as Critically Endangered for Northwestern Himalaya. It has immense medicinal importance and is used under the local name of '*Gul-e- Kahzaban'* or '*Gaozaban'*. Plant is the source of various important phytochemicals which have high efficacy against various ailments. This plant is also known as 'Himalayan Arnebia'. The most common threats are overgrazing, over exploitation for local use and landslides. Conservation efforts are underway to save this medicinal plant from extinction.

The plant has antiseptic, antibacterial, antifungal and anti-inflammatory properties, as well as wound healing ones. In traditional medicine systems it is used as a stimulant, diuretic and expectorant as well as for throat and tongue problems. It is also used in other herbal preparations for cardiac troubles.

The native tribes in the Himalayas, dry and boil to prepare a special type of tea (without milk), locally known as 'Kahwa' is used to cure the respiratory troubles. The flowering shoots are harvested and made into a conserve or in the preparation of sharbat (syrup) and used for the throat, tongue and heart.

Leaves yield Shikonin, Resin, Essential oils, and are used against Heart ailments, fever [1]. Dry roots are first dipped in mustard oil, and then applied on hair to prevent them from falling [2]. Root of the plant soaked in the oil of apricot and applied to the hair at least once a day as hair tonic [3]. Dry plant yields essential oil Leaves which is used against High fever [4].

2. Taxonomical Classification
Kingdom : Plantae
Division : Tracheophyta
Class : Magnoliopsida
Superorder : Asteranae
Order : Boraginales
Family : Boraginaceae
Tribe : Lithospermeae
Genus : *Arnebia*
Species : *A. benthamii*

3. Botanical Description
Arnebia benthamii (Wall. ex G. Don) I. M. Johnston, J. Arn. Arb. 35:56. 1954.
Echium benthamii Wall. ex G. Don
Lithospermum benthamii (Wall. ex G. Don) I. M. Johnston
Macrotomia benthamii (Wall.) A. DC.

Perennial herb up to 80 cm tall. Roots thick, exuding a purplish dye. Stem solitary, simple, arising from a cluster of basal leaves, hollow, hairy; longer hairs stout and stiff, 2-2.6 mm long, arising from a swollen base, intermixed with shorter weak hairs. Basal leaves 15-22 x 10-26 mm, cauline ones smaller, lanceolate entire, hairy on both surfaces; hairs weak, ± appressed. Inflorescence a cylindrical spike up to 23 cm in fruit, dense flowered, bracteate; 15-27 mm long, densely hairy; lobes linear-lanceolate, slender. Corolla blue to bluish-purple, tubular-campanulate, shorter than calyx in length; tube 10-12 mm long; limb c. 6 mm broad; lobes ovate-obtuse, c. 2.7 mm long. Anthers 2.8 mm long, elongated, attached c. the middle of corolla tube. Style c. length of tube, slender. Stigmas 2, capitate. Nutlets ± 33 mm long, ovoid, rugose tuberculate, acutish at one end, keeled [5].

3.1. Local Names: *Gul-e- Kahzaban'* or '*Gaozaban'*

3.2. English Name: Himalayan Arnebia

3.3. Flowering Period: June-July.

3.4. Distribution: A plant of alpine areas from 3000-3900 m. It occurs in the alpine and subalpine Himalayas, distributed in the Hindukush Himalayan range across Afghanistan, Pakistan, India and Nepal at an altitude range of 3000-4300 m above sea level. From India it has been reported from Jammu & Kashmir, Himachal Pradesh and Uttaranchal.

4. Phytochemistry

Use of Methalonic and ethanolic solvents resulted in extraction of alkaloids, saponis, tannins and phenolics, glycosides, proteins and amino acids, steroids and terpenoids, flavonoids and carbohydrates [6].

A normal phase-high performance thin-layer chromatography (NP-HPTLC) method for concurrent determination of shikonin and β,β-dimethylacryl shikonin in A. *benthamii* was established. Method development of naphthoquinones in the methanol extract was done using hexane-ethyl acetate-methanol (40:7.5:2.5, v/v/v) solvent system at 520 nm. The developed method showed good band separation for shikonin (Rf, 0.37) and β,β-dimethylacryl shikonin (Rf, 0.58) [7].

A simple, precise, and rapid high-performance thin-layer chromatographic (HPTLC) method for the simultaneous quantification of pharmacologically important naphthoquinone shikonin (1) together with its derivatives acetylshikonin (2), and beta-acetoxyisovalerylshikonin (3) in four species of genus Arnebia (*A. euchroma, A. guttata, A. benthamii,* and *A. hispidissima*) [8].

4. Threat Status

Local distribution in Kashmir is found in six different populations (Apharwat, Rayil, Thajwas, Nagbaren, Munwersar and Ducksum). *Arnebia benthamii* occurs as small populations on moist shady open slopes or among on very steep rocks or in rock crevices at an altitude of 3100 to 4000 m.

4.1. Evaluation of Threat Status

In order to assess the threat status of the species in accordance with the IUCN guidelines, Area of Occupancy (AOO), Extent of Occurrence (EOO), population size in the form of mature individuals and the different types of threats to the species are recorded. The most common threats are overgrazing, over exploitation for local use and landslides. The total AOO of *Arnebia benthamii* in Kashmir valley is 24 km^2, calculated by summation of all sub-populations in the Kashmir valley. The total EOO of *Arnebia benthamii* is 127.12 km^2, calculated by summing the areas of all triangles. As the EOO and AOO of the species is 127.12 km^2 and 24Km^2 which is less than 5,000 Km^2 and 5, 00 Km^2 respectively and there is the continuing decline in the number of mature individuals. Thus, the plant species meets the criteria for Endangered (EN) category under the criteria B1b (v) c(iv), B2b (v) c (iv) and Cc2a (i) [9].

In 1997 IUCN also assigned the species Endangered in Jammu & Kashmir [10]. In 1998 IUCN assigned the plant species as Critically Endangered for Northwestern Himalaya [11]. In 2003, IUCN categorized Endangered threat category to the species for J & K [12].

5. Conservation

Various conservation strategies have been developed so that plant could be multiplied at higher rate and simultaneously ensuring that least loss of active principle occurs. Various strategies adopted are:

5.1. Propagule Collection, Enhanced Rooting and Seedling Survival

The investigation on conservation and utilization of *Arnebia benthamii* (Wall. ex G. Don) Johnston was carried out to identify optimum stage of the collection of propagules, improve upon the rooting of root cuttings and identification of optimum conditions for seedling survival. Individuals at reproductive maturity were found suitable for collection of propagules because of the occurrence of 3–5 buds at the terminal growing end of the root. These buds can be effectively utilized for vegetative propagation. Chilling for 40 days significantly ($P < 0.05$) improved rooting of root cuttings. Seedling survival and growth performance were significantly ($P < 0.05$) higher at a high-altitude village Lata, thereby facilitating the establishment of herbal gardens in the vicinity of natural population. This activity will not only reduce pressure on the natural population, but also has the potential to generate rural economy. Further, the possibilities of revegetating the degraded natural habitats and creating nursery centres at low-altitude areas are discussed. This study will help in developing conservation strategy for optimum utilization of *A. benthamii* [13].

5.2. *In Vitro* Seed Germination

The study depicted that the seeds have a very high viability (98%) and contain oil as the reserve food material. The seeds imbibe water nicely and there is no physical dormancy imposed by the seed coat. Among the many pretreatments used to increase percentage germination and reducing mean germination time (MGT), scarification (seed coat removal) proved most effective. The scarification treatment enhanced seed germination to 96.66% and reduced mean germination time to 4.03 days, followed by Kinetin (50 ppm) with 90.83% seed germination and MGT of 4.15 days, as against control, with 31.66% germination and MGT of 9.18 days. Furthermore, when the scarified seeds were treated with seed coat extract, the percentage germination depleted drastically to 28.33% which is suggestive of the fact that the seed coat contains the chemical inhibitors which do have a regulatory or inhibitory effect on seed germination. The study also revealed that the seeds do not need chilling for witnessing germination [14].

Germinability and seedling survival studies on *Arnebia benthamii* - was carried out under ex situ conditions at 1550m. Among various treatments given to the seeds to enhance germinability, scarification/complete removal of the seed coat was found to be most effective. This was primarily due to the presence of inhibitors in the seed coat. GA_3 treatment of 25 and 50 ppm was most effective but higher concentrations (100ppm and 200 ppm) decreased the seed germination. A relationship was observed between seed mass and percentage germination [15].

5.3. Tissue culture

A tissue culture protocol was developed for *A. benthamii* for the first time in the Himalayan region using varied combinations and proper media formulations, including various adjuvants Murashige and skoog (MS) media, growth hormones, sugars, agar, etc.). The influence of different media combinations was estimated, and the MS + thiodiazuron (TDZ)+Indole 3-acetic acid (IAA) combination favors a higher regeneration potential. The higher amounts of chemical constituents were also recorded on the same treatment. The *in vitro* plant samples also showed the noteworthy effect of scavenging of hydroxyl radicals vis a vis protection from oxidative DNA damage. The *in vitro* raised plants are good candidates for the development of antioxidant molecules [16].

5.4. *In vitro* multiplication

An efficient *in vitro* multiplication and propagation system was developed for A. *benthamii*. Half-strength Murashige and Skoog (MS) medium augmented with different concentrations of 6-benzyladenine (BA) were used for shoot multiplication from shoot tip explants. The best response, i.e., multiple shoot formation, was with 5 µM BA. In another experiment, the combined effect of BA with 1 µM indole-3-butyric acid (IBA) was tested. The maximum number of multiple shoots was obtained on half-strength MS medium supplemented with 4 µM BA and 1 µM IBA. Different concentrations of IBA, indole-3-acetic acid (IAA) and-naphthaleneacetic acid (NAA) were used to induce roots from shoots. Roots formed best on half-strength MS medium supplemented with 4 µM IBA, and 80% of plantlets transferred to field conditions survived [17].

6. Pharmacological Activity

6.1. Free Radical Scavenging Activity

Study investigation of the radical scavenging potential of folklore medicinal herb – *Arnebia benthamii* and its competence in protection against DNA damage. The presence of shikonin (5,8-dihydroxy-2-(1-hydroxy-4-methyl-3-pentenyl)-1,4-naphthoquinone) in the plant was confirmed by HPLC quantification from its roots. The ethyl acetate extract of 50 µg/ml yields the 5.19 µg/g shikonin. This ethyl acetate extract exhibited complete protection of DNA by quenching of hydroxyl radicals. The activity of plant extract was also compared with the synthetic shikonin which also validates the presence of dye like substance for the augmenting antioxidant defense system [18].

DPPH radical scavenging and hydroxyl radical scavenging potential of the plant revealed that the extract to be active radical scavenger. Reducing ($Fe^{(3+)}$- $Fe^{(2+)}$) power and lipid peroxidation inhibition efficiency (TBARS assay) of the extract was also evaluated and the extract showed promising activity in preventing lipid peroxidation and might prevent oxidative damages to biomolecules. The extract offered a significant protection against plasmid and calf thymus DNA damage induced by hydroxyl radicals. The extract was also evaluated on different bacterial strains and the maximum antibacterial activity was exhibited against Escherichia coli (E. coli) when compared with standard drug [19].

6.2. Anti-Depressant Activity

Study was designed to evaluate the antidepressant activity of aqueous root extract of *Arnebia benthamii* in rats through behavioral assessment such as Force swim test and Tail suspension test and biochemical assessment such as superoxide dismutase, nitrite level, brain gluthathione and lipid peroxidation in the rat brain. The test drug was administered orally in three doses (75, 150 & 300 mg/kg p.o) for a period of 14 days. Imipramine (standard), 10 mg/kg p.o, was used as a standard treatment. Forced swim test and tail suspension test were used to assess antidepressant activity. On the 14th day, through behavioral testing, effect of the drug was assessed on reduced gluthathione, lipid peroxidation, superoxide dismutase and nitrite in the rat brain tissue. The aqueous root extract of *Arnebia benthamii* (75, 150 & 300 mg/kg) showed significant reduction in immobility time in forced swim test and tail suspension test. Aqueous root extract of *Arnebia benthamii* significantly increased brain gluthathione level, SOD level as compared to the control group and decreased the lipid peroxidation and nitrite as compared to the control group [20].

6.3. Antioxidant and Cytotoxic Activity

In vitro antioxidant and anticancer activity of different extracts of *Arnebia benthamii* were investigated. Antioxidant potential of plant extracts was evaluated by means of total phenolics, DPPH, reducing power, microsomal lipid peroxidation, and hydroxyl radical scavenging activity. The highest phenolic content (TPC) of 780 mg GAE/g was observed in ethyl acetate, while the lowest TPC of 462 mg GAE/g was achieved in aqueous extract. At concentration of 700 µg/mL, DPPH radical scavenging activity was found to be highest in ethyl acetate extract (87.99%) and lowest in aqueous extract (73%). The reducing power of extracts increased in a concentration dependent manner. We also observed its inhibition on $Fe^{(2+)}$/ascorbic acid-induced lipid peroxidation (LPO) on rat liver microsomes *in vitro*. In addition, *Arnebia benthamii* extracts exhibited antioxidant effects on Calf thymus DNA damage induced by Fenton reaction.

Cytotoxicity of the extracts (10-100 µg/mL) was tested on five human cancer cell lines (lung, prostate, leukemia, colon, and pancreatic cell lines) using the Sulphorhodamine B assay. The antiproliferative activity was analyzed higher on HOP-62(lung) and A549(lung) than the known anticancer drug Paclitaxel. And comparable inhibition showed by ethyl acetate extract on THP-1(leukemia), MIA-Pa-Ca (pancreatic) and HCT-116(colon) cell lines [21].

6.4. Antimicrobial Activity

Antimicrobial activity of the plant extract (250–500 µg/ml concentration) was analyzed against *Escherichia coli* CD0006, *Pseudomonas aeruginosa* CD0023, *Shigella flexneri* CD0033, *Klebsiella pneumonia* CD0049, *Salmonella typhimurium* CD0003, *Staphylococcus aureus* CD0001, *Aspergillus versicolor* CDF0011, *Candida albicans* CDF0032, *Candida kruesie* CDF0016, *Candida parapsilosis* CDF0013, *Aspergillus flavus* CDF0024, and *Acremonium* spp. CDF0027. Comparative analysis reveals that the aerial

part exhibited the highest antibacterial activities against almost all tested bacterial strains with the highest inhibition zone diameter (IZD) (30 ± 0.54) was recorded on *P. aeruginosa* CD0023 and *E. coli* CD0006. All the fungal strains except *C. parapsilosis* CDF0013 were more or less inhibited by both aerial and root part extracts of the plant. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values recorded revealed that the *P. aeruginosa* CD0023 was inhibited by the least concentration of 75 µg/ml of the aerial part methanol extract [22].

The purified extracts i.e., Arnebia root Chloroform (ARCH), Arnebia root Ethyl Acetate (AREA), Arnebia root Acetone (ARAT), Arnebia root methanol (ARAL), Arnebia flower Chloroform (AFCH), Arnebia flower Ethyl Acetate (AFEA), Arnebia flower Acetone (AFAT), Arnebia flower methanol (AFAL), Arnebia leaf Chloroform (ALCH), Arnebia leaf Ethyl Acetate (ALEA), Arnebia leaf Acetone (ALAT) and Arnebia leaf methanol (ALAL), were subjected to biological studies and were tested for anti-bacterial, antifungal, and Hemolytic activity. Study found that chloroform fraction (ALCH) is the most active fraction against microbes followed by ethyl acetate fraction (ALEA), ALAT and ALAL. The chloroform extract of leaves of *A. benthamii* had minimum hemolytic activity and high antimicrobial activity equivalent to standards [23].

6.5. Hepatotoxic Activity

Investigation aimed at assessing the effect of aqueous extract of *Arnebia benthamii* on dichromate induced hepatotoxicity and nephrotoxicity in a rat model were performed. The effect was seen by comparing the serum hepatic and renal marker levels in treated and toxic model with control as an index for hepatotoxicity and nephrotoxicity. Hepatic markers, alkaline phosphatase, alanine and aspartate aminotransferases were found to be significantly increased in the serum of rats treated with dichromate (10 mg/kg b.w, i.p.), suggesting hepatic damage. Likewise, marked increase in kidney function markers i.e., BUN and creatinine were observed in dichromate administered rats. Pre-treatment with aqueous extract of *Arnebia benthamii* further increased the levels of serum markers for hepatotoxicity, providing an insight towards its effect as hepatotoxic. However, no significant change in kidney function markers was observed in treated group as compared to the toxic group [24].

Study of *Arnebia benthamii* with regard to pyrrolizidine alkaloids (PA) determination was undertaken. By using column Zorbax SB-Aq and acetonitrile-water gradient as the mobile phase, HPLC results showed that the aerial parts of the plant were pyrrolizidine alkaloids (PA) positive, and (1) Europine, Heliotrine (2), Lycopsamine (3), and Echimidine (4) were identified [25].

7. Conclusions

Arnebia benthamii is traditionally used against various ailments. Recent experimental evidence with reference to phytochemicals extracted and their pharmacological activity has corroborated to its efficacy against various diseases. Plant has come under threat due to its illegal harvesting and accordingly various conservation strategies have been formulated to increase its population. Need of the hour is its conservation by both in-situ and ex-situ methods and further exploration of plant for bioactive molecules which could prove to be an essential step in drug formulations.

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