Pharmaceutical Sciences, 2024, 30(1), x-x
doi:10.34172/PS.2023.1
https://ps.tbzmed.ac.ir/

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Review Article

Taxonomic Revision and Clinical Importance of *Phlomoides* Genus: A Comprehensive Review

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Article Info

Article History:
Received: 20 Nov 2022
Accepted: 5 Jan 2023
ePublished: 13 Aug 2023

Keywords:
-Anti-inflammatory Agent
-Bone Development
-Classification
-Iridoid
-*Phlomoides*
-Phytochemical

Abstract

Phlomoides (L.) Moench belongs to the Lamiaceae family. It has recently undergone significant changes in taxonomy, with many species from *Eremostachys* and *Phlomis* added to the genus. The aforementioned species were studied in terms of morphological and phytochemical systematics. Species of *Phlomoides* are distinguished from *Phlomis* by their densely bearded upper corolla lip and nutlet. However, *Eremostachys* and *Phlomoides* have a lot in common morphologically. Plant chemosystematics present iridoids, phenylethanoids, and furanolabdanes as dominant constituents of *Phlomoides* species. Long-term traditional uses, such as bone fracture therapy, local analgesic, and wound healing actions, pique researchers' interest in these plants. The species and their secondary metabolites have been implicated in drug discovery by their anti-inflammatory and bone-development properties *in vitro*, *in vivo*, and clinically. A review of the taxonomic status based on phytochemical and morphological characteristics, as well as the clinical importance of the *Phlomoides* genus, is presented in the current study to provide a basis for further investigations.

Introduction

For millenniums, plants have been used as food and medicine. Today, plants are substantial sources of drugs as well as traditional medicine. Plant secondary metabolites are used originally or as lead compounds in pharmaceutical research and industries. Hundreds of examples indicate the importance of natural sources in drug development. For instance, artemisinin, which plays a fundamental role in malaria treatment, is derived from the Artemisia genus. Paclitaxel, obtained from *Taxus brevifolia*, is a crucial anti-cancer agent.[1] This valuable, ages-long experience of medicinal plant application is an opportunity that leads to a low incidence of side effects. However, using herbal materials could be expensive and harmful to the environment. Indiscriminate and unprincipled harvesting endangers natural resources. Following the identification and isolation of active ingredients, synthetic and semisynthetic methods are studied to develop an efficient industrial production of desired components. Therefore, screening flora for novel compounds remains an attractive topic in pharmaceutical research to discover effective medications against various diseases.[2]

The Lamiaceae or Mint family of angiosperms is a prominent example of a medicinal and nutritional plant source. For example, peppermint (*Mentha* × *Piperita* L.), a representative of this family, is usually prescribed for gastrointestinal disorders such as irritable bowel syndrome (IBS) and is also used as a food ingredient.[3] The mint family contains 245 genera and 7886 species. *Phlomoides* (L.) Moench, comprising 168 accepted species, is one of the largest genera of the Lamiaceae family. This genus was recently revised by adding some *Phlomis* and *Eremostachys* species.[4,5] From a phytochemical viewpoint, iridoids, phenylethanoids, flavonoids, and several other compounds have been isolated from this genus. *Phlomoides* species have a relatively low essential oil yield, from 0.02% to 0.9%. Non-terpene hydrocarbons such as alcohols and aldehydes are the major components of volatile oil.[6,7]

The reported pharmacological effects of various *Phlomoides* species include menopausal symptoms relief,

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anti-inflammatory activity, and anti-osteoporosis activity. Concerning the anti-osteoporosis activity, loganin and morroniside (iridoid glycosides) can stimulate the differentiation of osteoblasts through diverse mechanisms such as increasing collagen type 1 and inhibiting their apoptosis through anti-inflammatory effects. An *in vivo* study on ovariectomized female mice revealed the osteogenic effect of *P. umbrosa*. Increasing mineralization ratio and bone mineral density are two of the attributed mechanisms of this action.[8-10] In addition to modern usages, these species have several traditional applications. For example, in Turkey, *P. tuberosa* was used for its wound-healing effects and in Iran, it is still used as a food ingredient. Traditional uses could be inspiring for novel drug innovation.[11] Plants of this genus are distributed throughout Asia and some European countries such as Turkey, Armenia, Georgia, and Azerbaijan. Forty-two various *Phlomoides* species are found in China, and 59 diverse species grow in central Asian countries.[12]

Methodology

The evaluated papers were screened based on the inclusion criteria: (1) articles written in English and (2) articles containing data on species classified within the *Phlomoides* genus. In addition, the following exclusion criteria were applied: (1) papers that did not discuss systematics, morphology, extracts′ phytochemistry, or biological activities of *Phlomoides* species and (2) Articles with unavailable full text.

Up until 2022, search engines and databases such as PubMed/Medline, Scopus, Google Scholar, Google Books, Google Patents, and Cochrane Library were combed through. The search terms were "*Phlomoides*," "*Phlomis*," and "*Eremostachys*" in the article titles, abstracts, and keyword sections. We initially extracted the papers on the confirmed species currently classified under the genus *Phlomoides* by looking through all the retrieved publications and using the World Flora Online plant list (http://www.worldfloraonline.org/). To proceed, we selected articles from the remaining 200 that were relevant to the outline of the present study and did not include duplicate information. Subsequently, articles were placed in the defined categories comprising taxonomy, morphology, phytochemistry, ethnomedicine, *in vitro*, *in vivo*, and clinical studies. EndNote software was used to manage and organize the references. Finally, About 120 scientific papers were incorporated in the text.[13]

Taxonomy

Taxonomy reflects the evolutionary progress of plants and determines their ancestors. it is also highly beneficial to study medicinal plants and authenticate herbals. Incorrect or inaccurate nomenclature of herbs may lead to either the omission or misuse of articles while searching the database. The use of synonyms or common names instead of confirmed ones in manuscripts is a frequent mistake. Various parameters such as morphological characters, chromosome number, DNA sequences in chloroplast or nuclear regions, and phytochemical features are involved in the categorization of plants. Moreover, parsimony, maximum likelihood, and Bayesian analysis are some methods applied to draw phylogeny trees. Nevertheless, ongoing updates to our information may improve the current classifications.[14,15]

The Lamiaceae family is divided into seven subfamilies (Table 1). Some genera, however, cannot be classified into any of these sections for several reasons. For example, a plant may possess the morphological characteristics of one group but the DNA sequence specifications of another. The plants mentioned herein belong to the incertae sedis class, which means uncertain position. Nepetoideae is the most populous subfamily of Lamiaceae and is genetically related to Symphorematoideae and Viticoideae in its evolutionary progress, but Lamioideae seems to be genetically independent of the other groups. In molecular data, Scutellarioideae is the closest subfamily to Lamioideae. The style is commonly terminal or subterminal within the Lamiaceae family, whereas it is gynobasic in Nepetoideae and Lamioideae. Despite similarities in style type, these two subfamilies have some differences. Lamioideae genera are mostly nonaromatic; their pollen is usually tricolpate; and Iridoids are their frequent phytochemicals. Hexacolpate pollen, however, is an essential characteristic of the Nepetoideae genera. They are commonly aromatic and comprise rosmarinic acid.[16]

Further investigations were accomplished to classify the Lamioideae subfamily at the tribal level. Scheen *et al.*[17] reported Lamioideae as a monophyletic subfamily, but morphological features cannot singularly substantiate this. Based on molecular phylogenetic studies, Lamioideae consists of Pogostemoneae, Gomphostemmateae, Synandreae, Stachydeae, Phlomideae, Leonureae, Lamieae, Marrubieae, and Leucadeae tribes. Some genera, such as *Colquhounia,* also remain unclassified within the subfamily. *Ajugoides* and *Matsumurella*, which were not included in the aforementioned work, were classified by Bendiksby *et al.*[18] based on molecular data and DNA sequence within a newly introduced tribe, Paraphlomideae.

The Phlomideae tribe used to have six members;

Table 1. Classification of Lamiaceae family according to "The families and genera of vascular plants" book by Kubitzki K.

Subfamily	Tribe	Genus example
Symphorematoideae	-	*Sphenodesme*
Viticoideae	-	*Vitex*
Ajugoideae	-	*Karomia*
Prostantheroideae	Chloantheae	*Physopsis*
	Westringieae	*Hemigenia*
Scutellarioideae	-	*Scutellaria*
Lamioideae	-	*Phlomis*
Nepetoideae	Elsholtzieae	*Collinsonia*
	Mentheae	*Mentha*
	Ocimeae	*Lavandula*
Incertae sedis	-	*Tectona*

however, according to the "world checklist of selected plant families" database, the species of the *Eremostachys*, *Pseuderemostachys*, *Notochaete*, and *Lamiophlomis* genera are now classified within the *Phlomoides* genus. Therefore, *Phlomis* and *Phlomoides* genera are the principal members of the Phlomideae tribe.[17,18] Despite the close relationship between *Eremostachys* and *Phlomoides*, however, some *Eremostachys* species studied by Mathiesen *et al.*[19] retained their last systematic positions. Moreover, Ryding introduced *Eremostachys* as a monophyletic and independent genus to make *Phlomoides* less heterogeneous.[20] Salmaki *et al.*[21] conducted a molecular phylogeny study in this regard and identified several intermediate species with both *Phlomoides* and *Eremostachys* characteristics within the referred genera.

Furthermore, the *Phlomoides* genus cannot be considered monophyletic by eliminating the *Eremostachys* species. Thus, *Eremostachys* is treated as a subclass of *Phlomoides*, which confirms the hypothesis proposed by the "world checklist of selected plant families" database.[21] The two principal genera of this tribe have an essential difference in their chromosome number. *Phlomis* and *Phlomoides* have x=10 and x=11 chromosomes, respectively.[19] Moreover, the existence of the indumentum is a common characteristic of Lamiaceae plants. Therefore, trichomes morphology may affect the plants phylogeny. For example, branched and multinodal trichomes can be considered as a synapomorphic feature of *Phlomis* species. This characteristic is also observed in some *Phlomoides* species. The appearance of branched and multinodal trichomes is a plesiomorphic feature of the sister group *Phlomoides.*[22]

Phlomoides is considered a non-monophyletic genus. It was introduced in 1794 by Moench when he transferred *Phlomis tuberosa* to a distinct and new category based on variations of corolla and fruit characteristics.[23] Five sections have been established within the genus *P. sect. Filipendula* and *P. sect. Phlomoides*, two populous sections introduced based on morphological characteristics identified by Kamelin and Makhmedov. For example, *Filipendula* species, such as *P. tofetisowii*, are commonly identified by bicolor corolla and pinnatisect leaves.[22] According to Kamelin and Makhmedov's classification, *P. sect. Phlomoides* chiefly consists of the former *Phlomis* species, and *P. sect. Filipendula* mainly comprises the *ex-Eremostachys* species.[19] Subsequently, Sennikov and Lazkov presented *Eremostachys*, *Paraeremostachys*, and *Moluccelloides* sections, which were circumscribed using DNA sequence data and information about the recently transferred species.[18,24] For example, Ranjbar and Mahmoudi[23] evaluated the morphological and taxonomic characteristics of *P. sect. Thyrsiflorae*, while Rechinger presented this section in 1982 as a subclass of *Eremostachys* genus.

Morphology

In terms of morphology, a determinant parameter of plant systematics, the variation rate is high among the family but it becomes more limited in the subclasses. For example, the Lamiaceae family comprises trees, shrubs, and herbaceous plants, while the *Phlomoides* genus includes herbaceous species.[16] In the following paragraph, some of the most outstanding general characteristics of the Lamiaceae family are discussed.

Essential oil-secreting glandular trichomes other than covering hairs are present on the surface of the calyx (e.g., *Lavandula angustifolia* Mill.), leaves (e.g., *Rosmarinus officinalis* L.), and other aerial parts of most Lamiaceae members. Therefore, these plants are chiefly aromatic. They typically bear condensed flowers (verticillaster), opposite leaves, and quadrangular stems. The flowers possess corollas with two upper and lower lips and more than two segments. *Lavandula* L. corollas, for example, consist of two divisions on the upper lip and three on the lower one. There are usually two pairs of stamens within the corollas, and the pairs differ in size.[25,26] In addition, the Lamioideae subfamily can be discerned by gynobasic style, tricolpate pollen, and being less aromatic compared to the other Lamiaceae subfamilies. The lower lip of the corolla usually has three smaller divisions with a larger central one. The upper lip bears two parts and infrequently a single part due to the segments merging. Small bracteoles and dry schizocarpic fruits are common in Lamioideae plants.[16]

Phlomoides species are perennial herbaceous plants. The lateral roots are occasionally tuberiform. As with other Lamioideae species, they bear gynobasic style and schizocarpic fruits. There are four fertile stamens with the anterior higher pair within the corollas. Stellate and simple hairs cover the calyx surface. *Phlomoides* species own arch-shaped upper corolla lips. Moreover, some principal features are needed to discriminate between *Phlomoides* and its sister group *Phlomis*. *Phlomis* species are distinguished with their laterally compressed upper corolla lip. Unlike *Phlomoides*, however, the margin of the upper corolla lip and nutlet of *Phlomis* species are not densely bearded. According to a study on the pericarp structure, the sclerenchyma region in *Phlomis* species is another distinguishing characteristic.[20,21,27]

As previously discussed, the systematic position of *Eremostachys* is relatively controversial. The distinctive features of *Eremostachys* and *Phlomoides* have been addressed by various studies. Leaves of the *Eremostachys* species are mostly pinnatisect, while they are often simple in *Phlomoides* with a cordiform to triangular and oval shape. The nutlet pericarp of the *Eremostachys* class is thicker than most Lamioideae genera. Compared to the *Phlomoides*, *Eremostachys* have huge flowers. However, similar characteristics are also discussed. For example, *Eremostachys* represents the same morphological aspects, referred to in the previous paragraph, as *Phlomoides*. In regards to their cytology, the chromosome number is X = 11 for both groups.[19-21] Figure 1 indicates the morphological features of *Phlomoides labiosa*, a former *Eremostachys* member.

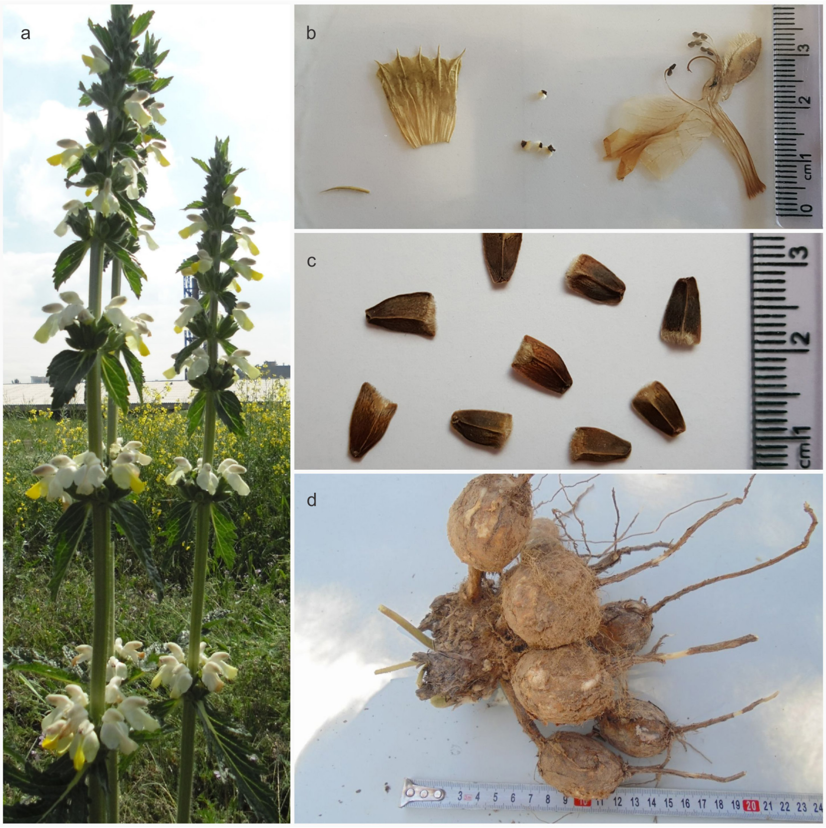

Figure 1. *Phlomoides labiosa*, a member of the *Filipendula* section, was formerly recognized as *Eremostachys labiosa*, and it was a subset of the *E*. sect. *Phlomoides* Bunge. a) Floral whorls are arranged with some intervals on verticillasters. b) *P. labiosa* has needle-like bracteoles, calyxes with five lobes, and typical characteristics of *Phlomoides* corollas. Also, hairs on four ovary lobes are apparent. c) Nutlets are almost hairy on top. Nevertheless, in contrast to most *Phlomoides* nutlets, they are not densely bearded. d) Tuberiform roots of *P. labiosa* were collected at Khalaj Mountains, Khorasan province, Iran, in May 2020.

Phytochemistry

Investigating structural similarities is a critical tool for classifying plants. Structural resemblances of secondary metabolites show the presence of similar metabolic pathways. To make inferences about phylogenetic links, it may be helpful to obtain networks of these compounds. Given the importance of plant chemicals from the perspective of biological activities, the aforementioned classifying system, plant chemosystematics, could be beneficial and practical in the discovery of drugs based on herbal metabolites.[28] In this regard, the isolated compounds of various *Phlomoides* species have been compiled and are listed in Table S1 in the supplementary data. Several secondary metabolites belonging to distinct phytochemical groups were evaluated for structural similarities based on the Tanimoto value using Open Babel and Cytoscape software programs as well as the Chembioserver website (Figure 2). The network of links with Tanimoto values greater than 0.4 was provided, and the top nodes were determined employing degree analysis (Figure 3). It is worth noting that Stachydrine (Alkaloid) had the least structural resemblance to the other components, and the associated Tanimoto values were all less than 0.4. Following that, the chemicals were categorized through clustering coefficient analysis (Table 2), and the correlations of clusters and species were assessed. As shown in Figure 4, furanolabdanes, iridoids, and phenylethanoids (top node: cluster 15) were the dominant secondary metabolites of the studied species (Figure 5).[29]

Ethnomedicine

Ethnomedicine refers to traditional practices orally passed through generations based on long-time observations. Traditional medicine depends mainly on well-known herbals which are valued in a particular location. Herbal products have always played an essential role in human life. Their application as medicines and foods predates written history. Herbals were the primary therapeutic agents used in earlier centuries. Today, plants also play a vital role in pharmacotherapy. A high proportion of the world's population still trusts and relies on traditional medicine for their healthcare, especially in developing countries.[30] Some *Phlomoides* species are also used in traditional medicine. An ethnobotanical survey in a village in Turkey showed that the leaves of *P. tuberosa* are used as a compress for wound healing.[31] In addition, Rehman *et al.*[32] revealed the application of a *P. laciniata* decoction for the treatment of headache and liver problems in Karak district, Pakistan. *P. umbrosa* is known in China as Xu Duan, which means "can reconnect broken bones." The roots of this plant are prescribed to accelerate bone fracture healing.[33] Reported folk uses are summarized in Table 3.

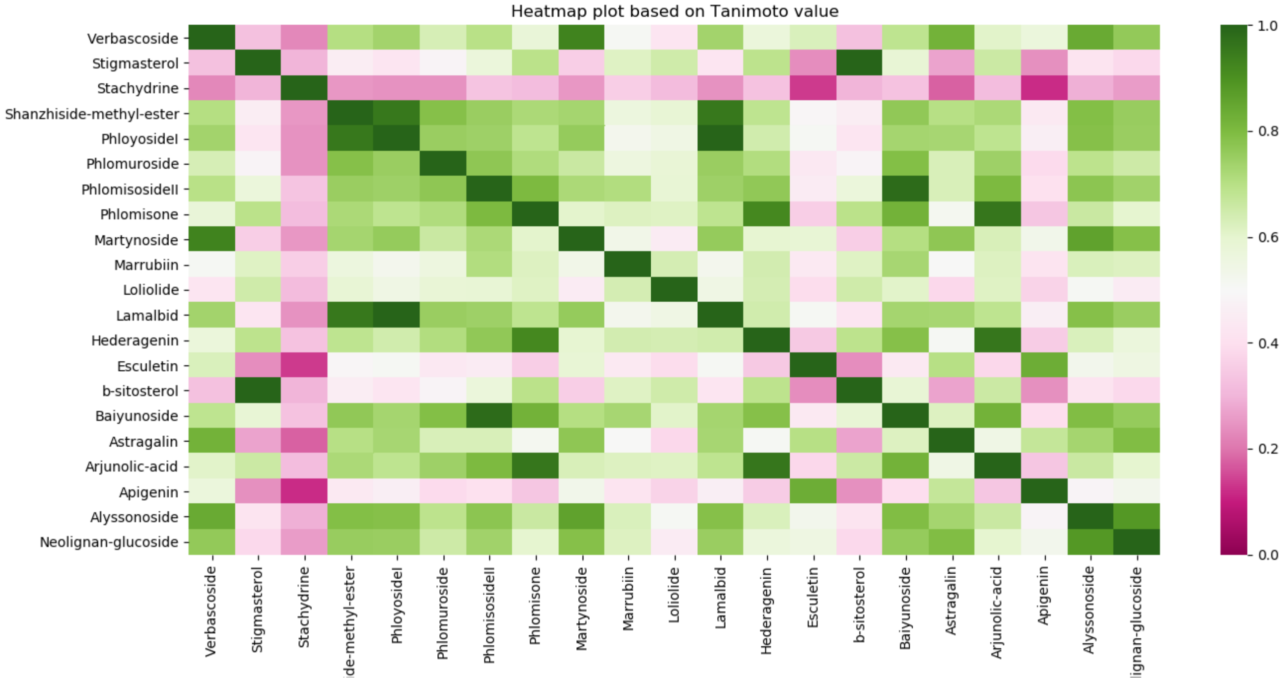

Figure 2. Heatmap of Secondary metabolites′ Tanimoto value.

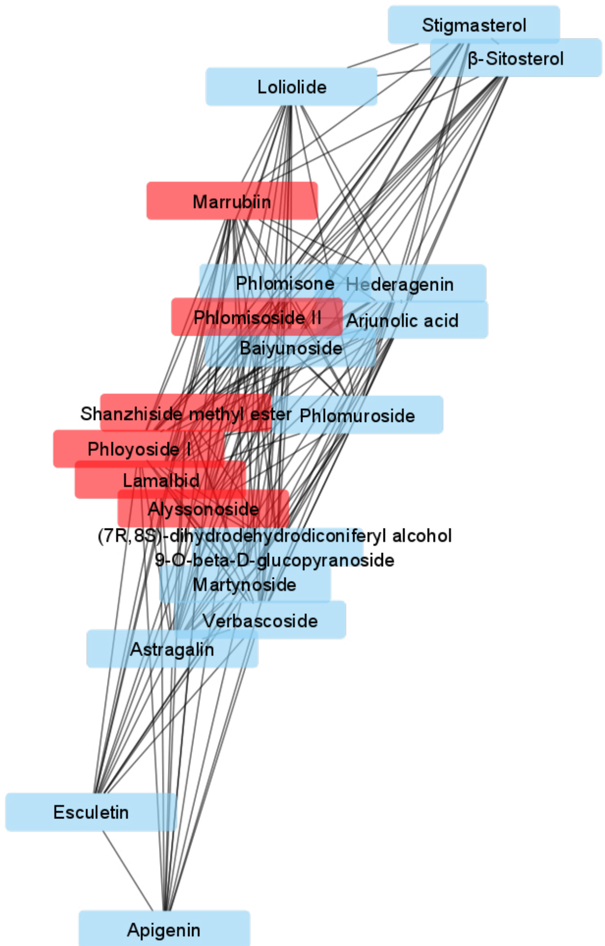

Figure 3. Structural similarity analysis based on Tanimoto value (Top nodes: Alyssonoside, Lamalbid, Phloyoside I, Shanzhiside methyl ester, Phlomisoside II, and Marrubiin).

Table 2. Categories of clustering coefficient analysis.

Rank	Name	Score
1	Stigmasterol (Steroid)	1.0000
1	β-Sitosterol (Steroid)	1.0000
3	Apigenin (Flavonoid)	0.9744
3	Esculetin (Coumarin)	0.9744
5	Loliolide (Benzofuran)	0.9500
6	Arjunolic acid (Saponin)	0.9338
6	Hederagenin (Saponin)	0.9338
6	Phlomisone (Triterpene)	0.9338
9	Astragalin (Flavonoid)	0.9333
10	(7R,8S)-dihydrodehydrodiconiferyl alcohol 9-O-beta-D-glucopyranoside (Neolignan glucoside)	0.9191
10	Verbascoside (Phenylethanoid)	0.9191
10	Martynoside (Phenylethanoid)	0.9191
13	Phlomuroside (Misellaneous)	0.9020
13	Baiyunoside (Furanolabdane)	0.9020
15	Phlomisoside II (Furanolabdane)	0.8655
15	Shanzhiside methyl ester (Iridoid)	0.8655
15	Lamalbid (Iridoid)	0.8655
15	Phloyoside I (Iridoid)	0.8655
15	Alyssonoside (Phenylethanoid)	0.8655
15	Marrubiin (Furanolabdane)	0.8655

In Vitro Studies

Antioxidant effect

DPPH (2,2-diphenyl-1-picrylhydrazyl), suppression of PMNs′ oxidative burst (polymorphonuclear leukocytes),

Table 3. Applications of Phlomoides species in ethnomedicine.

Species	Region	Uses	Plant part used	Administration	Ref
P. tuberosa	Turkey	Wound healing	Leaves	Topical-Compress	31
	Iran	Culinary uses	Leaves	Oral-Grilled	34
P. laciniata	Pakistan	Headache Liver problems	Whole plant	Oral-Decoction	32
	Iran	local analgesic anti-inflammatory	Roots and flowers	Topical-Compress Oral-Decoction	35
P. umbrosa	Korea	Brain function enhancement Immunomodulation	Roots	Oral-Decoction (A combination of 18 dried herbs)	36
	China	Bone fractures	Roots	Oral	33
P. bracteosa	India	Stomach disorders	Aerial parts	Oral-Taken in warm water (A combination of 5 dried herbs)	37

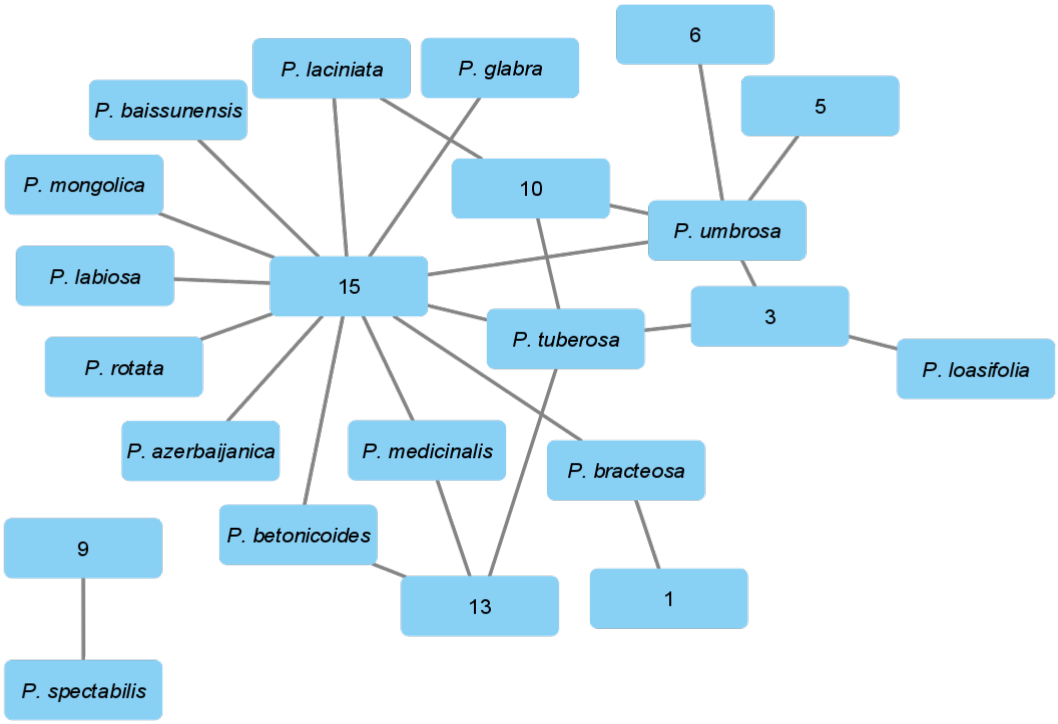

Figure 4. Correlations of clustering coefficient categories and *Phlomoides* species.

ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)), FRAP (ferric reducing antioxidant power), β-Carotene-linoleic acid, DNA damage protection potential, and H_2O_2-luminol chemiluminescence assays have indicated the significant antioxidant capacity of several *Phlomoides* species such as *P. bracteosa*, *P. maximowiczii*, *P. megalantha*, and *P. laciniata.*[38-41] The radical scavenging activity of the genus is attributed to some secondary metabolites. Some identified active compounds include a flavonoid (luteolin-7-O-rutinoside) and a phenylethanoid (verbascoside) from the methanolic extract of *P. azerbaijanica*, phenylethanoid derivatives from *P. umbrosa* roots, phloloside G, (an iridoid from *P. likiangensis*), protocatechic and rosmarinic acids, all major phenolic components of *P. megalantha* and *P. umbrosa.*[41-44] Former studies have also shown a positive correlation between antioxidant activity and total phenolic content.[45] The volatile components of *Phlomoides* species, in contrast, do not bear antioxidant activity.[46] In addition, *P. labiosiformis* demonstrated *in vitro* neuroprotective effects in an Alzheimer's disease model by reducing Amyloid-peptide-induced ROS (reactive oxygen species) level.[47]

Cytotoxicity

MTT and BSLT (Brine Shrimp Lethality Test) are the two most frequently used cytotoxicity assays.[48] Cancerous cell proliferation may also be studied using cell counting kits. Employing cell counting kit-8, the phenylethanoid verbascoside, isolated from *P. nissoli*, showed anti-cancer effects on the cell lines MCF7 and MDA-MB-231.[49]

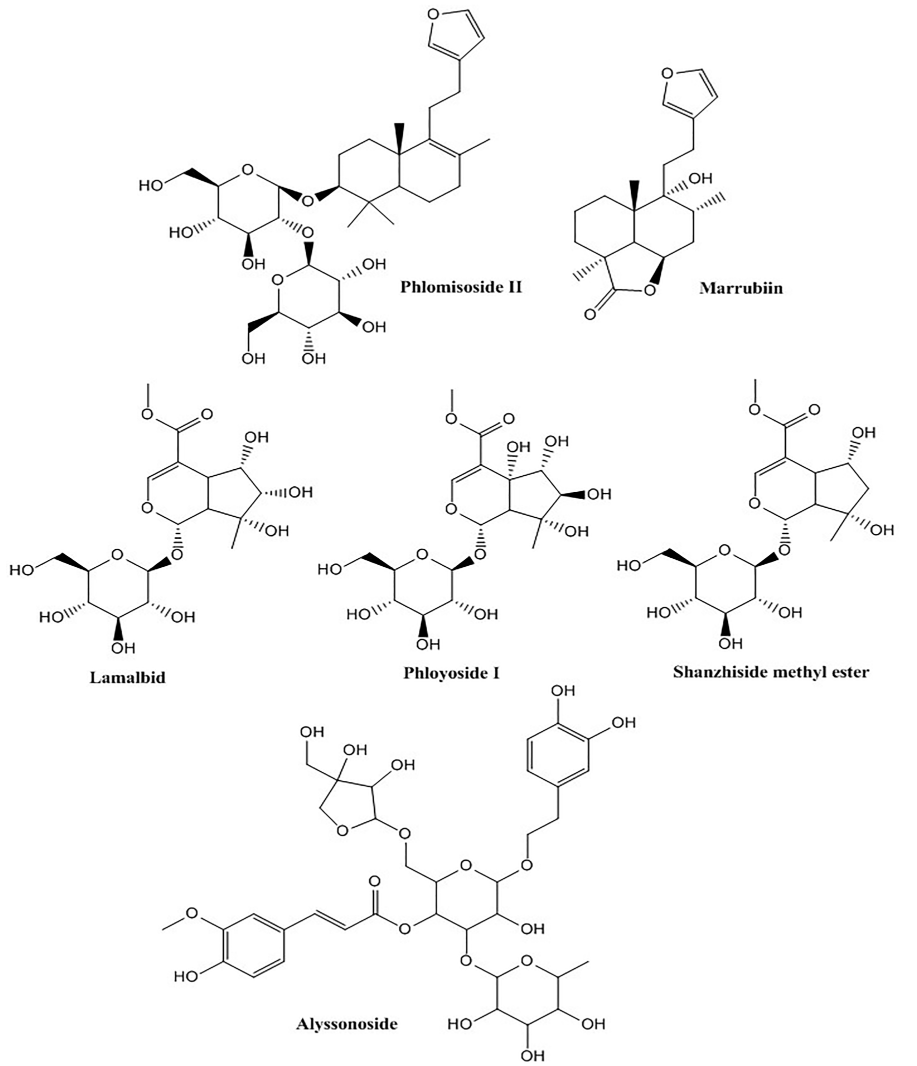

Figure 5. The chemical structures of the dominant secondary metabolites (Cluster 15).

However, iridoid glycosides purified from the underground parts of *P. laciniata* did not exhibit significant cytotoxic activity in the BSLT test.[50] Asgharian *et al.*[48] revealed the cytotoxicity of *P. azerbaijanica* dichloromethane and n-hexane extracts comprising sterols, terpenoids, and cardiac glycosides.[48] In addition, nanoencapsulation does not improve the cytotoxicity of *P. labiosa* dichloromethane extract, which might be a result of limited extract release through liposome lamella.[45]

Antimicrobial effect

Various *Phlomoides* species have been investigated for antimicrobial properties. *P. azerbaijanica* lacks antibacterial action, while *P. macrophylla* and *P. tuberosa* show significant activity against *Staphylococcus aureus.*[48,51] Pulchelloside I, an iridoid glycoside purified from *P. laciniata* rhizomes, was indicated to have a MIC value of 0.05 mg/mL for the strains of *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, and *Proteus mirabilis.*[50] Anti-rotavirus activity was reported from iridoids and isobenzofuranone derivatives of *P. betonicoides.*[52] Moreover, sesquiterpene, coumarin, and steroid derivatives are assumed to be responsible for the antimalarial effects of *P. azerbaijanica.*[53] The consequences of nanoencapsulation are inconsistent. Silver nanoparticles of *P. bracteosa* demonstrate antibacterial activity equivalent to the standard antibiotic agent; however, *P. labiosa* liposomes are less effective than the free extract.[45,54]

Miscellaneous effects

The genus has also been reported to engage in other notable activities. By lowering macrophage nitric oxide generation, *P. labiosa* methanol extract has an anti-inflammatory effect.[55] In a combination of twelve medicinal herbs, *P. umbrosa* inhibits inflammatory mediators.[56] Catabolic and anabolic indicators of cartilage maintenance differ significantly using an herbal formulation including *P. umbrosa* and two additional species, which have been traditionally used to attenuate menopausal symptoms.[10] The formulation also demonstrates no rise in estrogenic carcinogenesis; hence, it may be safe for the aforementioned applications.[57] To evaluate the efficacy of *P. umbrosa* in osteoporosis and enhancing bone development, the Saos-2 osteoblast cell line was treated with increasing concentrations of the plant extract, and the production of osteoblast differentiation factors was measured. Following treatment, the mineralization ratio in differentiated osteoblasts rose significantly, as did the Runx2 level.[8] Iridoid glycosides derived from *P. likiangensis* exhibited nitric oxide-dependent vasodilation in rat aortic rings.[58] The glucosidase inhibitory activity of the ethyl acetate fraction of the *P. tuberosa* extract, including diterpenoids, iridoids, and flavonoids, is comparable to that of the positive control acarbose.[59]

In Vivo Studies

Anti-inflammatory effects

Mice with collagen-induced arthritis were given a mixture of 12 herbs, including *P. umbrosa*, determine any possible therapeutic benefits. Macroscopic analysis of paws and ankle TNF-α and IL-1β levels demonstrated that the mixture has a significant cartilage-protecting effect.[60] The aqueous extract of *P. umbrosa* was tested for its anti-inflammatory and anti-nociceptive properties utilizing several techniques, including the acetic acid-induced writhing test (anti-nociceptive activity) and the carrageenan-induced paw edema test (anti-inflammatory activity). In the majority of these experiments, significant dose-dependent effects were seen. The above-mentioned benefits are attributed to the extract's predominant component, iridoid glucosides.[61] The species was also evaluated in combination with *Angelica gigas* and *Cynanchum wilfordii*. Consequently, the mixture (200 mg/Kg) and celecoxib (60 mg/Kg) demonstrated equivalent inhibition percentages employing the carrageenan-induced paw edema assay.[10] The monosodium iodoacetate-induced osteoarthritis model was employed to assess the protective properties of *P. umbrosa* extract. The extract reduced serum cytokine production, improved weight-bearing distribution, and ameliorated histological characteristics of osteoarthritic knee tissue.[62] Regulating several genes, including those associated with the osteoarthritis pathway, was predicted as the molecular mechanism. By modulating the transcription factors, *P. umbrosa* extract reduces cartilage damage factors such as matrix metalloproteinases and increases chondrogenesis.[63] A systemic allergic response test was used to study the aqueous extract of *P. umbrosa* root; as a result, plasma histamine level and death rate were reduced in dose-dependent and time-dependent manners.[64] In addition, *P. umbrosa* was tested in an ovalbumin-induced asthma model using a 70% ethanol extract. Many parameters were affected, such as the production of inflammatory cytokines, airway inflammation, and eosinophilia. The findings introduced *P. umbrosa* as a potential agent for asthma management.[65] The carrageenan-induced paw edema test revealed an anti-inflammatory effect comparable to the positive control (aspirin) from the *P. laciniata* ethyl acetate fraction.[66] Moreover, the Tail Flick assay showed its analgesic and sedative properties in the crude extract and several fractions, particularly the chloroform fraction.[67] Analgesic effect's LD50/ED50 ratio of iridoids isolated from *P. labiosa* exceeds diclofenac in the acetic acid-induced writhing assay and the hot plate test.[68]

Bone effects

Oral administration of *P. umbrosa* to the ovariectomized mice for six weeks increased serum calcium concentration, bone mineral content, bone mineral density, and hyperplasia of the femoral growth plate.[8] Unlike previous investigations, *P. umbrosa* in a mixture of 14 herbs showed a negligible impact on the protection of ovariectomized and calcium shortage-caused bone loss.[69] The ability of a standardized *P. umbrosa* root extract containing 6.62 mg/g shanzhiside methyl ester to improve bone development in adolescent female rats was investigated. The findings imply that the extract stimulates chondrocyte proliferation and hypertrophy with an increase in circulating insulin-like growth factor binding protein-3, which in turn enhances longitudinal bone growth.[33] Additionally, the combination of *Eleutherococcus senticosus*, *Astragalus membranaceus*, and *P. umbrosa* found in HT042 was examined in this respect. Consequently, enhancement was seen in trabecular bone mass, longitudinal bone growth, and bone microarchitecture during growth.[70] Some other studies with comparable results are also reported. In this context, the application of *P. umbrosa* mixture as a milk additive revealed a significant impact.[71] However, Kim *et al.*[72] showed that HT042 was ineffective for longitudinal bone growth in spontaneous dwarf rats.

Miscellaneous effects

In a carbon tetrachloride-induced liver damage model, the hepatoprotective activity of *P. maximowiczii* buthanolic extract was examined because of its substantial antioxidant action *in vitro* and the fact that oxidative stress is one of the mechanisms responsible for liver injury. In lowering the amount of malondialdehyde (a sign of oxidative stress) and raising the level of superoxide dismutase, the effects of this plant were comparable to those of the positive control (Bifendate).[39]

Moreover, the antidepressant effect of *P. laciniata* was evaluated using a forced-swim test. Apigenin and luteolin were assumed responsible for the initial anti-depressive effect and the sedative properties at higher doses, respectively.[73]

Safety studies

HT042 oral toxicity was studied in Sprague-Dawley rats by Song *et al.*[74] The fatal dosage was more than 5000 mg/Kg orally for the mixture and every species, including *P. umbrosa*. Moreover, sub-chronic toxicity tests up to 4000 mg/kg/day did not demonstrate any adverse effects.

Clinical Trials

Generally, the effects of *Phlomoides* species have been investigated in seven different clinical trials to date (Table 4). Two clinical trials in Iran evaluated the analgesic effects of *P. laciniata*. A study by Gharabaghi *et al.*[75] examined

Table 4. Clinical studies on Phlomoides species.

Status	Design	Country	Herbal extract	Population (n=patients)	Intervention group(s)	Comparison group(s)	Primary outcomes	Ref
					Analgesic Effects			
Completed	A Double-blind randomized, placebo-controlled parallel study	Iran	Extract of *P. laciniata* (As suppository)	(N=90) females older than 35 years and candidate for selective hysterectomy	(N=30) Suppository of *P. laciniata* adminestered(35mg) 24h before to 24h after surgery every 12h	Case I(N=30): Suppository of placebo (contained starch and cacao butter) adminestered 24h before surgery and Suppository of *P. laciniata* adminestered 24h after surgery every 12h Case II(N=30): Suppository of placebo adminestered 24h before to 24h after surgery every 12h	A higher pain mitigation rate was observed in the patients who were given herbal extract before and after surgery compared to the placebo group. Results of pain severity evaluation after surgery showed that the herbal extract group was less painful than the placebo group. Prescribed sedative doses were also less.	75
Completed	A triple-blind controlled clinical trial	Iran	Rectal *P. laciniata* suppository was prepared from a 3.5% total rhizome extract	(N=86) women who gave childbirth by cesarean section	35 mg *P. laciniata* suppository administered every 8 h up to three doses (8, 16, and 24 h after surgery)	50 mg rectal diclofenac suppository administered at the same time	According to Friedman's test, a significant difference was found between the control group's distress score and the intervention group's score 24 hours after cesarean section. Wound healing scores also differed significantly between the two groups, indicating that rectal diclofenac suppository was more effective. than *P. laciniata*. In both groups, no side effects were observed.	76
					Anti-Inflammatory Effects			
Completed	A Double-blind, Randomized Clinical Trial	Iran	Methanol extract of *P. laciniata* (As Ointment)	(N=40) patients between 15 and 65 years with mild and moderate CTS and without any other neurological problems	*P. laciniata* ointment was applied topically to the palmar wrist area twice a day for a period of 4 weeks	Eucerin ointment (as placebo) was applied topically twice a day for a period of 4 weeks	After four weeks, the herbal extract did not affect hand grip power. Also, this herbal extract had no significant effect on nerve conduction parameters.	77
Completed	A single-blinded randomized clinical trial	Iran	Methanol extract of *P. laciniata* (As Ointment)	(N=137) patients between 18-80 years with inflammatory diseases, e.g., osteoarthritis, rheumatoid arthritis and Reiter's syndrome.	The 5% *P. laciniata* ointment were gently massaged around the affected joint two times a day, for a consecutive 14 days.	The 5% piroxicam ointment were gently massaged around the affected joint two times a day, for a consecutive 14 days.	After 14 days of treatment with the *P. laciniata* and piroxicam ointments, all groups showed significant improvement compared to the control groups. *P. laciniata* (5%) ointment induced better initial therapeutic response than piroxicam (5%) onitment.	78

Table 4. Continued.

				Bone Effects			
Completed	A double-blinded, randomized, placebo-controlled study	South Korea	Multi-herbal mixture consisting of *Eleutherococcus senticosus*, *Astragalus membranaceus* and *P. umbrosa* (HT042)	(N=99) children aged from 7 to 12 years with initial height below the 25th percentile for age and sex	750 mg of HT042 administered twice daily for 12 weeks	Placebo administered twice daily for 12 weeks	In the HT042 group, fat-free mass, height percentile, and SDS increased, and fat mass notably decreased from baseline to week 12. A significant difference in the level of IGFBP-3, but not GH or IGF-1, was shown between the placebo and HT042 groups. There is no significant difference between the two groups in the nutrient intake or the amount of time spent exercising at the end of the study. 79
Active, not recruiting	A 6 month, multicenter, randomized, double-blind, placebo-controlled parallel study	South Korea	HT042 consists of the lyophilized 70% ethanolic extracts of three medicinal plants: the roots of *A. membranaceus*, the stems of *E. senticosus*, and the roots of *P. umbrosa*.	(N=140) children aged 6–8 years with height ranked below the 25th percentile	750 mg of HT042 administered twice daily for 24 weeks	Placebo administered twice daily for 24 weeks	After 24 weeks, the HT042 group had a significantly greater height gain than the placebo group. Compared with baseline, serum IGF-1 and IGFBP-3 levels were significantly higher in the HT042 group. However, the group difference was not significant. 80
				Estrogenic Effects			
Completed	A randomized double-blind, Placebo-controlled Study	USA	Mixture of standardized extracts of *Cynanchum wilfordii*, *P. umbrosa* and *Angelica gigas* (EstroG-100)	(N=64) pre-, peri- and postmenopausal White Hispanic, White non-Hispanic and African American women	(N=31) one tablet (EstroG-100) administered twice a day orally for 12 weeks	(N=33) one placebo tablet administered twice a day orally for 12 weeks	A significant reduction in mean Kupperman menopause index (KMI), a significant improvement in constituting symptoms of vasomotor, paresthesia, insomnia, nervousness, melancholia, vertigo, fatigue, and rheumatic pain, as well as a significant amelioration in vaginal dryness in the intervention group compared to the placebo group, were reported. 81

the analgesic effect of *P. laciniata* suppositories on women undergoing a hysterectomy. The results demonstrated that the rate of postoperative pain mitigation was higher in the intervention group than in the placebo group. After surgery, an assessment of pain intensity at different time intervals revealed that the group receiving herbal extract experienced less pain than the placebo group. The prescription of a total dose of sedatives was also declined. Mohammad Pour *et al.*[76] evaluated the analgesic effects of *P. laciniata* suppositories on pain and distress after cesarean delivery. According to their results, a rectal suppository of *P. laciniata* could effectively manage pain and distress following cesarean delivery with low side effects and acceptable performance. However, rectal diclofenac suppository as control was significantly more effective than the extract. Anti-inflammatory effects were evaluated in two different clinical trials in Iran. Eftekharsadat *et al.*[77] investigated the effects of *P. laciniata* ointment compared with a placebo group on patients suffering from carpal tunnel syndrome (CTS). The herbal extract did not affect handgrip strength. Besides, it did not significantly alter nerve conduction parameters over four weeks. Additional studies with larger sample sizes are needed to assess the long-term efficacy of this therapy. A clinical trial conducted by Delazar *et al.*[78] revealed that topical *P. laciniata* extract could be a safe and effective complementary treatment for patients with arthritis, rheumatoid arthritis, and Reiter's syndrome.Two clinical trials in South Korea investigated the effects of HT402 extract on bones. Studies were performed on children aged 7 to 12 years for three months,[79] and children aged 6 to 8 years for six months,[80] a nd the results were compared with those of placebo groups. These studies indicated that HT042 treatment for short children increased height and changed body composition positively. HT042 supplementation contributed to height growth in children without skeletal maturation, mainly for those who were much shorter, by increasing serum levels of IGF-1 and IGFBP-3.[79,80] The estrogenic effects of *P. umbrosa* were investigated in a randomized, double-blind, placebo-controlled trial by Chang *et al.*[81] A twelve-week therapy with EstroG-100 (a combination of *Angelica gigas, Cynanchum wilfordii*, and *P. umbrosa*) improved many menopausal ailments and vaginal dryness. The use of EstroG-100 was not associated with any adverse effects. Unlike hormone replacement therapy, no significant alterations in serum FSH, serum estrogen, BMI, body weight, and liver enzymes were reported. According to this study, EstroG-100 is a safe and effective supplement for women in the various menopausal phases.

Conclusion

Plant systematics undergo permanent modifications through ongoing studies. Common categorization approaches include morphology, genetics, and phytochemistry. Chemotaxonomy is of great importance because of its association with drug development. Recently, some species formerly classified in the genera *Eremostachys* and *Phlomis* were moved to the *Phlomoides* genus. It appears that evaluating all species under the latest classification might prevent future misunderstandings and biases in the area of position changes and names. Ethnomedical applications of these species, including wound healing effects, treatment for stomach disorders, and bone fracture therapy, have provided the basis for further evaluations. Their main identified secondary metabolites, iridoids, furanolabdanes, and phenylethanoids, are well known for various biological activities, such as anti-inflammatory effects. A United States patent (US8790727B2) introduced some iridoid-rich plant mixtures, including *Phlomoides glabra*, as nutraceuticals having potent anti-inflammatory characteristics. Clinical trials, *in vivo*, and *in vitro* studies have also suggested potential therapeutic effects of the species. *P. umbrosa* mixtures significantly improved children's height and alleviated menopausal symptoms. *P. laciniata* was clinically effective as an analgesic and anti-inflammatory agent. As societies age, the prevalence of arthritis, inflammatory joint issues, bone fractures, and menopausal problems rises. In addition, due to the identification of plants as trustworthy sources of medicine, further studies on these plants could be beneficial and of interest.

Author Contributions

Samin Mohammadi: Formal Analysis, Investigation, Writing - Original Draft. Behzad Jafari: Formal analysis, Writing - Original Draft. Samira Pourtaghi Anvarian: Investigation, Writing - Original Draft. Hossein Nazemiyeh: Writing - Review & Editing. Solmaz Asnaashari: Writing - Review & Editing. Abbas Delazar: Supervision. Parina Asgharian: Conceptualization, Methodology, Funding acquisition, Writing - Review & Editing.

Acknowledgements

This is a report of database from PhD thesis registered in Faculty of Pharmacy, Tabriz University of Medical Sciences with the grant number of 64124.

Conflict of Interest

The authors report no conflicts of interest.

Supplementary Data

Supplementary data, Table S1, are available at https://doi. org/10.34172/PS.2023.1.

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