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REVIEW ARTICLE

Medicinal plants and phytotherapy in Iran: Glorious history, current status and future prospects

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ABSTRACT
This study is an endeavour to analyse the status of medicinal plants research in Iran. Because of its exceptional phytogeography, Iran has a unique and diverse flora. It is estimated that, 8167 species of vascular plants are present in Iran of which about 2075 have medicinal importance. Situated at the heart of the Silk Road, Iran enjoys a mix of cultures providing a rich backbone for the development of traditional herbal medicine practices. Notwithstanding the brilliant history in traditional medicine and success of investigation to produce herbal medicines, attempts in recent decades, face many challenges. Many text and paper about these concerns were never translated in English. Strong need was felt to record such data of medicinal plants of Iran, their conservation status and related information. The scattered literature over medicinal plants of Iran were collected, analysed and presented in this review, highlighting not only their therapeutic potential but also concerns about product authenticity, quality, safety and efficacy. This will provide ways for future scientific research in this area. Awareness of critical issues in traditional medicinal herbs can play a pivotal role in the discovery and development of plant based drugs and to sustain consumer confidence.

Introduction

Iran covers an area of about 1.6 million square kilometre. It is situated between Central Asia and Himalaya in the east and Caucasus and Anatolia in the west. Altitudinally, it ranges from 26 m b.s.l. along the shore of the Caspian Sea up to 5671 m a.s.l. at Damavand Mountain in centre of Alborz. Climatically, it contrasts from humid to subtropical humid weathers, varying from hot/dry deserts with rainfall of not more than 25 mm/yr in central areas to southern coast of the Caspian Sea with rainfall more than 1800 mm/yr (1).

Iran has very rich botanical wealth and plant diversity, because of its considerable phytogeographical position amidst three main phytochoria of the Old World, including Irano-Turanian, Euro-Siberian and Saharo-Sindian, and influences by Mediterranean and Somalia-Masaei species (2-4). The Iranian Plateau is considered as a bridge for migration of numerous plant species, linking the eastern and western floras of Eurasia (1).

Out of 308312 vascular plants species on earth, over 80000 herbal species are being employed in folk medicines for therapeutic purposes (5, 6). The flora of Iran is rich regarding to its number of plant species. It is estimated that 8167 species of vascular plants are present in Iran, of these about 2597 species are (sub) endemic (1, 7).

It is also a rich country in terms of medicinal and aromatic plants and it has been estimated that Iranian flora contains about 2075 medicinal plant species with phytochemical and therapeutic potential (8). Among them, about 400-500 medicinal plant species are utilized by native people in traditional and folk medicines in various regions of the country (8). Iran is known for its great diversity of *Artemisia* L. and *Astragalus* L. that are renowned for their medicinal and cosmetic properties (8, 9).

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Over the past few decades, there is increase in the usage of folk remedies in the world, particularly in herbal products. According to the World Health Organization (WHO) for primary healthcare needs, 60% of world's population is dependent on traditional drugs and 80% people of developing countries is dependent on medicinal plants to get herbal drugs (10).

In Iran, similar to many other countries, we have observed growing interest to use of traditional medicine. Iranian Traditional Medicine (ITM) is largely based on the Unani system, which is a good example of the oldest medical systems from ancient Persia. It is a holistic approach for prevention and treatment of various ailments that is mainly derived from medicinal plants and also other natural resources like minerals, metallic and animal origin. Iran is among the seven countries in Asia with the maximal use of medicinal herbs. There are over 130 plant-based medicines in Iran (8). Nowadays traditional medicine in Iran is still linked to the local ethnobotanical studies. Ethnobotanical surveys, carried out throughout the Iranian territory confirm that medicinal plants are the major component of ITM (11).

However, despite the rich knowledge that lies behind the traditional uses of the Iranian medicinal plants, few attempts have been made to evaluate the key issues that these herbs face in the country.

Therefore, this study presents the first comprehensive report associated with the status of medicinal plants in Iran. The review highlights the significant role of the Iranian medicinal plants in primary healthcare system, and also focuses on the recent serious challenges in product authenticity, quality, safety, efficacy, identification and authentication of them. A considerable part of this paper is dedicated to the identification and authentication challenges of Iranian medicinal plants. The conservation status of Iranian medicinal flora, their sustainable utilization and protection of the related traditional knowledge have also been discussed. The gaps in knowledge are identified, and prospects for further investigations are recommended in the context of ethnobotany and medicinal plants.

A holistic search of scientific content data-bases such as PubMed/Medline, Google Scholar, Scopus and Science Direct, English and non-English reference books was made. After a comprehensive survey, a total of 107 publications that described valuable data dealing with the different aspects of medicinal plants and traditional medicine in Iran were reviewed. Author and scientific names of all the documented plant taxa were carefully scrutinized for most recent alterations via "The Plant List" (http://www.theplantlist.org).

Traditional medicinal systems: the global view

Traditional medicine is a cultural database that embedded in the knowledge of human societies and is the entirety of information, expertnesses and practices according to the principles, faiths and experiences indigenous to various cultures that are employed to preserve health, as well as to hinder, diagnose, ameliorate or remedy physical and mental diseases. Folk medicine that has been accepted by other people (outside its aboriginal culture) is often called complementary and alternative medicine (CAM) (12, 13).

Since ancient times, various categories of traditional medicine system, including Traditional Chinese Medicine, Iranian Traditional Medicine (also known as Persian medicine), Islamic Traditional Medicine, Traditional Korean Medicine, Traditional African Medicine, Ayurveda, Unani and homeopathy, are the most important and popular traditional methods in providing healthcare around the globe. The core discipline or similarity among all the traditional systems of medicine is herbal medicine, as well named phyto-medicine or phyto-therapy, which is based on the use of plants for therapeutic purposes (6). The first documentary sources for the treatment with medicinal plants are older than the memories. Although the earliest written evidence of therapeutic plants dated back at least 5000 years to the Sumerians, who defined good established therapeutic usages for some plants such as *Laurus nobilis* L. (Lauraceae), *Carum carvi* L. (Apiaceae) and *Thymus vulgaris* L. (Lamiaceae), archaeological surveys have demonstrated that the practice of botanical medicine dates since 6000 years before in Iraq and 8000 years before in China (6).

Among all the different traditional healthcare systems, Traditional Chinese Medicine (TCM) is currently the most commonly, and is gaining importance in the global market. Currently, more than 8000 different kinds of plant derived yields are exported from China to over 130 countries across the world. Recently, China has devoted a great deal of efforts and economic resources to enhance study and progress in the field of Chinese Herbal Medicine which is unmatched by other traditional medicine systems worldwide. Ayurvedic medicine (also known as Indian Herbal Medicine) is intensely rooted in Indian culture, and 70% of Indians depend on it for major healthcare needs (6). African Traditional Medicine is considered as one of the earliest of the traditional systems of medicine. African traditional healthcare system in its varied forms is holistic involving both the body and the mind. The traditional medicinal practitioners usually identify and treats the psychosomatic source of a sickness before suggesting plant based drugs (6, 13).

The people of Islamic countries have a great faith in Islamic Traditional Medicine, which has the history of hundreds of years. The most popular traditional drug in folk medicine practices around the Islamic countries is the use of medicinal plants. In the period of Islamic or the early medieval era, the Iranian scholars and doctors, including Avicenna, Rhazes and Jorjani etc. flourished the medical sciences. Due to these attainments, this era is known as the Islamic Golden Age (6, 14).

Some of the most celebrated scholars and physicians who were instrumental in the development of Islamic countries are indicated in Table 1 (15).

Table 1. Some of the most important scholars and relevant texts in the Islamic Traditional Medicine

Islamic scholars	Book	Language	Living period
Ahwazi Arjâni, AA.	Kamel al-Sinâh aṭ-Ṭibbiyah	Arabic	930–994 C.E
Akhawayni Bukhari, RA.	Hidâyat-al-Mutâllimin fi aṭ-Ṭibbe	Persian	10th century
Antaki, DO.	Taḏkirat Oli al-Albâb wa al-Jâme le al-Ajb al-Ujâb	Arabic	1535–1599 C.E.
Ansâri, AH.	Ekhtiyârât Badiʿi	Persian	?–1403 C.E.
Aqili Khorasani, MH.	Makhzan al-Adwiah	Persian	18th century
Biruni, MA.	Aṣ-Ṣaydanah	Arabic	973–1048 C.E.
Ghasani, AM.	Ḥadiqat al-Azhâr fi Mâḥiyyat al-ushb wa al-uqqâr	Arabic	1547–1611 C.E.
Herawi, AR.	Al-Abniyah an Ḥaqâyeq al-Adwiah	Persian	10th century
Husseini Tonekaboni, MM.	Toḥfah al- Moʿmenin	Persian	17th century
Ibn Al-Baytâr, AA.	Al-Jâmee le Mofradât al-Adwiah wa al-Aghḏiah	Arabic	1193–1248 C.E.
Ibn Nafis Qarshi	Ash –Shamel fi aṭ-Ṭibbe	Arabic	1210-1288 C.E.
Ibn Sina, HA.	Al-Qânun fi aṭ-Ṭibbe	Arabic	980–1037 C.E.
Jorjâni, SI.	Ḏakhireh Khârazmshâhi	Persian	1042–1136 C.E.
Jorjâni, SI.	Al-Aghrâḍaṭ-Ṭibbiah wa al-Mabâhethi al-Alâiiah	Persian	1042–1136 C.E.
Razi, MZ.	Al-Hâwi fi aṭ-Ṭibbe	Arabic	865–925 C.E.
Tabari, MA.	Ferdows al-Hekmah fi aṭ-Ṭibbe	Arabic	773–861 C.E.
Torkamâni YO.	al-Mo'tamad fi al-Adwiyah al-Mofradah	Arabic	1222–1294 C.E.

Traditional medicinal system in Iran

Persia (ancient Iran) is celebrated as one of the earliest civilizations in the world. Iran has a worthy history in traditional medicine, that relate to Babylonian-Assyrian civilization era. Traditional medicine in Iran is largely based on the Unani system, which is a good example of the oldest medical systems from ancient Persia. Also, Iran has long tradition in therapeutic plants usages for the management of different illnesses (8, 11). Avicenna (Abu Ali Sina), one of the most well-known doctors and philosopher, wrote 456 books in numerous topics including his most prominent compendium, "Canon of Medicine", which is a reference book in medicine with a special emphasis on plant based drugs. In this invaluable document which is still an authentic reference in a lot of medical schools across the world, about 1500 herbal drugs and almost 800 species of medicinal vascular plants have been discussed in detail. The present form of Unani medicine greatly owes to him (16-18).

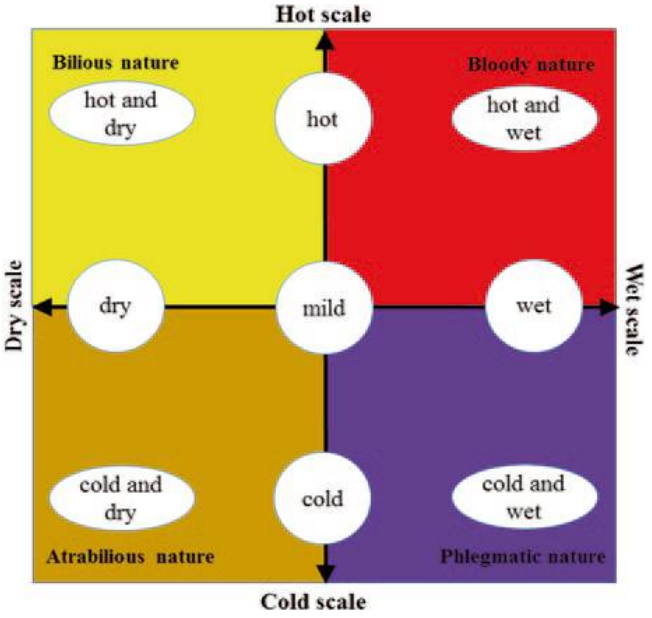

Fig.1. Schematic diagram of human nature in Iranian Traditional Medicine.

According to the basic principles of Iranian Traditional Medicine (based on Unani system of medicine), body is made up of the four basic components including: fire (that is hot), water (wet), earth or soil (dry) and air (cold). Nature or temperament of body is an outcome of mixing four special elements including: blood (which is hot and wet), bile (hot and dry), lymph or phlegm (cold and wet) and atrabilious (cold and dry). Any imbalance in the components of a nature can be resulted in creation of an illness (Fig. 1). In the traditional healthcare system of Iran, medicinal plants are major source of traditional medicine. Herbal medicine is still broadly used in Iran and the Unani system has been accepted and integrated into the national health system (11, 19).

Ethnobotany in Iran: Trends and Gaps

Ethno-botany is the organized survey of plants and their applied usages through the folklore information of an autochthonous culture and people. Iran is not only rich in its biodiversity but it is also well known as a country with high diversity ethnicities. Iran is a multi-ethnicity country with various ethnic groups such as Persians, Turkic Arabs, Turkmen, Lurs, Kurds and Baluchs communities. Thus, it enjoys a mix of cultures which is considered as a rich backbone for the expansion of ethnobotanical knowledge and plant based medicines. The study of traditional uses of medicinal plants is a major part of ethnobotany which is known as medical ethnobotany, ethnomedicine or ethnopharmacology (20-22).

Historic sign demonstrates the fact that Iranians are one of the earliest people in consuming the medicinal plants. The origin of Iranian therapeutic ethnobotany can be found in the distant periods. The first doctor trained in the universe was an Iranian named Sryta, whose name has been stated in the book of Avesta, the most ancient scriptures of Zoroastrianism). Therefore, the framework of Iranian ethnomedicine and medical ethnobotany are rooted in ancient times (23, 24).

In the last decades, several ethnobotanical investigations have been reported in various geographical regions of the country (9, 11, 25-33). Ethnobotanical studies carried out throughout the Iranian territory confirmed that medicinal plants are the major component of Iranian Traditional Medicine. Nowadays, in all towns and rural areas, there are medicinal plant or product stores (called Attari), where traditional medical practitioners (Attars) give receipts and sell therapeutic plants (11).

Medicinal herbs of Iran are used to treat various types of illnesses and health conditions, which are grouped in 12 broad categories according to WHO's International Classifications of Disease (34), that could be adapted to ethnobotanical surveys. Table 2 details the most efficient medicinal plants of Iran for the treatment of different ailments.

The analysis of researches related to ethnomedicinal plants published from 2004 to 2016 revealed that, although a broad array of diseases was stated for those plants, digestive system diseases (30.15%) and respiratory illnesses (14.28%), were the most cited (21).

According to literature review in the Iranian territory, the ethnobotanical research gaps include two main issues; the lack of scientific identification and insufficient statistical information.

Ethnobotany has always been to some extent an interdisciplinary science. In Iran, most ethnobotanical surveys have been conducted by pharmacognosists and anthropologists and botanists are not actually involved in this interdisciplinary field (35). However, the ethnobotany and

Table 2. The most efficient medicinal plants of Iran for treating ailments.

No.	Ailment categories	Taxon name	References
1	Digestive system diseases	*Achillea santolinoides* subsp. *wilhelmsii* (K.Koch) Greuter., *Anethum graveolens* L., *Artemisia dracunculus* L., *Bunium persicum* (Boiss.) B.Fedtsch., *Capsicum annuum* L., *Cassia fistula* L., *Curcuma longa* L., *Curcuma zedoaria* (Christm.) Roscoe, *Coriandrum sativum* L., *Cuminum cyminum* L., *Dysphania botrys* (L.) Mosyakin & Clemants, *Ferula gummosa* Bioss., *Foeniculum vulgare* Mill., *Glycyrrhiza glabra* L., *Heracleum persicum* Desf. ex Fisch., C.A.Mey. & Avé-Lall., *Laurus nobilis* L., *Matricaria chamomilla* L., *Mentha longifolia* (L.) L., *Mentha spicata* L., *Myristica fragrans* Houtt., *Nigella sativa* L., *Ocimum basilicum* L., *Pimpinella anisum* L., *Piper longum* L., *Trachyspermum ammi* (L.) Sprague, *Satureja hortensis* L., *Senna italica* Mill., *Terminalia chebula* Retz., *Teucrium polium* L., *Ziziphora clinopodioides* Lam., *Zataria multiflora* Boiss.	(26 ,14 ,11)
2	Respiratory system diseases	*Amaranthus caudatus* L., *Caccinia macranthera* (Banks & Sol.) Brand, *Dorema ammoniacum* D.Don, *Dysphania botrys* (L.) Mosyakin & Clemants, *Echinops cephalotes* DC., *Hyssopus officinalis* L., *Malva neglecta* Wallr., *Malva sylvestris* L., *Myrtus communis* L., *Nepeta binaloudensis* Jamzad, *Nepeta bracteata* Benth., *Nymphaea alba* L., *Origanum vulgare* L., *Papaver rhoeas* L., *Perovskia abrotanoides* Kar., *Stachys lavandulifolia* Vahl, *Trigonella foenum-graecum* L., *Tussilago farfara* L., *Urtica pilulifera* L., *Viola odorata* L., *Zataria multiflora* Boiss.	(11, 91)
3	Genitourinary system diseases	*Acorus calamus* L., *Areca catechu* L., *Astragalus hamosus* L., *Prunus avium* (L.) L., *Coriandrum sativum* L., *Crocus sativus* L., *Gentiana lutea* L., *Juniperus sabina* L., *Panax ginseng* C.A.Mey., *Petroselinum crispum* (Mill.) Fuss, *Physalis alkekengi* L., *Pinus gerardiana* Wall. ex D.Don, *Polygonatum orientale* Desf., *Rheum ribes* L., *Rosa beggeriana* Schrenk ex Fisch. & C.A.Mey., *Sesamum indicum* L., *Syzygium aromaticum* (L.) Merr. & L.M.Perry, *Tribulus terrestris* L., *Zea mays* L.	(11, 15, 92)
4	Circulatory system diseases	*Echium amoenum* Fisch. & C.A.Mey., *Berberis integrrima* Bunge, *Calendula officinalis* L., *Allium sativum* L., *Camellia sinensis* (L.) Kuntze, *Centaurea depressa* M.Bieb., *Citrus* spp., *Cucumis sativus* L., *Descurainia sophia* (L.) Webb ex Prantl, *Equisetum arvense* L., *Rhus coriaria* L., *Hibiscus sabdariffa* L., *Physalis alkekengi* L., *Rheum turkestanicum* Janisch., *Ribes khorasanicum* Saghafi & Assadi, *Rosa beggeriana* Schrenk ex Fisch. & C.A.Mey., *Urtica dioica* L., *Vaccinium arctostaphylos* L., *Viola odorata* L.	(11, 93-97)
5	Infectious and parasitic diseases	*Allium cepa* L., *Allium sativum* L., *Artemisia absinthium* L., *Artemisia dracunculus* L., *Capparis spinosa* L., *Coriandrum sativum* L., *Dorema ammoniacum* D.Don, *Dysphania botrys* (L.) Mosyakin & Clemants, *Embelia ribes* Burm.f., *Ferula foetida* (Bunge) Regel, *Ferula gummosa* Boiss., *Helichrysum graveolens* (M.Bieb) Sweet, *Heracleum persicum* Desf. ex Fisch., C.A.Mey. & Avé-Lall., *Lawsonia inermis* L., *Mentha longifolia* (L.) L., *Mentha spicata* L., *Nigella sativa* L., *Ocimum basilicum* L., *Peganum harmala* L., *Perovskia abrotanoides* Kar., *Rheum turkestanicum* Janisch., *Satureja hortensis* L., *Syzygium aromaticum* (L.) Merr. & L.M.Perry, *Terminalia citrina* Roxb. ex Fleming, *Tribulus terrestris* L., *Zataria multiflora* Boiss., *Ziziphora clinopodioides* Lam., *Ziziphora tenuior* L.	(11, 63, 98)
6	Musculoskeletal system diseases	*Abelmoschus esculentus* (L.) Moench, *Acacia senegal* (L.) Willd., *Cinchona officinalis* L., *Ephedra major* Host, *Fritillaria imperialis* L., *Matricaria chamomilla* L., *Commiphora mukul* (Hook. ex Stocks) Engl., *Rosmarinus officinalis* L., *Scrophularia striata* Boiss., *Urtica dioica* L., *Zataria multiflora* Boiss., *Zingiber officinale* Roscoe	(11, 26)
7	Skin diseases	*Arnebia euchroma* (Royle) I.M.Johnst., *Calendula officinalis* L., *Falcaria vulgaris* Bernh., *Fumaria vaillantii* Loisel., *Juglans regia* L., *Matricaria chamomilla* L., *Myrtus communis* L., *Olea europaea* L., *Origanum vulgare* L., *Plantago major* L., *Sesamum indicum* L., *Viola odorata* L., *Ziziphus spina-christi* (L.) Desf.	(11, 26)
8	Pregnancy, childbirth and the puerperium	*Anastatica hierochuntica* L., *Anethum graveolens* L., *Apium graveolens* L., *Aristolochia rotunda* L., *Capparis spinosa* L., *Carthamus tinctorius* L., *Crocus sativus* L., *Curcuma longa* L., *Dorema ammoniacum* D.Don, *Ferula gummosa* Boiss., *Lupinus luteus* L., *Matricaria chamomilla* L., *Physalis alkekengi* L., *Rosa foetida* Herrm., *Ruta graveolens* L., *Salix alba* L., *Salix aegyptiaca* L., *Vitex negundo* L., *Zataria multiflora* Boiss.	(11, 91)
9	Eye, ear, nose and throat problems	*Adiantum capillus-veneris* L., *Alcea* sp., *Cannabis sativa* L., *Chamaecrista absus* (L.) H.S. Irwin & Barneby, *Cordia myxa* L., *Cydonia oblonga* Mill., *Echinops cephalotes* DC., *Lepidium sativum* L., *Malva neglecta* Wallr., *Malva sylvestris* L., *Salvia macrosiphon* Boiss.	(11, 26)

10	Endocrine and metabolic diseases	*Berberis integrrima* Bunge, *Coriandrum sativum* L., *Cichorium intybus* L., *Cynara scolymus* L., *Cassia fistula* L., *Descurainia sophia* (L.) Webb ex Prantl, *Alhagi graecorum* Boiss., *Alhagi maurorum* Medik., *Dysphania botrys* (L.) Mosyakin & Clemants, *Malva sylvestris* L., *Fumaria vaillantii* Loisel., *Plantago major* L., *Plantago ovata* Forssk., *Adiantum capillus-veneris* L., *Cotoneaster nummularius* Fisch. & C.A.Mey., *Curcuma longa* L., *Curcuma zedoaria* (Christm.) Roscoe, *Salix alba* L., *Salix excelsa* S.G.Gmel., *Nasturtium officinale* R. Br., *Peganum harmala* L., *Salvia leriifolia* Benth., *Securigera securidaca* (L.) Degen & Dorfl., *Silybum marianum* (L.) Gaertn., *Rheum ribes* L., *Rheum turkestanicum* Janisch., *Rhus coriaria* L., *Ribes khorasanicum* Saghafi & Assadi, *Rumex acetosella* L., *Teucrium polium* L., *Tribulus terrestris* L., *Toddalia asiatica* (L.) Lam., *Trigonella foenum-graecum* L., *Vaccinium arctostaphylos* L., *Viola odorata* L., *Ziziphus jujuba* Miller	(11, 14, 32, 95, 99-101)
11	Injury, wound healing and fungal infection	*Aloe vera* (L.) Burm.f., *Althaea officinalis* L., *Doronicum pardalianches* L., *Falcaria vulgaris* Bernh., *Indigofera argentea* Burm.f., *Lawsonia inermis* L., *Malva sylvestris* L., *Myrtus communis* L., *Quercus infectoria* Oliv., *Trichodesma incanum* (Bunge) A.DC., *Tussilago farfara* L., *Ziziphus spina-christi* (L.) Desf.	(11, 26)
12	Nervous system disorders	*Achillea santolinoides* subsp. *wilhelmsii* (K.Koch) Greuter., *Aloysia citriodora* Palau., *Artemisia dracunculus* L., *Boswellia sacra* Fluek., *Citrus × aurantium* L., *Coriandrum sativum* L., *Crocus sativus* L., *Cyperus rotundus* L., *Dracocephalum lindbergii* Rech.f., *Echium amoenum* Fisch. & C.A.Mey., *Elettaria cardamomum* Maton., *Ferula gummosa* Bioss., *Hypericum scabrum* L., *Humulus lupulus* L., *Lavandula angustifolia* Mill., *Melissa officinalis* L., *Nardostachys jatamansii* (D.Don) DC., *Panax ginseng* C.A.Mey., *Papaver rhoeas* L., *Passiflora caerulea* L., *Perovskia abrotanoides* Kar., *Rosmarinus officinalis* L., *Stachys lavandulifolia* Vahl., *Stachys turcomanica* Trautv., *Terminalia chebula* Retz., *Tilia cordata* Mill., *Vitex negundo* L.	(26, 33, 56)

ethnopharmacology researches can contain a few documents with ambiguous details, owing to the absence of taxonomic services or botanical expertise. For example, in the literature review of Iranian ethnobotany, we identified that *Astragalus ammodendron* Bunge (Fabaceae), *Eryngium campestre* L. (Apiaceae) and *Lavandula binaludensis* (this species does not exist) have been recorded for ethnobotanical and ethnopharmacological applications (36-38). However, according to Flora Iranica and recent monographs, these taxa do not exist in Iran (39, 40). Hence, accurate identification of plant taxa is the foundation of ethnobotanical investigation and the species must only be validated by a panel of specialists including taxonomists (41).

Moreover, there is a need to compile available information and validation of traditional knowledge through appropriate statistical methodologies to ensure the accuracy of ethnobotanical data.

In the last few decades, with the intention of boost the indicative importance of ethnobotanical surveys, there have been efforts to develop the traditional compilation style method via combining proper measurable ways like multivariate statistical analysis. In modern ethnobotany, such novel scientific approaches can help build the highest quality information and also helps ensure the accuracy and reliability of the information (26, 42).

Currently, it was found that majority of the ethnobotanical surveys reported in Iran, devoid of insufficient statistical information (22).

Ethnobotanical works may thus serve as the fastest way to species collection for phytochemical and pharmaceutical surveys and such data should be preserved for the production of plant based medicine research in the future (31, 43).

Iranian flora wealth in pharmacological and chemical surveys: a compendium of 2075 medicinal species

Medicinal plants have served as precious resource of therapeutics since ancient times. Almost 200 years ago, our medical practices were mainly dominated by plant-derived drugs. However, the therapeutic application of plants went into a fast decrement in the West since the appearance of more foreseeable artificial medicines with their rapid properties and facile accessibility. However, as a result of different adverse impacts of synthetic drugs, people are now switching to plant-based medicines for health benefits. Plant derived drugs are known for their wide biological functions and are of immense therapeutic potential in traditional system of medicine (44-46). Recently, the renewed attentiveness to plant-based products research, has resulted in the development of new medicines, such as the earliest antimalarial agent, Quinine isolated from bark of *Cinchona officinalis* L. (Rubiaceae); Aspirin isolated from *Salix* species; Digoxin isolated from *Digitalis* species; Vinca alkaloids-Vinblastine and Vincristine obtained from *Catharanthus roseus* (L.) G. Don (Apocynaceae); Taxol obtained from *Taxus brevifolia* Nutt. (Taxaceae), Etoposide and Teniposide obtained from roots of *Podophyllum* species; Ephedrine isolated from *Ephedra* species; Artemisinin isolated from *Artemisia annua* L. (Asteraceae) (the current WHO recommended antimalarial agent); and Metformin isolated from *Galega officinalis* L. (Fabaceae) (the anti diabetic agent). Aside the therapeutic advantages of plant secondary metabolites, herbal extracts are now broadly used in perfumery and food flavouring as well as agrochemicals and pesticides (47-49).

In recent years, many studies have addressed the pharmacological and chemical properties of plants of Iranian Traditional Medicinal System (32, 44, 50-67).

Iran comprises an immense wealth of medicinal herbs (2075 species) suitable for pharmacological and chemical analysis and this source has not yet been fully evaluated. The vascular flora of Iran possesses a total of 2597 endemic or sub-endemic taxa. Many of these taxa from Fabaceae (687 taxa), Asteraceae (618 taxa), Lamiaceae (155 taxa), Apiaceae (127 taxa) and Brassicaceae (88 taxa) have not been studied well.

These taxa are good candidates for future research work (1, 8).

In Iranian Traditional Medicine, the noticeable roles of different plant families in the treatment of different illnesses are widely documented. In the recent review papers related to ethnobotanical studies published from 2004 to 2016, it was found that Labiatae was the most cited plant family (34 citations), that could be attributed to its broad distribution throughout Iran and multiple features of its plants (21). In the present work, it was found that Asteraceae is the second most reported plant family (33 citations) in Iranian Traditional Medicine. Other families including Fabaceae, Apiaceae, Brassiacaceae, Rosaceae and Solanaceae are also described. The most cited plant families in Iranian Traditional Medicine are as follows:

Lamiaceae in Iran and its ethnomedicinal use

The family contains *ca.* 241 genera and 7530 species/infraspecific taxa in the world (5). Family Lamiaceae comprises a wide diversity of chemical components particularly volatile oils, saponins, tannins, quinones and irodoids. Plants belonging to this family are commercially significant either for their uses as seasoning or their essential oils. The Lamiaceae (Labiatae) is one of the utmost important families of Iranian flora and its aromatic members including *Lallemantia iberica* (M.Bieb.) Fisch. & C.A.Mey., *Marrubium vulgare* L., *Melissa officinalis* L., *Mentha* spp., *Nepeta binaloudensis* Jamzad, *Ocimum basilicum* L., *Rosmarinus officinalis* L., *Salvia leriifolia* Benth., *Satureja hortensis* L., *Stachys lavandulifolia* Vahl, *Teucrium polium* L., *Vitex negundo* L., *Zataria multiflora* Boiss. and *Ziziphora clinopodioides* Lam. are broadly employed in Iranian Traditional Medicine for the cure of respiratory problems, digestive disorders, urinary problems, metabolic disorders, abdominal complaints, inflammation and infections (11, 68, 69).

Ethnomedicinal use of Asteraceae in Iran

The Asteraceae contains *ca.* 1623 genera and 24700 species/infraspecific taxa and is considered as the second largest family of vascular plants (after Orchidaceae *ca.* 736 genera, *ca.* 28000 species) in the world (5). Family Asteraceae has been known to produce a wide spectrum of secondary metabolites containing sesquiterpenes, lactones, saponins, coumarins, cyclitols and flavonols. Moreover, various kinds of alkaloids (pyridine, pyrrolizidine, quinoline, and diterpenoids) exist in this family. Asteraceae is also the second-largest plant family (after Fabaceae) in the flora of Iran, including many therapeutic and aromatic plants. Different taxa of this family such as *Achillea santolinoides* subsp. *wilhelmsii* (K.Koch) Greuter, *Arctium lappa* L., *Artemisia* spp., *Calendula officinalis* L., *Carthamus tinctorius* L., *Cichorium intybus* L., *Helichrysum graveolens* (M.Bieb) Sweet, *Matricaria chamomilla* L., and *Silybum marianum* (L.) Gaertn. are the most popular plants in Iranian folk medicine and are often used for the treatment of digestive illnesses, respiratory diseases, skin problems, neurological disorders, urinary problems, metabolic disorders, infections and inflammation (11, 21, 68).

Ethnomedicinal use of Fabaceae (Leguminosae) in Iran

This is the third major family of vascular plant in the world and contains *ca.* 751 genera and 19500 species/ infraspecific taxa (5). Among the chemical components, unusual aminoacids and tannins occur in the family, often with alkaloids and sometimes cyanogenic. The Fabaceae (Leguminosae) is the largest plant family in Iranian flora, including many medicinal plants. Various species of this family including *Alhagi maurorum* Medik., *Astragalus* spp., *Cassia fistula* L., *Glycyrrhiza glabra* L., *Indigofera argentea* Burm.f., *Medicago sativa* L., *Securigera securidaca* (L.) Degen & Dorfl., *Senna italica* Mill. and *Trigonella foenum-graecum* L. are the most popular plants in Iranian traditional remedies and are often used for the cure of urinary disorders, gastrointestinal ailments, respiratory diseases and metabolic problems. *Astragalus* L. comprises of *ca.* 2900 annual and perennial species which is the largest genus in the plant kingdom and widely utilized as ornamental, medication, food and fuel (9, 11, 21, 68).

Ethnomedicinal use of Apiaceae (Umbelliferae) in Iran

The family comprises of *ca.* 442 genera and 3575 species/infraspecific taxa in the world (5). Family Apiaceae comprises a broad diversity of chemical components particularly volatile oils, different types of coumarins, terpenes, triterpenoid resins and saponins acetylenic complexes. The Apiaceae is one of the biggest plant families in the flora of Iran, including many aromatic medicinal plants. Different species of this family including *Anethum graveolens* L., *Apium graveolens* L., *Bunium persicum* (Boiss.) B.Fedtsch., *Coriandrum sativum* L., *Cuminum cyminum* L., *Dorema ammoniacum* D.Don, *Ferula* spp., *Ducrosia anethifolia* (DC.) Boiss., *Eryngium billardierei* F.Delaroche, *Falcaria vulgaris* Bernh., *Foeniculum vulgare* Mill., *Kelussia odoratissima* Mozaff., *Oliveria decumbens* Vent., *Petroselinum crispum* (Mill.) Fuss, and *Pimpinella anisum* L. are very popular in Iranian folk medicine and are often used for the treatment of gastrointestinal problems, respiratory ailments, urinary complaints, skin disorders, wounds, infections and inflammation (11, 21, 31, 68).

Ethnomedicinal use of Brassicaceae (Cruciferae) in Iran

The family consists of *ca.* 328 genera and 3628 species/infraspecific taxa in the world (5). Several taxa of the family contain glucosinolates. Cardiac glycosides found in some genera and the seeds generally possess mucilage and fixed oil. Various species of Brassicaceae such as *Alyssum alyssoides* (L.) L., *Anastatica hierochuntica* L., *Brassica nigra* (L.) K.Koch, *Capsella bursa-pastoris* (L.) Medik., *Descurainia sophia* (L.) Webb ex Prantl, *Eruca vesicaria* (L.) Cav., *Isatis raphanifolia* Boiss., *Lepidium sativum* L. and *Nasturtium officinale* R.Br. are widely employed in Iranian Traditional Medicine, for the cure of respiratory disorders, gastritis, bronchitis, dermatitis and inflammation (5, 11, 21, 68).

Ethnomedicinal use of Iranian Rosaceae

The family comprises of *ca.* 91 genera and 2950 species/infraspecific taxa in the world (5). Among the chemical components, sugar alcohols, terpenoids, tannins, cyanogenic glycosides, saponins, mucilage and cyclitols occur in this family. The Rosaceae is one of the main families of Iranian flora, including many medicinal plants. Different species of this family including *Cotoneaster nummularius* Fisch. & C.A.Mey., *Cydonia oblonga* Mill., *Rosa beggeriana* Schrenk ex Fisch. & C.A.Mey., *Rosa* × *damascena* Herrm. and *Rosa foetida* Herrm. are the most popular in Iranian folk medicine, and are often used for the treatment of digestive ailments, neurological complaints, urinary disorders and diabetes (11, 21, 68).

Ethnomedicinal use of Solanaceae in Iran

The plant family contains *ca.* 100 genera and 2600 species/infraspecific taxa in the world (5). Diverse alkaloids like indole, tropane, pyridine, purine, pyrazole etc. are found in this family. Anthra-quinones, carotenoids, flavones, coumarins, withanolides, cyclitols and stroidal saponins are other types of alkaloids found in this family. Various species of this family such as *Atropa belladonna* L., *Capsicum annuum* L., *Datura stramonium* L., *Hyoscyamus niger* L., *Physalis alkekengi* L., *Solanum americanum* Mill., *Withania coagulans* (Stocks) Dunal and *W. somnifera* (L.) Dunal are very popular plants in Iranian folk medicine and are often used for the treatment of neurological illnesses, urinary disorders and abdominal complaints (8, 11, 21, 68).

Ethnomedicinal use of Ferns, Mosses, Lichens and Mushrooms in Iran

Very little information is available about ethnomedicinal aspects of ferns and mushrooms in Iran. In Iranian traditional medicine, two fern species including *Adiantum capillus-veneris* L. (Pteridaceae) and *Polypodium vulgare* L. (Polypodiaceae) are extensively applied in folklore medicine for the management of gastro-intestinal problems and respiratory ailments. The fruiting body of *Laricifomes officinalis* (Vill.) Kotl. & Pouzar (Fomitopsidaceae) is known as Gharighun and Iranian Traditional Medicine practitioners recommends it as anti-hemorrhage and laxative (11, 26). No ethnobotanical documents could be recognized for the use of mosses and lichens in Iran.

It could be noted that there is still an absence of pharmacological and phytochemical studies on a lot of species of Iranian flora and additional trainings are needed to take further their medicinal prospects, which would serve as promising precursors for the progress and genesis of new plant based medicines in the future (8, 31).

Challenges for plants of Iranian Traditional Medicine system: Quality, safety and efficacy

Identification and authentication challenges of Iranian Traditional Medicine System

Medicinal herbs are still broadly applied in Iran and ITM has played a very significant role in providing healthcare of the population. In all cities and villages, people use medicinal plants according to their cultural background and this practical knowledge has been transmitted in different ways from generation to generation (11, 28). However, there are several challenges for medicinal plants and herbal medicines, particularly their identification and authentication in the country. In Iran, medicinal plants are generally referred to by their local or common names rather than scientific names (8, 41). Due to the history of Iran and its situation at the heart of the Silk Road that connected it with other countries, only vernacular names have been employed in the traditional literature related to Iranian ethnomedicine. It is too cumbersome to match such names with botanic names due to the immensely varied flora, language and diversity in the country. Local names are likely to cause obscurity as one plant species may have several vernacular names or one local name may be used for several different species. For instance, the popular name “Gol-e-babooneh” (in Persian), that is matched with *Matricaria chamomilla* L. (real babooneh) and six other species from Asteraceae (ie. *Anthemis nobilis* L., *Anthemis wiedemanniana* Fisch. & C.A.Mey., *Tripleurospermum disciforme* (C.A.Mey.) Sch.Bip., *Tanacetum parthenium* (L.) Sch.Bip., *T. persicum* (Boiss.) Mozaff. and *Microcephala lamellata* (Bunge) Pobed.). Another example is “Avishan” (in Persian), that is employed for any of fourteen species of *Thymus* L. and one species of *Zataria* Boiss. in various parts of Iran (22, 41, 70, 71). Further to nomenclatural obscurity, the folk medicines sold in herbal markets in Iran are adulterated or exchanged with quite irrelevant plant substances. In general, adulteration is characterized as a practice of adding an external material from a different species to the authentic plant with an intention of enhancing the weight or strength of the product or to reduce its price. A national survey in Iran revealed that remarkable contributions of therapeutic plants existing in the herbal shops (Attari) are facing identification crisis along with adulteration and substitution problems. The Attaris have their own in house standards and mostly still practice organoleptic methods like taste, odour and touch to distinguish a medicinal plant which is considered unscientific. The spurious material may have different compounds than genuine medicinal plant that can cause health and safety concerns. To confirm safety and effectiveness of plant medicines, accurate documentation, validation and omission of adulteration are necessary and medicinal plant species must only be confirmed using a panel of specialists particularly experienced plant taxonomist (41). Moreover, it will be prudent to have dependable devices for differentiating genuine drugs from their adulterants. A wide range of methods can be used for identification and authentication of medicinal plants, including conventional morphology and phytochemistry based methods and modern molecular methods (72).

Conventional approaches for medicinal plant authentication

Conventionally, authentication and quality control depend mostly on morphological and phytochemical

analyses, detailed in pharmacopoeias. In Iran, plant taxonomists tend to identify medicinal plants by macro and micro morphological methods. Micromorphological characterizations (botanical microscopy) is an exquisite method for authentication and quality assurance of herbal components as well as an inherent part of almost all pharmacopoeias (19, 73). In a recent study, the taxonomic evaluation of crude herbal drugs have shown a lot of misidentification, adulteration and substitution in the markets of Iran (see Table 3). In these herbal markets, some of the herbal drugs are misidentified, confused and adulterated with locally available herbal drugs. As can be seen in Table 3, *Bunium cylindricum* (Boiss. & Hohen.) Drude (an adulterant) was admixed with Zire-siah (*Bunium persicum* (Boiss.) B.Fedtsch.) and sold in the herbal shops, which leads to deprivation of the value and efficacy of the original medicine. *Adiantum capillus-veneris* L. is commonly admixed with adulterants like *Thalictrum sultanabadense* Stapf (Ranunculaceae), owing to identical morphological characters or replaced by cheap materials in the market. *Rheum turkestanicum* Janisch. (Polygonaceae) is largely adulterated or substituted with *Rheum ribes* L. which can lead to the loss of its efficacy. Moreover, the replacement and adulteration of the medicinal plants can create safety and health issues (41).

Table 3. Some of the most common adulteration and substitution of crude drug in the different herbal markets of Iran (on the basis of macro- and micro-morphological methods).

No.	Drug name	Authentic drug	Substituent/adulterants	Plant part used	References
1	Afsantin	*Artemisia absinthium* L.	*Helichrysum graveolens* (M.Bieb.) Sweet	Flower	(41)
2	Anjedane-roomi	*Levisticum officinale* W.D.J.Koch	*Zosima absinthifolia* Link	Fruit	(41)
3	Barge-moord	*Myrtus communis* L.	*Haplophyllum perforatum* Kar. & Kir.	Leaf	(39)
4	Dome-asb	*Equisetum arvense* L.	*Anabasis haussknechtii* Bunge ex Boiss.	Aerial parts	(41)
5	Eshghan	*Rheum turkestanicum* Janisch.	*Rheum ribes* L.	Root	(41)
6	Havachoobe	*Arnebia euchroma* (Royle) I.M.Johnst.	*Onosma longilobum* Bunge	Root	(41)
7	Kakanaj	*Physalis alkekengi* L.	*Hibiscus trionum* L.	Flower	(41)
8	Marzanjush	*Origanum vulgare* L.	*Ziziphora clinopodioides* Lam.	Aerial parts	(41)
9	Mokhallaseh	*Scrophularia striata* Boiss.	*Tanacetum parthenium* (L.) Sch. Bip.	Aerial parts	(8)
10	Pare-siavashan	*Adiantum capillus-veneris* L.	*Thalictrum sultanabadense* Stapf	Aerial parts	(41)
11	Zire-siah	*Bunium persicum* (Boiss.) B.Fedtsch.	*Bunium cylindricum* (Boiss. & Hohen.) Drude	Fruit	(41)

Phytochemistry methods would serve as standard reference for correct identification of medicinal plant species but requires costly techniques, including X-ray, FTIR (Fourier-Transform Infrared Spectroscopy), HPLC (High Pressure Liquid Chromatography) NMR (Nuclear Magnetic Resonance), and TLC (Thin Layer Chromatography). Moreover, phytochemistry methods have limitations derived from the intricacy of investigation segmentation or powdered materials do not let comprehensive identification of the material (74, 75).

Modern approaches for medicinal plant authentication

Whereas differentiating power of structural and biochemical methods for species identification have limitations, molecular approaches are far more efficient, accurate and dependable (75). In recent years, progresses in the molecular genetics have provided workers with a range of new techniques for efficient and dependable identification of therapeutic plants. Among the popular genome-based approaches to dominate the complexity of traditional taxonomy, DNA barcoding has been found to be successful in the identification of plant species (76). Biomolecular procedures, like DNA barcoding and meta barcoding, have thus emerged as efficient ways for identification of plant ingredients in powder and complex herbal products. DNA barcoding can be applied for verifying produces based on components from different plants and DNA-meta barcoding for evaluation of components from different species or varieties from particular plant in treated produces (73). Even though this is an upward area of scientific attention, very little research has been done on the base of molecular techniques for authentication of medicinal plants in Iran (71, 77, 78). In a recent study, the DNA barcoding of plant matter in herbal shops in Iran has shown a lot of adulteration and substitution. It was shown that 18 samples (26 %) of the therapeutic herbs sampled from the market were not having the species documented in the respective plant pharmacopeia. The species intended for therapeutic usage, as recognized by the plant pharmacopeia, are adulterated locally with other species from the same genus or different species altogether. Commercial medicinal plants like Marzeh and Maryam goli were some instances, where DNA barcoding revealed that *Urtica dioica* L. (Urticaceae) was being sold instead of *Satureja laxiflora* K.Koch and *Satureja hortensis* L. (Marzeh) and also *Althaea cannabina* L. (Malvaceae) was replaced or admixed with *Salvia officinalis* L. (Maryam goli) (71). Therefore, the implementation of such methods for the confirmation of medicinal plants will warrant top quality plant based therapeutic produces, devoid of adulterants and lacking side effects that would have marked influence on the health of the consumers.

Challenges of collection, drying and storage of medicinal plants

In Iran, there is a general belief amongst the consumers of medicinal plants, that herbal drugs are always safe due to their natural origin and long history of traditional uses, but the lack of regulation of Iranian medicinal plants and inappropriate

methods of gathering, drying and storage establishes no such assurance.

Collection of medicinal plants is the first step of phytochemical or related investigations and is one of the most important concerns for its quality. Medicinal plants gathered from the natural could be mixed with additional species or plant segments via mistaken identification. Poisoning from folk medicines is mostly as a result of wrong identification. For example, due to some morphological similarities, *Anabasis haussknechtii* Bunge ex Boiss. (Amaranthaceae) is mistakenly sold as *Equisetum arvense* L. (Equisetaceae) which may result in adverse effects and toxic effects (41, 79, 80). Therefore, scientific identification and provision of voucher specimens are essential which can reduce such errors and support researchers with an improved understanding of their topics and relatively efficient investigation of their properties (9). Furthermore, collection of medicinal plants can be influenced by several factors, for instance, physiological (the age of the plant) and environmental (eg. sunlight, temperature, rainfall, soil features and height above sea level). This is necessary for the determination of reproducible outline of plant metabolites. Another major concern that remains is drying conditions of medicinal plants in Iran. Inadequate drying may result in mould growth and microbial fermentation, which can lead to the degradation of plant products (80, 81).

Concerns have also been raised regarding methods of storage of medicinal plants and produces in Iran. Recent studies on Iranian herbal water (plant water) revealed that its oral use and even vapour coverage is seriously poisonous for humans due to the presence of methanol and a low standard of processing for the duration of fabrication or storage of such plant waters through the fallouts of enzymes on pectins in the cell wall. The existence of more wooden structures in a plant could make it more sensitive to methanol fabrication. Therefore, if the woody organ of a plant is reduced to the maximum probability and direct vapour distillation is employed for the period of fabrication causing lesser enzyme property, methanol concentration will be much lesser in the final output (82, 83). Thus, the processing stages from sorting of medicinal plants to the distillation, needs to be modified in order to diminish methanol concentrations. Moreover, comprehensive investigation and the standardization are indispensable to regulate the quality of raw herbal medicines and to authenticate their usages in the up to date health care schemes.

Challenges of poisonous plants used in traditional medicine

Undoubtedly the demand for plant based remedies is greater than before globally. Keeping this in view, the efficacy of herbal medicine needs improvement in terms of their quality and safety. Plant kingdom possess many secondary metabolites, and thus some plants are very poisonous. Herbal therapy in other complementary usage carries a higher potential of adverse effects, hazards and toxicity (47, 84). Among secondary metabolites, pyrrolizidine alkaloids are very dangerous and are synthesized in almost all species of Boraginaceae and in a number of species of Asteraceae (subfamily Senecioninae) and Fabaceae (tribe Crotalarieae). Activation of these compounds in liver of animal/human causes production of dehydropyrrolizidines as a reactive pyrroles which finally formed alkylated DNA bases. These DNA alkylations can result in mutation and cell dying (particularly in liver). Moreover, mutations can result in abnormalities in pregnant animals/humans and in the cancer of liver, kidneys and lungs. Several pyrrolizidine alkaloids comprising plants are employed in folk phyto medicine to remedy bloodshed or diabetes and common as herbal tea (*Crotalaria* L., *Heliotropium* L., *Petasites* Mill., *Senecio* L.); *Symphytum officinale* L. (Boraginaceae) and other Boraginaceae species to remedy wounds and broken or damaged bones. Others, such as *Symphytum* x *uplandicum* Nyman are commonly provided on local herbal shops as “healthy” salad components. It should be noted that plants containing pyrrolizidine alkaloids should be avoided and are banned as medicines (85).

Toxicity by traditional plant based therapies in Iran is not scarce. Several medicinal plants with a long history of folk usage are suspected to be carcinogenic and/or hepatotoxic. For example, recent studies reported hepatotoxicity cases due to inappropriate consumption of *Echium amoenum* Fisch. & C.A.Mey. (Gole-Gavzaban) (Boraginaceae) as a famous herbal medicine in Iran, resulting in hepatic failure and hospital admission (86, 87). The most important Iranian traditional medicinal plant species that can pose critical threat to the health of humans are presented in Table 4 and images of few of them are shown in Fig. 2.

Challenges of conservation of Iranian medicinal plants

One of the most important challenges for medicinal plants is the loss of endemic, rare and narrow-range taxa, because of the non-principled use, mismanagement and overexploitation. Many species of endemic medicinal plants of Iran are harshly threatened in the wild and are severely harvested consequently, are now endangered. Iran has a unique habitat due to its biodiversity and endemism of a number of plant species. The concept of endemism and the proportion of endemic species to the total number of species is very important in biodiversity and conservation biology (1, 8).

The Iranian vascular flora encompasses a total of 2597 endemic or sub-endemic species. The Irano-Turanian phytochoria harbours 88% of the Iranian endemics. There are no endemic families, but 26 endemic and sub-endemic genera. Dicots include 2421 endemic taxa in Iran, monocots contain 175 endemics and gymnosperms have only one (1). Lamiaceae is a noteworthy medicinal family in the Iran flora with 155 endemic taxa. The other important medicinal families in this category are Apiaceae with 127, Brassicaceae with 88, Fabaceae with 687 and Asteraceae with 618 endemic taxa. Several endemic species of these medicinal families

Table 4. Some of the most important poisonous plants used in folklore medicine of Iran.

No.	Drug name & part used	Scientific name	Family	Ethnomedicinal uses	Toxic substance	Side effects/ Modes of action	References
1	Agir Torki (Root)	*Acorus calamus* L.	Acoraceae	Treatment of Urinary incontinence, diuretic, carminative, stimulant, hematinic	Phenylpropanoids (asarone)	It is converted to epoxides in the liver, which can alkylate proteins and DNA (resulting in mutation and tumour)	(11, 85)
2	Shokaran (Root)	*Conium maculatum* L.	Apiaceae	Cholagogue, depilator, treatment of dermal allergies	Piperidine Alkaloids	Extremely toxic and teratogenic	(11, 85)
3	Zaravand (Root)	*Aristolochia rotunda* L.	Aristolochiaceae	Emmenagogue, diuretic, anti-atherosclerosis, tonic, treatment of rheumatism	Aristolochic acids	It causes DNA alkylations, which can cause mutation and after long-term use, cancer (especially in the liver)	(11, 85)
4	Asarun (Root)	*Asarum europaeum* L.	Aristolochiaceae	Tonic, stimulant	Phenylpropanoids (asarone)	It is converted to epoxides in the liver, which can alkylate proteins and DNA (resulting in mutation and tumour)	(11, 85)
5	Onsol, Gaav Piazi (Bulb)	*Drimia maritima* (L.) Stearn (Syn. *Urginea maritima* (L.) Baker)	Asparagaceae	Emmenagogue, hair tonic, toothache, kidney stones, rheumatism, joint pains	Cardiac Glycosides	Strong neurotoxin, which causes death through cardiac and respiratory arrest (inhibits Na+,K+-ATPase)	(11, 85)
6	Bumadaran (Aerial parts)	*Achillea* spp.	Asteraceae	Treatment of gastrointestinal diseases, treatment of osteoarthritis, blood flooding, hypoglycemic, nerve tonic	Thujone	Thujone can alkylate important proteins of the neuronal signal transduction, therefore causing neuronal disorder	(11, 85)
7	Afsantin (Aerial parts)	*Artemisia absinthium* L.	Asteraceae	Anthelmintic, appetizer, indigestion	Thujone	Thujone can alkylate important proteins of the neuronal signal transduction, therefore causing neuronal disorder	(11, 85)
8	Pa Khari (Aerial parts)	*Tussilago farfara* L.	Asteraceae	Expectorant, antitussive, mouth wounds, treatment of furuncles	Pyrrolizidine Alkaloids	It causes DNA alkylations, which can cause mutation and after long-term use, cancer (especially in the liver)	(11, 85)
9	Gole gavzabane pirzani (Flower)	*Anchusa aegyptiaca* (L.) A.DC.	Boraginaceae	Skin dermatitis, herpes	Pyrrolizidine Alkaloids	DNA alkylations can cause mutation and after long-term use, cancer (especially in the liver)	(85, 102)
10	Gul-guzan, Gole gaav Zaban (Flower)	*Anchusa azurea* Mill. (Syn. *A. italica* Retz.)	Boraginaceae	Cold, sedative, influenza	Pyrrolizidine Alkaloids	DNA alkylations can cause mutation and after long-term use, cancer (especially in the liver)	(26, 85, 102)
11	Havachoobeh (Root)	*Arnebia euchroma* (Royle) I.M.Johnst.	Boraginaceae	Treatment of dermal disorders, hair tonic	Pyrrolizidine Alkaloids	DNA alkylations can cause mutation and after long-term use, cancer (especially in the liver)	(11, 85)
12	Gavzaban sabz (Aerial parts)	*Caccinia macranthera* (Banks & Sol.) Brand	Boraginaceae	Sedative, treatment of cough, expectorant	Pyrrolizidine Alkaloids	DNA alkylations can cause mutation and after long-term use, cancer (especially in the liver)	(11, 85)
13	Gole Gavzaban (Flower)	*Echium amoenum* Fisch. & C.A.Mey.	Boraginaceae	Antihypertensive, nerve tonic, diuretic, antistress, blood cleanser, cardiac tonic	Pyrrolizidine Alkaloids	DNA alkylations can cause mutation and after long-term use, cancer (especially in the liver)	(11, 85)
14	Kalak (leaf)	*Heliotropium dasycarpum* Ledeb. ex. Eichw.	Boraginaceae	Itching	Pyrrolizidine Alkaloids	DNA alkylations can cause mutation and after long-term use, cancer (especially in the liver)	(22, 85)
15	Kalak (leaf)	*Heliotropium europaeum* L.	Boraginaceae	Itching	Pyrrolizidine Alkaloids	DNA alkylations can cause mutation and after long-term use, cancer (especially in the liver)	(22, 85)
16	Alaf-esimkesh (Aerial parts)	*Trichodesma incanum* (Bunge) A.DC.	Boraginaceae	Treatment of bone fracture	Pyrrolizidine Alkaloids	DNA alkylations can cause mutation and after long-term use, cancer (especially in the liver)	(11, 85)
17	Zabun Gueri (Seed)	*Rindera lanata* Bunge	Boraginaceae	Joint pains	Pyrrolizidine Alkaloids	DNA alkylations can cause mutation and after long-term use, cancer (especially in the liver)	(85, 102)

18	Hanzal (Fruit-Seed)	*Citrullus colocynthis* (L.) Schrad.	Cucurbitaceae	Purgative, anodyne, hypoglycemic	Anthraquinones	Anthraquinones can intercalate DNA long-term usage	(11, 85)
19	Karchak (Seed)	*Ricinus communis* L.	Euphorbiaceae	Purgative	Lectins (ricin)	Lectins are toxic when taken orally and bind to cells via the haptomer and become internalized by endocytosis. Once in the cell they have an affinity for ribosomes and the A-chain (the effectomer, which has N-glycosidase activity) blocks ribosomal protein translation by inactivating elongation factors EF1 and EF2. A cell that no longer is able to make proteins will die.	(11, 85)
20	Cheshm Khorus (Seed)	*Abrus precatorius* L.	Fabaceae	Contraceptive	Lectins (abrin)		(11, 85)
21	Kachuleh (Seed)	*Strychnos nux-vomica* L.	Loganiaceae	Antiallergic, eczema, sedative	Indole Alkaloids	Neuromuscular blocking agents	(11, 85)
22	Joze Buya (Seed)	*Myristica fragrans* Houtt.	Myristicaceae	Treatment of gastrointestinal diseases	Phenylpropanoids (myristicin)	Myristicin is converted to epoxides in the liver, which can alkylate proteins and DNA (resulting in mutation and tumour)	(11, 85)
23	Gol Angoshtaneh (Flower)	*Digitalis purpurea* L.	Plantaginaceae	Cardiac tonic	Cardiac Glycosides	Strong neurotoxin, which causes death through cardiac and respiratory arrest (inhibits Na+,K+-ATPase)	(11, 85)

are frequently used in Iranian Traditional Medicine. *Zhumeria majdae* Rech.f. & Wendelbo (Lamiaceae) and *Nepeta binaloudensis* Jamzad are important endemic medicinal plants, which have been severely harvested and are now endangered with narrow distribution and low abundance. *Nepeta binaloudensis* is commonly known as "Ostokhodus", has been recommended to cure pulmonary infections, rheumatism and as antiasthmatic, antitussive and cardiac tonic. *Ribes khorasanicum* Saghafi & Assadi (Grossulariaceae) is another endemic species with a small distribution range in Iran which is exposed to heavy usage by inhabitants of the area. Because of overharvesting, these species are calling a wake-up alarm for conservation (1, 11, 88). *Ferula latisecta* Rech.f. & Aellen and *Dorema kopetdaghense* Pimenov are endangered medicinal plants belonging to Apiaceae family. Continued overutilization and habitat degradation of these invaluable species for therapeutic and food purposes may lead to the eradication from the area. *Zataria multiflora* Boiss. is another medicinal plant in Iran, known from ancient times, is also severely harvested and because of its low reproduction, it should be considered in conservation management programmes. There are also concerns around some other medicinal species such as *Dorema aucheri* Boiss., *Echinophora cinerea* (Boiss.) Hedge & Lamond (Apiaceae), *Ferula hezarlalehzarica* Ajani, *Heracleum gorganicum* Rech.f. and *Kelussia odoratissima* Mozaff. which are constricted range endemics and found just in a few particular niches (30, 31, 88, 89). Some of the important endangered medicinal plant species of Iran are illustrated in Table 5 and are shown in Fig. 3. Diverse applications of traditional medicine, continued collection from wild populations and destructive harvesting approaches, particularly elimination of subterranean part will inevitably result in decrease in populations, loss of genetic diversity and local extinctions of these invaluable taxa and it alarms for an impending disaster.

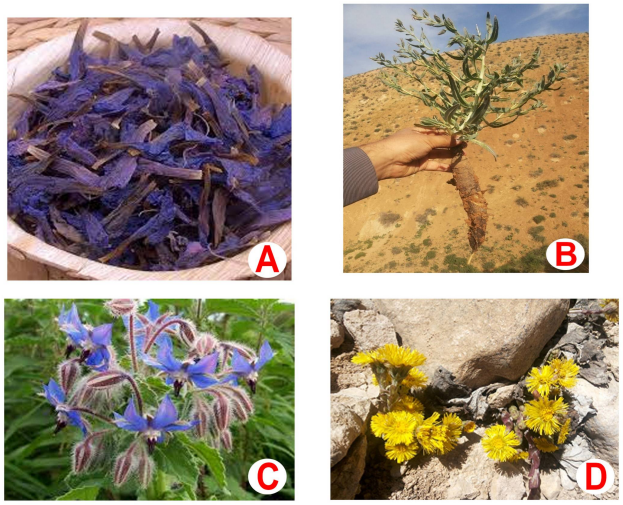

Fig. 2. Some of the most important traditional medicinal plants contaning pyrrolizidine alkaloids in the markets of Iran: **(A)** *Echium amoenum* Fisch. & C.A.Mey., a popular poisonous plant used in folklore medicine of Iran; **(B)** *Caccinia macranthera* (Banks & Soland.) Brand, a poisonous species occur in the bazaars of Iran; **(C)** *Borago officinalis* L., a poisonous plant occur in some bazaars of Iran; **(D)** *Tussilago farfara* L., a poisonous species found in the markets of Iran.

Unfortunately, the continuous and enhancing anthropogenic pressures containing deforestation, inappropriate overgrazing, amplification of agriculture, drainage of wetlands, industrialized development, road construction and plant material overexploitation as a source of income for native poor people, have already influenced the growth, endurance and distribution of native species in Iran, particularly the rare and endemic species (31, 88, 89). Therefore, there is a strong need to develop conservation strategies for better protection of all common endemic medicinal plant species assigned to a threat category. To achieve this, different sets of modalities have been recommended, such as providing both *in-situ* conservation (natural reserves and wild nurseries) and *ex-situ* conservation (botanic

Table 5. List of the most important threatened medicinal plant species of Iran.

No.	Family	Species/infraspecific taxa	Red list categories and criteria	Ethnobotanical uses	References
1	Amaryllidaceae	*Allium stipitatum* Regel (Syn. *A. hirtifolium* Boiss.)	EN	Used as a spice within foods	(88)
2	Amaryllidaceae	*Allium ellisii* Hook.f.	VU	Used as a spice within foods	(88, 89)
3	Apiaceae	*Dorema ammoniacum* D.Don	LR	Treatment of gastrointestinal and respiratory problems	(31, 88)
4	Apiaceae	*Dorema aucheri* Boiss.	LR	Treatment of gastrointestinal and respiratory diseases, burn healing	(31, 88)
5	Apiaceae	*Echinophora cinerea* (Boiss.) Hedge & Lamond	LR	Stimulant and an invigorator of the stomach, diuretic, anti-cancer	(31, 88)
6	Apiaceae	*Echinophora platyloba* DC.	LR	Dissolves renal calculi, anti aphthous (mouth wash), antifungal	(31, 88)
7	Apiaceae	*Ferula assa-foetida* L.	EN	Treatment of gastrointestinal and respiratory problems	(31, 88)
8	Apiaceae	*Ferula latisecta* Rech.f. & Aellen	EN	Indigestion and anthelmintic	(31, 89)
9	Apiaceae	*Ferula macrocolea* Boiss.	LR	Anti-nausea, anti-stomach acid	(88, 103
10	Apiaceae	*Ferulago angulata* subsp. *carduchorum* (Boiss. & Hausskn.) D.F.Chamb. (Syn. *F. carduchorum* Boiss. & Hausskn.)	LR	Dermal wounds	(29, 88)
11	Apiaceae	*Haussknechtia elymaitica* Boiss.	VU	Diabetes, hypertension	(88, 102)
12	Apiaceae	*Heracleum gorganicum* Rech.f.	LR	Flavoring, digestive disorders	(26, 88)
13	Apiaceae	*Kelussia odoratissima* Mozaff.	EN	Treatment of gastrointestinal and respiratory diseases, sedative, hypertension, cardiovascular diseases, inflammation ulcers	(31, 104)
14	Apiaceae	*Prangos cheilanthifolia* Boiss.	LR	Treatment of flatulency	(57, 88)
15	Apiaceae	*Psammogeton canescens* Vatke	LR	Disinfectants	(27, 88)
16	Asparagaceae	*Danae racemosa* (L.) Moench	EN	Fruits are used for dying silk	(26, 88)
17	Grossulariaceae	*Ribes khorasanicum* Saghafi & Assadi	EN	Antihypertensive, diabetes, depurative	(11, 89)
18	Lamiaceae	*Dracocephalum kotschyi* Boiss	EN	Fever, analgesic, rheumatism	(88, 105)
19	Lamiaceae	*Nepeta binaloudensis* Jamzad	EN	Treatment of gastrointestinal and respiratory diseases, treatment of rheumatism, cardiac tonic	(11, 89)
20	Lamiaceae	*Satureja bachtiarica* Bunge	LR	Flatulence, edible	23, 88)
21	Lamiaceae	*Satureja khuzistanica* Jamzad	VU	Inflammation, toothache, common cold, antiseptic, analgesic	(88, 105)
22	Lamiaceae	*Thymus daenensis* Celak.	LR	Fever, diuretic, vermifuge, flatulence, appetizer, toothache	(88, 105)
23	Lamiaceae	*Zataria multiflora* Boiss.	LR	Treatment of gastrointestinal and respiratory diseases, menstrual pains, dysmenorrheal, anthelmintic	(11, 88)
24	Lamiaceae	*Zhumeria majdae* Rech.f. & Wendelbo	EN	Stomachache, antiseptic, painful menstruation	(88, 105, 106)
25	Liliaceae	*Fritillaria imperialis* L.	EN	Treatment of joints pain	(11, 107)

Red list categories: CR = critically endangered, EN = endangered, VU = vulnerable, LR = low risk, LC = least concern, and DD = data deficient.

gardens and seed banks). Moreover, resource management (eg. good agricultural practices and sustainable use solutions) and biotechnological methods (eg. cell culture, micropropagation, artificial seed technology and molecular marker-based methodologies) should be effectively taken into account for the sustainable use and improved yield of medicinal plants. Enhanced cultivation contributes to reduction in the harvest volume of medicinal plants that can lead to the recovery of their wild resources (90).

Conclusion and future prospects

The growing global demand for plant based remedies has necessitated attention to increased concerns over different aspects of source plant material that constitutes the medicine. In Iran, plant based drugs are facing challenges of authenticity, quality, safety and efficacy.

Currently, there are no standards for identification and confirmation of medicinal plants and herbal products in Iran. Microscopy has been employed to identify herbal products in Iran that has shown a lot of adulteration and substitution in the herbal markets. Microscopic authentication is a fast and cost efficient method, but it has restricted applicability for powdered and mixtures samples. The use of molecular markers as analytic techniques and DNA barcoding or meta barcoding are proposed for the correct identification of medicinal plant species used in Iran and authenticated plant products.

Many medicinal plant species are sensitive to climatic situations, requiring appropriate drying and storage under controlled temperature and humidity. Improper approaches of collection, drying and storage with adverse pollutants (eg. pesticides, heavy metals, microbial pollutants, toxic plants and adulterants) in the products, have all contributed to the undesirable impact with regards to Iranian

Fig. 3. Selected rare and endangered medicinal plants of Iran: **(A)** *Ferula latisecta* Rech.f. & Aellen, an endangered medicinal species occurs in NE of Iran; **(B)** *Dorema kopetdaghense* Pimenov, an endangered medicinal plant found in NE of Iran; **(C)** *Ribes khorasanicum* Saghafi & Assadi, an endangered medicinal species occurs in a small area in NE of Iran; **(D)** *Nepeta binaloudensis* Jamzad, a highly endangered medicinal plant found in NE of Iran; **(E)** *Rheum turkestanicum* Janisch., a rare important medicinal plant distributed in NE of Iran; **(F)** *Dorema aucheri* Boiss., a threatened medicinal plant found in the western region of Iran; **(G)** *Kelussia odoratissima* Mozaff., a threatened medicinal species occurs in a small area in the western part of Iran; **(H)** *Fritillaria imperialis* L., a threatened medicinal plant distributed in the western region of Iran.

natural plant products. Evaluating and monitoring potentially detrimental substances are indispensable for improving the general quality and safety of extensively employed medicinal herbs.

It was found that majority of ethnobotanical studies reported in Iran suffer from insufficient statistical data. Therefore, modern ethnobotanical attempts with new methods for data analysis should continue, mainly in areas that have so far received fewer attention, particularly on multiethnic regions. The fastest manner to species selection for biological, phytochemical and pharmacological investigations, is by reviewing the ethnobotanical literature that accentuate the significance of such studies.

The absence of accurate translation and interpretation of the old traditional books is a key challenge in the verification of herbal materials used. In Iran, scientists are studying medicinal plants with reference to their therapeutic uses as documented in old books. Therefore, the improvement of ethnobotanical studies in Iran and correct scientific identification of medicinal plant species in the texts, need more involvement of botanists and experienced plant taxonomists.

Another major concern that remains is conservation status of medicinal plant species. Many Iranian medicinal plants are collected from the wild habitats, and they are becoming endangered at an alarming rate. The occurrence of threatened medicinal plants subjected to high anthropogenic pressure on these taxa. Some of these invaluable species have very limited distribution in the country and need special conservation strategies for their survival. If overexploitation and habitat destruction of such invaluable medicinal plants continues, they may vanish from the area within a few years.

The chemical variety of secondary metabolites from the plant kingdom, provide limitless opportunities for novel drug discovery. Recent investigations revealed that rare and endemic medicinal plants of Iran are rich in potent secondary metabolites that would serve as promising precursors for developing potent plant-based drugs. There is no doubt that Iranian Traditional Medicine, together with endemic medicinal species in Iran, includes a golden source of potential modern drugs and health products. Hence, we suggest that Iranian rare endemic taxa reported with high medicinal value should be involved in cultivation practices for their sustainable usage and also should be engaged in subsequent pharmacological studies and clinical trials in order to evaluate efficacy and safety of their traditional uses.

Overall, notwithstanding the achievements of conventional medicine, the Iranian people continues to actively use medicinal plants for health improvement and it is foreseen that in the near future, the Persian traditional herbal remedies will be incorporated into the modern allopathic medicine. Therefore, more collaborative attempts of Iranian ethnobotanists, phytochemists, pharmacists and physicians could be a practical strategy to channel the gap between the traditional plant based healing practices, laboratories and clinics.

To conclude, this study reviewed the status, advantages and challenges of Iranian traditional medicinal plants in order to raise public awareness and improve further scientific works. Considering the increasing demand of medicinal plants and existence of several critical concern over the herbal products in Iran, it will be vital to have quality control standards and legitimate regulation of medicinal plants throughout supply chain from plant raw materials to the end product to reorganize Iranian Traditional Medicinal plants and phytotherapy sector and to ensure health and safety of consumers.

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Conflict of interests

The authors declare no conflict of interest.

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