REVIEW

# The traditional medicine aspects, biological activity and phytochemistry of *Arnebia spp.*

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## ABSTRACT

*Arnebia*, a sub cosmopolitan and important genus of the Boraginaceae family, comprises 25 species distributed among the world. Based on the studies of Persian medicine texts, there are some promising bioactivities for this genus that is unknown in modern medicine and some of them are still the basis of new remedies. This article presents *Arnebia* according to the most important ancient information by the most famous Persian medicine books like Makhzan Al Advieh, Tohfat Al-Momenin, Al-Qanun, Al-Seidaneh and Ekhtiarate Badiei. A search of electronic databases including PubMed, Scopus, Science Direct, and Google Scholar was done to find articles published between 1991 and 2017 on pharmacology and phytochemistry of *Arnebia* spp. In Persian medicine texts, *Arnebia*'s different exclusive forms of preparations are effective for treatment of some disorders such as diarrhoea, amenorrhea, gout, kidney stone, jaundice, chronic fever and burn wounds. There are some activities that are the same in Persian and modern medicine research such as burn wound healing and fever amelioration. Phytochemical investigations on the title genus have led to characterization of many secondary metabolites. Naphthoquinones such as alkannins, shikonins, and their derivatives are the major constituents that have shown pharmacological activities in different *Arnebia* species. Among the major properties of *Arnebia*, only two of them (burn healing and fever amelioration) were investigated in modern medicine. The major aforementioned properties discussed in details in ancient sources might be a novel research sources leading to important discoveries in clinical usages of *Arnebia*.

**Key words:** Boraginaceae, Persian medicine, temperament, shikonins, pyrrolizidine alkaloids

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## INTRODUCTION

According to fossil records, it can be claimed that the relationship of humans and herbs has not been cut over the centuries. Traditional medical systems (such as Persian Medicine) are treasures of human experiences in medicine and their values are more than their historical aspects. Plants have the main roles in these systems and identification of their features, based on ancient medical texts, can inspire us to discovery of new drugs (1). Persian Medicine (PM) that has been known in the world with its famous physicians such as Al-Razi and Avicenna and their medical masterpieces such as Al-Hawi and Al-Qanun, is a creditable source for medicinal plants studies (2).

Boraginaceae is a sub cosmopolitan family of 1600 to 1700 species in around 90 genera, comprising the important genera such as *Pulmonaria, Pentaglottis, Symphytum, Borago, Lycopsis, Anchusa, Arnebia, Echium* and *Onosma* (3). The genus *Arnebia*, comprises 25 species (4) growing in different parts from Asia to Africa. Very prominent chemical components of *Arnebia*, found in the outer layer of the roots have widespread pharmacological properties (5). Different species of *Arnebia* are distributed in Iran from north to south. Several biological activities are related to *Arnebia* species in modern and ethnomedicine. *Arnebia euchroma* (Royle) I.M. Johnst is well-known in folklore and Persian Medicine, and is known as “Aboukhalsa” according to Al-Qanun, and “Havachoobeh” or “Sorkh Giyah” in Folklore medicine of Iran. The roots have been traditionally used for the treatment of the burn wounds and various skin disorders and inflammatory conditions in Iran (6). The goat lipid containing roots of *Arnebia euchroma* is widely used as a remedy for burn wounds in nomadic tribes (Bakhtyari) in southwest Iran (7-10).

Recent studies have shown different pharmacological activities that are related to the chemical constituents of *Arnebia*. Naphthoquinones such as shikonin, alkanin and isohexenylnaphthazarin ester derivatives are major and important components of the plant (11). These components have significant biological properties such as wound healing, anti-microbial, antitumor, anti-inflammatory and anti-platelet activities (12-15).

The purpose of this study was to elicit data on traditional and modern uses of *Arnebia* species as a medicinal plant. In addition, the present paper provides baseline data for future pharmacological and phytochemical studies.

In this article we used "comprehensive library of Islamic and Persian medicine software" and presented *Arnebia* according to the most important ancient information by most famous Persian medicine books. Of around one thousand books we chose six important Persian Medicine (PM) books such as Makhzan ul-Adwia, Tohfat al-Mu`minin, Al-Qanun, Al-Seidaneh and Ikhtiyarat Bdie. A search of electronic databases including PubMed, Scopus, Science Direct and Google Scholar was done to find articles on pharmacology and phytochemistry of *Arnebia* spp published between 1991 and 2017.

## BOTANICAL ASPECTS

### Morphology

There is a wide range of morphological types for Boraginaceae. Most of the species belonging to this family are herbaceous, but lianas, shrubs and trees also occur (16).

The plants of Borage family, also called “hound’s tongue”, are often rough and hairy, usually with simple, alternate leaves. The flowers are bisexual and mostly regular. They have 5 separate sepals and 5 united petals. There are 5 stamens; these are attached to the corolla tube, alternate with the petals. The ovary is positioned superior. It consists of 2 united carpels (bicarpellate) and produces 4 separate nutlets or sometimes achenes (dry seeds). False partitions may make the ovary appear 4-chambered. Some genera produce fewer than 4 nutlets due to abortion. The flower spikes often curl like a scorpion tail with the flowers blooming on the upper surface (17). *Arnebia* is a perennial plant, with thick underground shoots, whole part covered with trichrome, stems are erect, leaves are acuminate, sessile and alternate, flowers usually tubular or funnel-shaped, infundibular corolla and style simple or bifid with two stigmas (18,19).

### Distribution

The family Boraginaceae occurs worldwide, especially in tropical, subtropical and temperate regions. The centres of the highest diversity in the northern temperate zone are in the Irano-Turanian and Mediterranean regions. In the tropics the Boraginaceae are found in Central America and northern and central South America and Asia (20). *Arnebia* species are distributed in different parts of the word. *Arnebia benthamii* is one of the

high altitude medicinal herbs of this genus distributed in the subalpine-alpine Himalayas at an altitude ranging from 3000 to 3900 m (21). *Arnebia densiflorai* is widespread in Turkey and used as red colouring for dying by local people (22, 23). *Arnebia euchroma* is distributed in dry areas, usually between 3300-4500 m of altitude, in alpine western Himalaya, western Tibet and Nepal and Iran. It grows in different mountainous areas of Iran such as northern part (12,24). The location of *Arnebia* species is shown in Figure 5. As many of the alpine medicinal plants, *Arnebia euchroma* is potentially endangered and vulnerable taxa. Because alpine plants grow very slowly, they cannot quickly re-grow the lost leaves or flowers (25).

## ETHNOBOTANY AND TRADITIONAL MEDICINE ASPECTS

### Ethnobotany and traditional uses of *Arnebia* in different countries

In flora of Turkey the genus *Arnebia* are represented by 4 species, one of which, *Arnebia densiflora*, is widespread in Sivas district and known as "egnik" by local people and used as red colouring for dying carpets and rugs. *Arnebia densiflora* roots soaked in butter are used in local wound healing care (26). *Arnebia* species is locally used in different parts of Himalaya. In Indian Hymalayas, *Arnebia euchroma* and *Arnebia benthamii* roots were used as hair tonic, antiseptic and for fever treating by indigenous people. *Arnebia euchroma* is locally named "Demok" in Nubra Valley of Himalaya and its leaf is used to control cough and improve hair growth (27,28). In Manali Wildlife sanctuary, north western Himalaya, it is locally named "rattan jot" and used for wounds healings, ulcers, fever, headache and eye complaints (29). In a study about traditional knowledge and use of medicinal plants in the eastern desert of Egypt, it was found that *Arnebia hispidissima* root have anti-cancer properties and used for skin and hair disease (30). In an ethnobotany of Nara Desert, Sindh, Pakistan, *Arnebia hispidissima* is locally named "Khari". The paste of the plant roots is applied on inflamed injury by indigenous people (31). Among locally available plants of Bandipora district of Jammu & Kashmir, India, combinations of some plants with leaves and flowers of *Arnebia bentamii* is called "Sharbeth". The composite decoction of "Sharbeth" is given to cure jaundice, cough, cold, chronic constipation, fever and acts as a good blood purifier. It is also given to nursing mothers against dysgalactia (32). In Lahaul valley, India, *Arnebia euchroma* is locally named "Ratanjot, Khomig". The indigenous use the plant roots as abortifacient, hair tonic and for different complication such as backache, headache and blood pressure (33). According to traditional medicine of China *Arnebiae euchroma* root is effective in cardiovascular and skin diseases (34). "Shu Gan Huo Xue Zhi Tong Fang" is a Chinese traditional medicine formula which contains several plants such as *Arnebia euchroma*. Its decoction is used for post-herpetic neuralgia treatment (35). Chinese herbal medicines have shown to be effective in the treatment of atopic eczema. *Arnebia euchroma* is one of the ten herbs most commonly used in treating psoriasis (36). *Arnebia euchroma,* a traditional medicinal plant of cold desert Ladakh, India, is used against all kinds of kidney and urinary disorders, soothing, control of urine discharge, inflammation and bleeding in the kidney. Its root with admixture of other plant is used as a tablet three times a day for 8-10 days or until recovery (37).

### Temperament of *Arnebia* in Persian Medicine (intrinsic characteristic)

According to the literature available on Persian medicine, the nature of all beings is formed by the nature of four elements: earth, water, air and fire. They are called quadruplet pillars. Each of the elements has a special quality. By the action and reaction of these four elements, some qualities will be dominant in objects which are called temperament or nature. Fire is warm and dry, air is warm and wet, water is cold and wet, and soil is cold and dry. These four elements are responsible for some characteristics in things. Soil makes stability and shaping, water is responsible for flexibility and formability, air increases lightness and porosity and fire increases mobility of things. All beings have different proportion of these quadruple pillars and this makes the differences in the temperaments of beings. Medicines are graded into four degrees with different properties as follows: the first degree is related to a low dose of medicine that does not produce any dominant quality in the body but more and repeated doses will make minor changes in body's quality. The second degree is a low dose of medicine that produces a dominant quality in the body, and more

and repeated doses of it will not cause any harm. The third degree is related to a low dose of medicine that produces a dominant quality in the body and more and repeated doses will be toxic but it will not be lethal and the forth degree of medicine is lethal (2,38).

According to the literature available on Persian medicine, *Arneia* is warm and dry in second degree (39).

## Use in Persian medicine

Different therapeutic effects of *Arnebias*'s species are mentioned in Persian medicine texts. The main effective part is root used for therapeutic purposes. Treatment of burns, skin diseases such as malignant ulcer and vitiligo, diarrhoea, amenorrhea, gout, kidney stone, chronic fever, liver and spleen dysfunction, worms, and detoxification of animal poisons are propounded in the texts as some properties of *Arnebias*'s species (Table 1) (39-46).

**Table 1. The main uses of *Arnebia* in Persian Medicine**

| Organ | Disease | Part | Dosage | Preparation | Route of administration | Reference number |
|---|---|---|---|---|---|---|
| **Skin** | Fire burn | Root | - | Ghiruti* made from root powder and rose or olive oil | Topical | 39,40, 44-46 |
| | Injuries | Root | - | Root powder and rose oil | Topical | 39 |
| | Ichthyosis | Root | - | Root powder and rose oil<br>Grinded root macerated in vinegar | Topical<br>Tela‡ | 39,42, 44-46 |
| | Malignant ulcer | Root | - | Ghiruti* made from root powder and olive oil | Topical | 39-46 |
| | Vitiligo | Root | - | Grinded root macerated in vinegar | Tela‡ | 39-46 |
| | Erysipelas | Root | - | Plaster of root with barley flour | Topical | 39,41,42, 44-46 |
| | Diaphoresis | Root | - | Grinded root macerated in an oil | Topical | 39 |
| | Scabies | Root | - | Grinded root macerated in vinegar | Tela‡ | 41,42 |
| **Ear** | Otalgia | Root | - | Decoction of grinded root in rose or olive oil | Ear drop | 41-45 |
| **Liver and spleen** | Pain and Jaundice | Root | 6.36 g | Decoction of squashed root with 'maolgharaten'† | Oral (liquid) | 39,42, 44-46 |
| **Kidney** | Pain and kidney stone | Root | 6.36 g | Decoction of squashed root with 'maolgharaten'† | Oral (liquid) | 39,42, 44-46 |
| | Dysuria | Root | 6.36 g | Decoction of squashed root | Oral (liquid) | 41 |
| **Joints** | Gout | Root | 6.36 g | Decoction of squashed root with 'maolgharaten'†<br>Plaster of the root with lard or the fat of goat | Oral (liquid)<br>Topical | 39,40,42, 44,45 |
| | Sciatica | Root | - | Plaster of the root with lard or the fat of goat | Topical | 39,44 |
| **Intestine** | Diarrhea | leaf | 6.36 g | Decoction of squashed leaf with wine | Oral (liquid) | 39,40, 44-46 |
| | Worms | Root | 6.82 g | Decoction of squashed root with the same amount of Tamarix gallica and Lagoecia cuminoides | Oral (liquid) | 39,41, 42,44-46 |
| | Anal fissure | Root | - | Ghiruti* made from root powder | Toical | 40,44 |
| **Uterine** | Hard swelling of uterus | Root | - | Decoction of root | Homul¶ and immersion bath | 39,40,44 |
| | Amenorrhea | Root and flower | 4.55 – 6.82 g | Decoction of root and flower | Homul¶ and immersion bath and oral (liquid) | 39,40,42, 44 |
| | Induced abortion | Root and flower | 4.55 g | Decoction of root and flower | Homul¶ and immersion bath and Oral (liquid) | 39-42, 44-46 |
| **Others** | Scrofula | Root | - | Grinded root macerated in vinegar or<br>Plaster of the root with lard or the fat of goat | Tela<br>Topical | 39,40, 43- 46 |
| | Chronic fever | Root | 6.36 g | Decoction of squashed root with 'maolgharaten' | Oral (liquid) | 39,44,46 |
| | Snake bite | Root | 9.1 g | Root powder in wine | Oral (liquid) or Topical | 39,41,42, 44-46 |
| | Insect bite | Root | - | Plaster of the root | Topical | 39 |
| | aphth | Root | - | Extraction of root and honey | Gargling | 39,44 |
| | Hard swelling | Root | - | Plaster of the root with lard or the fat of goat | Topical | 39,41,44 |

**Ghiruti* is a kind of ointment that makes from bees wax and an oil such as olive oil as a base and a plant (39); †*Maolgharaten* is the mixture of honey and water (1:10) when boiling and 30% is evaporated (47); ‡Tela is a low concentrate liquid pouring on the body surface (2); ¶*Homul* is a fabric that impregnated with plant extract and used as vaginal or rectal suppository (2)

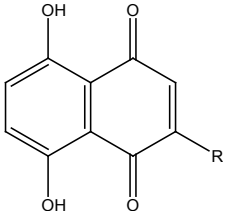
The consumption of more than 6.4 g of *Arnebia* may cause headache. It is contraindicated in pregnant women due to abortion.

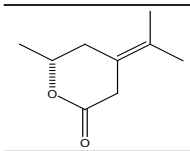
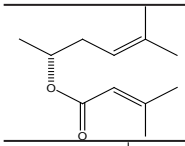
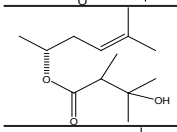
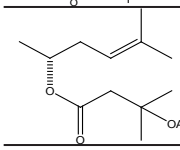
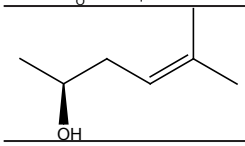
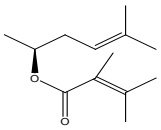
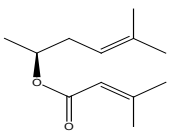
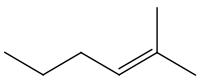
It is a fact that one quarter of all medical prescriptions are formulations based on substances derived from plants or plant-derived synthetic analogs, and according to the WHO, 80% of the world's population especially those in developing countries rely on plant-derived medicines (48). Many herbal drugs came into use in the modern medicine through the uses of plant material in folklore or medicinal traditional systems. Modern medicine has its roots in ancient medicine, and many important new remedies will be discovered and commercialized in the future (48).

## Chemical composition

The plant belonging to Borage family is very well-known for its pharmacological activities and chemical constituents. Different *Arnebia*'s constituents with their activities are listed in Table 2.

**Table 2. Different alkannins/shikonins and their activities in *Arnebia* spp. root**




| R group of naphtoquinone structure | Name | Biological properties and occurrence | Reference number |
|---|---|---|---|
|  | Acetylalkannin or arnebin-3 | Antimicrobial, inhibition of topoisomerase-I, antithrombotic, antitumor. Root of *Arnebia euchroma, A. hispidissima, A. nobilis* | 56, 57 |
|  | β, β- dimethylacrylalkannin or arnebin-1 | Inhibition of topoisomerase-I and anticancer, antimicrobial, antithrombotic, anti-inflammatory. Root of *Arnebia euchroma, A. gutatta, A. nobilis* | 65-67 |
|  | β-hydroxyisovalerylalkannin | Antimicrobial. Root of *Arnebia euchroma, A. hispidissima*. | 56, 57 |
|  | β -acetoxyisovalerylalkannin | Antimicrobial. Root of *Arnebia euchroma*. | 56, 57 |
|  | Shikonin | Antitumor, antipyretic and analgesic, antifungal and antibacterial, wound healing, chemopreventive, anti-inflammatory, stimulation of peroxidase, induction and secretion of nerve growth factor. Root of *Arnebia euchroma, A. hispidissima, A. guttata, A. tibetiana.* | 54-56, 68-70 |
|  | Teracrylshikonin | Antimicrobial. Root of *Arnebia euchroma, A. guttata.* | 56, 57 |
|  | β,β-dimethylacrylshikonin | Antimicrobial Root of *Arnebia euchroma, A. guttata, A. tibetiana.* | 56 |
|  | Deoxyalkannin, deoxyshikonin, or arnebin-7 | Anti-dermatophytic and antibacterial, antitumor. Root of *Arnebia decumbens*, *A. euchroma, A. hispidissima, A. guttata, A. nobilis* | 56, 57 |

*Arnebia* species are rich in naphthoquinones such as alkannins, shikonins and their derivatives, which are potent pharmaceutical substances with a wide range of biological properties.

Naphthoquinones are the major phytochemicals existing in the outer layer of *Arnebia*'s species root. Naphthoquinones fraction is composed of water-insoluble pigments such as shikonin, alkanin and isohexenylnaphthazarin ester derivatives, which have widespread pharmacological properties including anti-inflammatory, antimicrobial, wound healing and anti-tumorous activity (5). Pyrrolizidine alkaloids, triterpene derivatives, flavonoids and phenolic acids are other phytochemicals of *Arnebia* species (49-51).

### *In vitro* experimental studies

The anti-inflammatory effects of shikonin and some of its derivatives can be related to several mechanisms of action, for example, inhibition of the biosynthesis of leukotriene B4, suppression of mast cell degranulation, inhibition of the respiratory burst in neutrophils, alteration of phosphatidylinositol-mediated signalling or blockade of chemokine binding to the CCR-1 (52), also the naphthoquinone structure of shikonin and its derivatives have free radical scavengers activities. It was demonstrated that shikonin has a better potency as a COX inhibitor than alkannin, but also higher cytotoxicity and pro-oxidant activity (53). The role of shikonin in healing of some autoimmune-mediated inflammatory diseases such as arthritis and inflammatory bowel disease may confirm its anti-inflammatory properties (54, 55).

In 2002 Shen et al. (56) analysed the activity of shikonin and some derivatives against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium* and *E. faecalis*. Shikonin is an active naphthoquinone that is mainly isolated from the dried root of *Arnebia guttata*, *Arnebia euchroma* and *Lithospermum erythrorhizon*. Some shikonin derivatives have shown strong anti-bacterial activities. In 2002 a paper published by Sasaki et al. (57) comparing the effects of shikonin and the standard antifungal fluconazole showed that the fungicidal activity of shikonin was higher than fluconazole against *Candida krusei*, *Saccharomyces cerevisiae*, and the same as that of fluconazole against *C. glabrata*. The extract used in the study contained pigments of *Lithospermum erythrorhizon* and *Arnebia euchroma* roots.

Shikonin and its derivatives have cytotoxic and antitumor effects. Yang et al. (58) reported that shikonin is an inhibitor of tumour proteasome activity and cell death induction *in vitro* and *in vivo*. Zhen et al. (59) showed that shikonin induced apoptosis of human malignant melanoma A375-S2 cells via activated P53 and caspase-9 pathways. Yoon et al. (60) found that shikonin induced HL60 cells apoptosis via caspase-3 dependent pathways. In another study it was reported that shikonin reacted with cellular thiols such as glutathione and the depletion of cellular thiols led to inducing apoptosis in HL60 cells. Natural shikonin-like compounds also have significant *in vivo* antitumor effects (61). In 2008 Zeng et al. (62) showed that one shikonin derivative inhibited *in vitro* cell growth in human lung adenocarcinoma cell line A549, human hepatocellular carcinoma cell line Bel-7402, human breast adenocarcinoma cell line MCF-7 and mouse Lewis lung carcinoma (LLC) cell line.

### *In vivo* experimental studies

The effects of *Arnebia euchroma* in burns healing are very significant. Herbal products derived from *Arnebia euchroma* roots, is very effective for healing of burn wounds. The carboxymethyl cellulose topical gels containing concentrated hydro alcoholic extract of *Arnebia*'s root can significantly improve wound closure rate, fibroblast proliferation, volume density of collagen bundles, length density and mean diameter of the vessels in third degree burn wounds in rats (63). The ointment of *Arnebia euchroma* roots extraction have a good potential for acceleration of burn wound healing in rats (64).

In conclusion, Persian medicine systems have special view and method for understanding of human body and disease. Quadruplet pillars and resulting temperaments are the basic concept in Persian medicine that help us realize causes of the disease and the role of therapeutic agents such as herbs. *Arnebia*'s different therapeutic activities, route of administration and its different preparations are discussed in detail in Persian medical texts. Based on PM texts, different parts of *Arnebia* (root, leaf and flower) can be used in the treatment of burns, injuries, ichthyosis, malignant ulcer, vitiligo, erysipelas, diaphoresis, scabies, otalgia, pain and jaundice, pain and kidney stone, dysuria, gout, sciatica, diarrhoea, worms, anal fissure, hard swelling of uterus, amenorrhea,

scrofula, chronic fever, snake bite, insect bite, aphthous ulcer, hard swelling. The major aforementioned properties which discussed in details in ancient sources might be a novel research sources leading to important discoveries in clinical usages of *Arnebia*.

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## TRANSPARENCY DECLARATION

Conflicts of interests: None to declare

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