

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

Amirsaeed Hosseini¹, Fatemeh Mirzaee², Ali Davoodi^{2,3}, Hossein Bakhshi Jouybari^{2,3}, Mohammad Azadbakht²

¹Traditional and Complementary Medicine Research Centre, Addiction Institute, Mazandaran University of Medical Sciences, ²Department of Pharmacognosy, faculty of Pharmacy, Mazandaran University of Medical Sciences; Sari, Iran, ³Medicinal Plants Research Center, Ayatollah Amoli Branch, Islamic Azad University, Amol, Iran.

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, Tohfah Al-Momenin, Al-Qanun, Al-Seidaneh and Ekhtiarate Badii. 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, amenorrhoea, 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

Corresponding author:

Mohammad Azadbakht
Department of Pharmacognosy, Faculty of Pharmacy, Mazandaran University of Medical Sciences
Khazarabad Road, 48175-861 Sari, Iran;
Phone: +98 911 151 3032;
Fax: +98 113 354 3084;
Email: Azadbakht110@gmail.com
Amirsaeed Hosseini ORCID ID: orcid.org/0000-0002-6555-1298

Original submission:

13 October 2017;

Revised submission:

20 November 2017;

Accepted:

08 December 2017.

doi: 10.17392/926-18

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 credible 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. Johnston 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 pharmacologi-

cal 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, Tohfah 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 trichome, 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 world. *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 dyeing 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 dyeing 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 benthamii* 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 fourth 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, amenorrhoea, 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	Topical	
				Grinded root macerated in vinegar	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
Ear	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				Decoction of squashed root with 'maolgharaten'†	Oral (liquid)	
	Gout	Root	6.36 g	Plaster of the root with lard or the fat of goat	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
	Amenorrhoea	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				Grinded root macerated in vinegar or	Tela	
	Scrofula	Root	-	Plaster of the root with lard or the fat of goat	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.

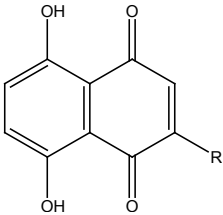
It is a fact that one quarter of all medical prescriptions are formulations based on substances derived from plants or plant-derived synthetic analogs, and according to the WHO, 80% of the world's population especially those in developing countries rely on plant-derived medicines (48). Many herbal drugs came into use in the modern medicine through the uses of plant material in

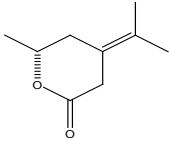
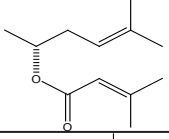
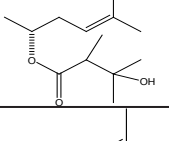
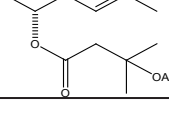
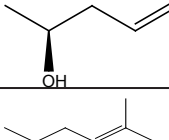
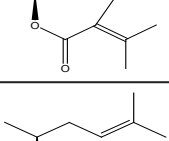
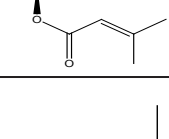
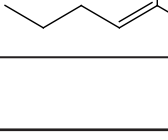
folklore or medicinal traditional systems. Modern medicine has its roots in ancient medicine, and many important new remedies will be discovered and commercialized in the future (48).

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 naphthoquinone structure	Name	Biological properties and occurrence	Reference number
	Acetylalkannin or arnebin-3	Antimicrobial, inhibition of topoisomerase-I, antithrombotic, antitumor. Root of <i>Arnebia euchroma</i> , <i>A. hispidissima</i> , <i>A. nobilis</i>	56, 57
	β , β -dimethylacrylalkannin or arnebin-1	Inhibition of topoisomerase-I and anticancer, antimicrobial, antithrombotic, anti-inflammatory. Root of <i>Arnebia euchroma</i> , <i>A. guttata</i> , <i>A. nobilis</i>	65-67
	β -hydroxyisovalerylalkannin	Antimicrobial. Root of <i>Arnebia euchroma</i> , <i>A. hispidissima</i> .	56, 57
	β -acetoxyisovalerylalkannin	Antimicrobial. Root of <i>Arnebia euchroma</i> .	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 <i>Arnebia euchroma</i> , <i>A. hispidissima</i> , <i>A. guttata</i> , <i>A. tibetiana</i> .	54-56, 68-70
	Teracrylshikonin	Antimicrobial. Root of <i>Arnebia euchroma</i> , <i>A. guttata</i> .	56, 57
	β , β -dimethylacrylshikonin	Antimicrobial Root of <i>Arnebia euchroma</i> , <i>A. guttata</i> , <i>A. tibetiana</i> .	56
	Deoxyalkannin, deoxyshikonin, or arnebin-7	Anti-dermatophytic and antibacterial, antitumor. Root of <i>Arnebia decumbens</i> , <i>A. euchroma</i> , <i>A. hispidissima</i> , <i>A. guttata</i> , <i>A. nobilis</i>	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*.

ACKNOWLEDGMENT

This research was the subject of a Ph.D. thesis written by Dr Amirsaeed Hosseini as student of Traditional and Complementary Medicine of

Mazandaran University of Medical Sciences, supervised by Professor Mohammad Azadbakht and funded by Mazandaran University of Medical Sciences in Sari, Iran.

FUNDING

This work was supported by Mazandaran University of Medical Sciences, Sari in Iran (funding code: 1325).

TRANSPARENCY DECLARATION

Conflicts of interests: None to declare

REFERENCES

- Fabricant DS, Farnsworth NR. The value of plants used in traditional medicine for drug discovery. *Envir Heal Persp* 2001; 109:69-75.
- Mirzaee F, Hosseini A, Jouybari HB, Davoodi A, Azadbakht M. Medicinal, biological and phytochemical properties of *Gentiana* species. *J Trad and Com Med* 2017; 7:400-8.
- Abbaspour KC, Faramarzi M, Ghasemi SS, Yang H. Assessing the impact of climate change on water resources in Iran. *Water Resour Res* 2009; 45:1-10.
- Manjkhola S, Dhar U, Rawal R. Treatments to improve seed germination of *Arnebia benthamii*: an endangered medicinal herb of high altitude Himalaya. *Seed Sci Tech* 2003; 31:571-7.
- Ashkani-Esfahani S, Imanieh M, Khoshneviszadeh M, Meshksar A, Noorafshan A, Geramizadeh B, Ebrahimi S, Handjani F, Tanideh N. The healing effect of *Arnebia euchroma* in second degree burn wounds in rat as an animal model. *Iran Red Cres Med J* 2012; 14:70-4.
- Nasiri E, Hosseinimehr SJ, Zaghi Hosseinzadeh A, Azadbakht M, Akbari J, Azadbakht M. The effects of *Arnebia euchroma* ointment on second-degree burn wounds: a randomized clinical trial. *J Ethnopharm* 2016; 189:107-16.
- Pirbalouti AG, Yousefi M, Nazari H, Karimi I, Koochpayeh A. Evaluation of burn healing properties of *Arnebia euchroma* and *Malva sylvestris*. *E J Bio* 2009; 5:62-6.
- Aliasl J, Khoshzaban F. Traditional herbal remedies for burn wound healing in canon of Avicenna. *Jundishapur J Nat Pharmaceut Prod* 2013; 8:192-6.
- Nasiri E, Hosseinimehr SJ, Azadbakht M, Madani SA. A review of natural products for burn healing based on the Iranian traditional medicine. *J Mazandaran Univ Med Sci* 2014; 23:263-80.
- Doulah A, Neisi N, Zekavati R, Farjam M. Antibacterial, antifungal and antioxidant activity of four species from *Arnebia* genus growing wild in Iran. *Iran J Sci Tech* 2014; 382:159-64.
- Sharma N, Sharma UK, Malik S, Bhushan S, Kumar V, Verma SC, Sharma N, Sharma M, Sinha AK. Isolation and purification of acetylshikonin and β -acetoxyisovaleryl shikonin from cell suspension cultures of *Arnebia euchroma* (Royle) Johnston using rapid preparative HPLC. *J Sep Sci* 2008; 31:629-35.
- Nasiri E, Hosseinimehr SJ, Azadbakht M, Akbari J, Enayati-Fard R, Azizi S, Masoud Azadbakht. The healing effect of *Arnebia Euchroma* ointment versus silver sulfadiazine on burn wounds in rat. *World J Plast Surg* 2015; 4:134-44.
- Damianakos H, Kretschmer N, Sykłowska-Baranek K, Pietrosiuk A, Bauer R, Chinou I. Antimicrobial and cytotoxic isohexenyl-naphthazarins from *Arnebia euchroma* (Royle) Jonst. (Boraginaceae) callus and cell suspension culture. *Molecules* 2012; 17:14310-22.
- Kundakovic T, Fokialakis N, Dobric S, Pratsinis H, Kletsas D, Kovacevic N, Chinou I. Evaluation of the anti-inflammatory and cytotoxic activities of naphthazarine derivatives from *Onosma leptantha*. *Phytomed* 2006; 13:290-4.
- Ko FN, Lee YS, Kuo SC, Chang YS, Teng CM. Inhibition on platelet activation by shikonin derivatives isolated from *Arnebia euchroma*. *BBA Mol Cell Res* 1995; 1268:329-34.
- Scheel R, Ybert J-P, Barth OM. Pollen morphology of the Boraginaceae from Santa Catarina State (southern Brazil), with comments on the taxonomy of the family. *Grana* 1996; 35:138-53.
- Elpel TJ. *Botany in a Day: The Patterns Method of Plant Identification*. 5th ed. Pony, MT: Hops Press; 2004.
- Mozaffarian V. *Identification of medicinal and aromatic plants of Iran*. Tehran: Farhangmoaser; 2013.
- Ambrish K, Srivastava S. Taxonomic studies on the genus *Arnebia* Forssk. (Boraginaceae) in India. *Taiwania* 2014; 59:315-25.
- Binzet R, Orcan N. A new species of *Onosma* (Boraginaceae) from Southern Turkey. *Novon* 2007; 17:8-10.
- Anonymous. *The wealth of India*. CSIR New Delhi, India; 1948.
- Mill R, Tan K, Davis P. *Flora of Turkey and the East Aegean islands*. United Kingdom: Edinburgh University Press; 1988.
- Baytop T. *A dictionary of vernacular names of wild plants of Turkey*. Turkey: The Turkish Language Society; 1994.
- Rajaei P, Maassoumi A, Mozaffarian V, Nejad Sattari T, Pourmirzaei A. Alpine flora of Hezar mountain (SE Iran). *Rostaniha* 2011; 12:111-27.
- Polunin O, Stainton A. *Flowers of the Himalaya*. Oxford University Press; 1984.

26. Kosger HH, Ozturk M, Sokmen A, Bulut E, Ay S. Wound healing effects of *Arnebia densiflora* root extracts on rat palatal mucosa. *European J Dent* 2009; 3:96-105.
27. Kala CP. Indigenous uses, population density, and conservation of threatened medicinal plants in protected areas of the Indian Himalayas. *Conserv Biol* 2005; 19:368-78.
28. Kumar G, Gupta S, Murugan M, Bala Singh S. Ethnobotanical studies of Nubra Valley-A cold arid zone of Himalaya. *Ethnobotanic Leaflets* 2009; 2009:9-20.
29. Rana MS, Samant S. Diversity, indigenous uses and conservation status of medicinal plants in Manali wildlife sanctuary, North west Himalaya. *Indian Journal of Traditional Knowledge* 2011; 10:439-59.
30. Mahmoud T, Gairola S. Traditional knowledge and use of medicinal plants in the Eastern Desert of Egypt: a case study from Wadi El-Gemal National Park. *J Med Plants* 2013; 1: 1-6.
31. Qureshi R, Bhatti GR, Memon RA. Ethnomedicinal uses of herbs from northern part of Nara desert, Pakistan. *Pak J Bot* 2010; 42:839-51.
32. Lone P, Bhardwaj K. Ethnomedicinal uses of certain locally available plants of Bandipora district of Jammu & Kashmir, India. *International J Med Arom Plants* 2013; 3:470-85.
33. Singh A, Lal M, Samant S. Diversity, indigenous uses and conservation prioritization of medicinal plants in Lahaul valley, proposed Cold Desert Biosphere Reserve, Indian. *International J Biodiv Sci Manag* 2009; 5:132-54.
34. Ma ZQ, Hu H, He TT, Guo H, Zhang MY, Chen MW, Wang YT. An assessment of traditional Uighur medicine in current Xinjiang region (China). *African J Trad, Comp Alter Med* 2014; 11:301-14.
35. Liang H, Coyle ME, Wang K, Zhang AL, Guo X, Li H, Xue C, Lu C. Oral Chinese herbal medicine for post-herpetic neuralgia: A systematic review and meta-analysis of randomized controlled trials. *European J Integ Med* 2017 ;10:46-56.
36. Tse T. Use of common Chinese herbs in the treatment of psoriasis. *Clin Exp Dermatol* 2003; 28:469-75.
37. Ballabh B, Chaurasia O, Ahmed Z, Singh SB. Traditional medicinal plants of cold desert Ladakh-used against kidney and urinary disorders. *J Ethnopharm* 2008; 118:331-9.
38. Ibn Sina H. The canon of medicine. Tehran: Soroush; 2010.
39. Aghili Khorasani MH. Makhzan al-Advieh. 1 ed. Tehran: Sabz Azarang; 2011.
40. Ansari A. Ekhtiarate Badi'ee. 1 ed. Tehran: Pakhshe Razi; 1992.
41. Antaki D. Tazkerah Olel Albab. 1 ed. Beirut Alaalami Lelmatbuaat; 2010.
42. Ghassaani Torkamaani MM. Al Mo'tamad fi al Adviat al Mufradah. 1 ed. Beirut: Dar Al Kotob Ilmiyah; 2000.
43. Heravi M. Al-Abniah An Haghayegh Al-Adviah. 1 ed. Tehran: Tehran University; 1967.
44. Ibn Baitar A. Al Jami ul Mufradat ul Advia wal Aghzia. 1 ed. Beirut: Dar Al Kotob Ilmiyah; 1991.
45. Ibn Jezlah Y. Menhaj-ul bayan. 1 ed. Cairo: Jami'at ad-Duwal al-'Arabiyah; 2009.
46. Ibn Sina H. Al Ghanoon fi Al Teb. Beirut: Dar-uhya'ut Turas'il Arabi; 2005.
47. Yousefi heravi Y. Tebbe Yousefi. 1 ed. Tehran: Iran University of Medical Sciences; 2003.
48. Gurib-Fakim A. Medicinal plants: traditions of yesterday and drugs of tomorrow. *Mol Aspects Med* 2006; 27:1-93.
49. Smyska-Wieleba N, Wojtanowski KK, Mroczek T. Comparative HILIC/ESI-QTOF-MS and HPTLC studies of pyrrolizidine alkaloids in flowers of Tussilago farfara and roots of *Arnebia euchroma*. *Phytochem Lett* 2017; 20:339-49.
50. Yuzbasioglu M, Kuruuzum-Uz A, Guvenalp Z, Simon A, Tóth G, Harput US, Kazaz C, Bilgili B, Duman H, Saracoglu I, Demirezer LO. Cytotoxic compounds from endemic *Arnebia purpurea*. *Nat Prod Commun* 2015; 10:595-6.
51. Yang M-H, Blunden G, O'neill M, Lewis J. Tormentic acid and 2 α -hydroxyursolic acid from *Arnebia euchroma*. *Planta Med* 1992; 58:227-35.
52. Kourounakis AP, Assimopoulou AN, Papageorgiou VP, Gavalas A, Kourounakis PN. Alkannin and shikonin: effect on free radical processes and on inflammation-a preliminary pharmacochemical investigation. *Arch Pharm* 2002; 335:262-6.
53. Landa P, Kutil Z, Temml V, Vuorinen A, Malik J, Dvorakova M, Marsik P, Kokoska L, Pribylova M, Schuster D, Vanek T. Redox and non-redox mechanism of in vitro cyclooxygenase inhibition by natural quinones. *Planta Med* 2012; 78:326-33.
54. Dai Q, Fang J, Zhang F-s. Dual role of shikonin in early and late stages of collagen type II arthritis. *Mol Biol Rep* 2009; 36:1597-604.
55. Andújar I, Rios JL, Giner RM, Miguel Cerdá J, Recio MdC. Beneficial effect of shikonin on experimental colitis induced by dextran sulfate sodium in BALB/c mice. *J Evid Based Complementary Altern Med* 2012; 20: 1-12.
56. Shen C-C, Syu W-J, Li S-Y, Lin C-H, Lee G-H, Sun C-M. Antimicrobial activities of naphthazarins from *Arnebia euchroma*. *J Nat Prod* 2002; 65:1857-62.
57. Sasaki K, Abe H, Yoshizaki F. *In vitro* antifungal activity of naphthoquinone derivatives. *Biol Pharm Bull* 2002; 25:669-70.
58. Yang H, Zhou P, Huang H, Chen D, Ma N, Cui QC, Shen S, Dong W, Zhang X, Lian W, Wang X, Dou QP, Liu J. Shikonin exerts antitumor activity via proteasome inhibition and cell death induction in vitro and in vivo. *Int J Cancer* 2009; 124:2450-9.
59. Wu Z, Wu L, Li L, Tashiro S-i, Onodera S, Ikejima T. p53-mediated cell cycle arrest and apoptosis induced by shikonin via a caspase-9-dependent mechanism in human malignant melanoma A375-S2 cells. *J Pharmacol Sci* 2004; 94:166-76.
60. Yoon Y, Kim Y-O, Lim N-Y, Jeon W-K, Sung HJ. Shikonin, an ingredient of *Lithospermum erythrorhizon* induced apoptosis in HL60 human premyelocytic leukemia cell line. *Planta Med* 1999; 65:532-5.
61. Gao D, Hiromura M, Yasui H, Sakurai H. Direct reaction between shikonin and thiols induces apoptosis in HL60 cells. *Biol Pharm Bull* 2002; 25:827-32.
62. Xiong W, Luo G, Zhou L, Zeng Y, Yang W. In vitro and in vivo antitumor effects of acetylshikonin isolated from *Arnebia euchroma* (Royle) Johnst (Ruanzicao) cell suspension cultures. *Chinese Med* 2009; 4:14-20.

63. Ashkani Esfahani S, Imanieh MH, Meshksar A, Khoshneviszadeh M, Noorafshan A, Geramizadeh B, Ebrahimi S, Handjani F, Nadimi E, Seyed Jafari SM. Enhancement of fibroblast proliferation, vascularization and collagen synthesis in the healing process of third-degree burn wounds by topical *Arnebia euchroma*, a herbal medicine. *Galen Med J* 2012; 1:53-9.
64. Pirbalouti AG, Koohpayeh A, Azizi S, Golparvar A, editors. Evaluation of the burn healing properties of *Arnebia Euchroma* Rolye (Johnst) in diabetic rats. *Int Conf Biosci Biochem Bioinform* 2011; Singapore: IACSIT Press.
65. Papageorgiou VP, Assimopoulou AN, Couladouros EA, Hepworth D, Nicolaou K. The chemistry and biology of alkannin, shikonin, and related naphthazarin natural products. *Angew Chem Int Ed* 1999; 38:270-301.
66. Papageorgiou VP, Assimopoulou AN, Samanidou V, Papadoyannis I. Recent advances in chemistry, biology and biotechnology of alkannins and shikonins. *Curr Org Chem* 2006; 10:2123-42.
67. Chen FP, Kung YY, Chen YC, Jong MS, Chen TJ, Chen FJ, Hwang SJ. Frequency and pattern of Chinese herbal medicine prescriptions for chronic hepatitis in Taiwan. *J Ethnopharm* 2008; 117:84-91.
68. Hayashi M. Pharmacological studies of Shikon and Tooki. Pharmacological effects of the water and ether extracts. *Nihon yakurigaku zasshi Folia pharmacol Japon* 1977; 73:177-91.
69. Hsu P-C, Huang Y-T, Tsai M-L, Wang Y-J, Lin J-K, Pan M-H. Induction of apoptosis by shikonin through coordinative modulation of the Bcl-2 family, p27, and p53, release of cytochrome c, and sequential activation of caspases in human colorectal carcinoma cells. *J Agri Food Chem* 2004; 52:6330-7.
70. Ge F, Wang X, Zhao B, Wang Y. Effects of rare earth elements on the growth of *Arnebia euchroma* cells and the biosynthesis of shikonin. *Plant Growth Regul* 2006; 48:283-90.