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Review Article

A Review of Phytochemistry and Phylogeny that Aid Bio-prospecting in the Traditional Medicinal Plant Genus *Ferula* L. (Apiaceae) in Iran

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Abstract

Ferula L. as one of the most economically important genera of Apiaceae comprises many species with numerous aromatic and bioactive compounds used in traditional and modern medicine. Based on these features of *Ferula* that were subject to phytochemical studies, we compare recent molecular phylogenetic findings inferred from nuclear ribosomal internal transcribed spacer (nrDNA ITS) and cpDNA regions (*rps16*, *rpoC1* introns and *rpoB-trnC* intergenic spacer) with the secondary metabolites inferred from available phytochemical data to investigate the phylogenetic relationships within the Iranian species of the genus. Totally 40 species including six species of *Leutea* and 34 species of *Ferula* belonging to three subgenera and seven sections in Iran were examined by phytochemical data that inferred from above 150 publications. Phytochemical compounds were typified in nine groups as 40 binary characters. The last phylogenetic tree was pruned for those Iranian species and the phytochemical data were mapped over. The phytochemical analyses indicate that the major chemical components such as organic sulphur, monoterpen and sesquiterpene compounds have concentrated within five sections of subgen. Narthex of the *Ferula* genus and the economically important species mostly placed closely within the sections Merwia and Scorodosma.

Keywords: *Ferula*, Molecular phylogeny, Phytochemistry, Medicinal herb, Apiaceae, Iran.

Introduction

The knowledge of phylogenetic relationships among organisms dose not only occupy the central core of biodiversity science but is also essential for conserving and sustainably using biodiversity [1]. Phylogenetic trees could establish a framework for understanding character evolution and predicting species features based on their evolutionary relationships, at least among closely related species [2]. The predictive value of phylogenetic trees seems to be particularly important for bio-prospecting that medicinal plants is not scattered randomly along phylogenies but they are concentrated in certain branches of the trees [3,4]. Possibly, another benefit of phylogeny to bio-prospecting include and introduce replacing rare and endangered species that are sources of bioactive compounds and have similar properties with their relatives.

Over the past years, more attention has been paid to natural products in the search for novel drugs in combination with new technology. Natural products, which have evolved over millions of years, have a unique chemical diversity that tend to diversity in their biological activities and drug properties [5]. More than 80% of drug substances were purely natural products or were inspired by the molecules derived from natural sources. Approximately from 295,383 described flowering

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plants, only 6% have been reportedly screened for biological activity until 2012 and about 15% have been screened for phytochemical activity [6,11]. However, only a small proportion has been screened for biological activity and the plants from some regions are fewer studied than others [3]. Although during the past two decades, the production of synthetic compounds have been increased in drug productivity but nature-derived drugs still constitute a substantial percentage of recently approved drugs. However, with the exception of the biodiversity and extinction rates, efforts of bio-prospecting are toward determining those species that are likely to yield new drugs [4]. It has been well documented that natural products played critical roles in modern drug development, especially for antibacterial and anticancer agents. With the riches of modern technology, such as in synthesis, fermentation, pharmacology__ together with biological diversity, chemo-diversity and great advances in evolutionary techniques or concepts__ combined with a wealth of knowledge about natural products, it will be possible to establish a large compound library for drug screening [5].

Umbellifers (Apiaceae) constitute one of the most economically important families of flowering plants and comprise several crops and condiments including carrot (*Daucus carota* L.), celery (*Apium graveolens* L.), parsley (*Petroselinum crispum* (Mill.) Fuss), fennel (*Foeniculum vulgare* Mill.), dill (*Anethum graveolens* L.), cumin (*Cuminum cyminum* L.), coriander (*Coriandrum sativum* L.), anise (*Pimpinella anisum* L.) and others. They contain numerous aromatic and bioactive compounds and this property has contributed to their use in traditional medicine since antiquity. All members of the family are rich in mono- and sesquiterpenoids; essential oils (used in medicine or perfumes) that are excreted in schizogenous canals in roots, stems, leaves, inflorescences and fruits [7]. These secondary constituents have been surveyed to distinguish related groups or tribes within the family [8] however, their distribution does not seem to exhibit any taxonomic pattern [9, 10]. Apiaceae includes approximately 466 genera and 3820 species [25] that about 120 genera and 363 species of the family have been recognized in Iran [12,13]. Generally from 850 species introduced as aromatic and medicinal species in Iran, about 50% are used medicinally, particularly to treatment in traditional medicine which including about 72 species from 42 genera of the family [14].

Ferula L. as one of the most promising genera of umbellifers with many species is sources of aromatic oleo-gum-resins that have been valued since antiquity as remedies, condiments and incense. Most species of *Ferula* are robust, tall perennials or biennials that have prominent taproots, stout stems, finely divided leaves with large inflated sheaths, and dorsally compressed fruits with plane commissural faces [15]. Taxonomically, Drude [16]. placed *Ferula* along with its allies in tribe Peucedaneae, subtribe Ferulinae; that they are characterized by closely appressed lateral wings [17]. Successful application of molecular data allowed to recognize a correct phylogenetic position of aforementioned taxa. Phylogenetic studies using nuclear ribosomal internal transcribed spacer (nrDNA ITS) sequence variation revealed that *Ferula* is placed among members of tribe Scandiceae and forms a clade with *Dorema* D.Don. and *Leutea* Pimenov that was successively recognized as subtribe Ferulinae [18]. However, subsequent analyses using nrDNA ITS and three cpDNA noncoding sequences showed that *Leutea* is sister to *Ferula*, while *Dorema* is nested within it [19]. After the monograph of Korovin [20] and infrageneric classification proposed by Safina and Pimenov [21-23]. that were based on habit and fruit features respectively, the molecular studies introduced a new infrageneric classification system for *Ferula* [24]. The genus *Ferula* includes 180-185 species that are distributed from the Canary Islands in the west through the Mediterranean region, Middle East and Central Asia to western China in the east and northern India in the south [20,25]. It represented by 53 species in the *Flora Iranica* area (with 33 endemics) that included c. 34 species in Iran (with 15 endemics) [12,15].

The popular Persian name for most of these species is “Koma” [12]. ΑΜΜΩΝΙΑΚΗ and ΝΑΡΘΞ of Dioscorides are *Ferula tingitana* L. and *F. communis* L., respectively [26] that their resins still bear the name of African ammoniacum as opposed to the Persian ammoniacum secreted by *F. ammoniacum* (D.Don) Spalik & al. (≡ *Dorema ammoniacum* D.Don) [27]. The most popular persian names for *F. ammoniacum* were Kandal, Vasha and Ushegh. It was traditionally used for the treatment of different diseases (such as cystitis, digestive, colic, furuncles, and asthma) and as an anthelmintic, emmenagogue and anti-convulsion agent. Another species of last genus *Dorema*, under name *Ferula aucheri* (Boiss.) Piwczyński & al. (≡ *D. aucheri* Boiss.) is used mostly in Iranian traditional medicine against asthma, bronchitis, parasites of digestive system, constipation and burns [28] that could be considered as a substitution for endangered *F. ammoniacum* [29].

Garlic-scented and bitter-tasting oleo-gum-resin asafetida has been used in Asia for centuries as a spice and medication, mostly as a carminative and an expectorant. The true asafetida is obtained from the Iranian *F. assa-foetida* L. while similar exudates are harvested from *F. alliacea* Boiss., *F. foetida* (Bunge) Regel, *F. rubricaulis* Boiss., *F. narthex* Boiss., *F. rigidula* Fisch ex DC. and *F. gabrielii* Rech.f. [30, 15]. Other oleo-gum-resins include sagapenum (*F. persica* Willd., *F. szowitsiana* DC.), and galbanum (*F. gummosa* Boiss.) [27]. The latter is a source of galbanum oil, which has an intense green scent with woody, balsamic and bark-like notes and is highly valued in perfumery or to treat as an anthelmintic, anticatarrhal, antiallergic, appetizer and emmenagogue agent [31]. Over harvesting of two important medicinal plants, *F. assa-foetida* and *F. gummosa* that listed in the Iranian Plant Pharmacopia, caused locally extinct which now introduced as endangered species and need to be conserved [32]. So, sustainable harvesting and domestication of these plants is a need for conservation which would guarantee these renewable resources for the future. These two important medicinally species are called Anghuzeh, Heltit or Gane-bu; and Barijeh or Ghasni respectively in Persian. The most frequent traditional uses of asafoetida are in respiratory diseases, including the treatment of asthma, bronchitis and whooping cough (as an expectorant), and gastrointestinal disorders [30, 33]. The mostly phytochemical compounds of *F. assa-foetida*, were a large number of different sesquiterpene cumarins and sulphur-containing compounds which plays an important role in the odor and taste of asafetida. Most of these compounds have been investigated in pharmacological view (*in vitro* or *in vivo*) to report the biological activities such as cancer chemoprevention [34,35], apoptosis induction in a melanoma cell line [36], anti-inflammatory action and antiviral activity [37] and also addressed potential toxicity of asafoetida in a case report [38]; but it need to study the acute toxicity and their compounds prior to clinical trials.

To date, there are only a limited number of *Ferula* species already subjected to phytochemical and medicinal approaches. Recent investigations have led to the discovery of some new biological activities of members of this genus like antimicrobial, anti-inflammatory, anti-oxidant, and hypotensive activities. Part of the biological activity of these plants can be attributed to their essential oils. Therefore, it is obvious that in the future, several other new compounds might be recognized as phytoconstituents of the *Ferula* genus and new biological activities may be explored [39]. This is particularly probable for the endemic entities since it has been largely confirmed that the endemism is a condition which may promote the metabolic diversity [40] in respect to species with a more wide area of distribution.

With respect to economical effect of *Ferula* specifically Iranian species, we decide to explore the phytochemistry of Ferulas of Iran from a phylogenetic perspective. Based on previously published studies, the Iranian *Ferula* species were placed in three subgenus Narthex, Ferula and Safinia that included in seven sections (Merwia, Scorodosma, Pachycarpa, Peucedanoides, Macrorrhiza, Soranthus and Stenocarpa) [24]. Also we identify those phylogenetic lineages that are most rich in bioactive compounds. We reviewed the mostly publications on phytochemical features of *Ferula* that were released from last 5 decades up to now (in Web of Science) to finally determine a framework for its phytochemistry. Our aim is the identification of major clades within *Ferula* that may be subject to medicinal aspect.

Material and Methods

Phytochemical Data

Over 150 publications were checked for phytochemical data for *Leutea* and *Ferula* species in Iran i.e., including also *Dorema* and *Schumannia* (Ferulinae subtribe, Table S1). The amount of most components (those selected with more than 5% abundant) in each part of plants used with the biological activity referred, have been indicated in Table S1 and finally the data were used to prepare a matrix. In total, 40 accessions including 34 Iranian species of *Ferula* and six species of *Leutea* were examined for phytochemical characteristics. Phytochemical compounds were typified in nine groups as 40 binary characters (Table 1). However, a cluster analysis was performed on the binary phytochemical matrix with an uncorrelated distance method in UPGMA by estimating 100 maximum trees using Mesquite 3.61 [42].

Mapping Phytochemical Characters

After gathering the whole literature data of phytochemical features, a typology of major chemical constituents of Ferulinae in Iran was prepared and these characters were scored for the species included in recent molecular analyses (Table 1). The evolution of these characters was evaluated with parsimony method using a simplified cladogram from molecular analyses. Phylogenetic mapping of phytochemical characters was performed using Mesquite 3.61 [42]. About 37 species including 33 *Ferula* and four *Leutea* were used for mapping the phytochemical data on the phylogenetic tree pruned from recent molecular analyses with 4 genome regions (nrDNA ITS and three noncoding cpDNA regions: *rps16* intron, *rpoC1* intron and *rpoB-trnC* intergenic spacer) [24]. Species names with authorities and voucher information for these 37 species were listed in Apendix 1 [24]..

Results

The tree resulted from cluster analysis of phytochemical data (Fig. 1) did not revealed any taxonomic classification pattern and is not congruence with last inferred phylogenetic results. However, when the categorical characters are traced on phylogenetic tree, it is defined those chemotaxonomic features that would be helpful (Fig. 2, a-L). The graphical tree inferred from UPGMA cluster analysis of major chemical constituents in Ferulinae members were prepared and after trace characters over trees, several of them have represented here (Fig. 3). Those chemical constituents that have occurred in one species and the typical components of the *Ferula* sections are indicated in Table 2 and Table 3, respectively.

The major constituents and their grouping between sections and species are explained here; Monoterenes (MT) as a major compound were occurred in most groups of *Ferula* and *Leutea* species except from sect. Soranthus and *L. avicennae* Mozaff. (Fig. 2, a) and these components are represented in two parts of the UPGMA tree (Fig. 3, a). Monoterpene hydrocarbons (MH) also have occurred in all the groups of *Ferula* but two sections Scorodosma and Soranthus (Fig. 2, b). However, Oxygenated monoterpenes (OM) have represented in a same route with monoterpene compounds exception of two sections Soranthus and Stenocarpa and subgen. Safinia (Table 3).

It seems that sesquiterpenes (SQ) have concentrated in five clades of *Ferula* including Merwia, Scorodosma, Pachycarpa, Peucedanoids and Macrorrhiza in Iran (Fig. 2, c) and specifically Oxygenated sesquiterpenes (OS) have mostly concentrated in Merwia and several Peucedanoides members (Figs. 2, d). As indicated in Fig. 3, Sesquiterpene hydrocarbons (SH) and Oxygenated sesquiterpenes (OS) have been occurred in the same track of the species (Fig. 3, b, c) that could ascertain the related evolved chemical pathways. Sesquiterpene Lactones (SL) could have a characteristic value for *F. alliacea* within sect. Merwia (Fig. 2, e) while it has been represented in three another species *F. orientalis* L., *F. oopoda* (Boiss. & Buhse) Boiss. and *F. diversivittata* Regel & Schmalh. When Sesquiterpene Esters (SE) has mapped on phylogenetic tree, those species contain this composition, placed in closely position including *F. flabelliloba* Rech.f. & Aellen and *F. karakalensis* Korovin from sect. Merwia and *F. orientalis*, *F. haussknechtii* H.Wolff ex Rech.f., *F. rigidula* and *F. ovina* (Boiss.) Boiss. from sect. Peucedanoides (Fig. 2, f). It has indicated that between Iranian species of *Ferula* have not reported any amount of Sesquiterpene ketones so we have to exclude this chemical character from the matrix.

Phenolic compounds (P) have concentrated on the species of last genus *Dorema* in sect. Peucedanoides while it could be also found within the five species belong to different sections of *Ferula* (Fig. 2, g). Cumarins as an important chemical components within *Ferula* group, is characterized in three Iranian sections Merwia, Scrodosma and Pachycarpa (known as *F. diversivittata*) while it is also represented in three other species (*F. hyrcana* (Koso-Pol.) Puchałka & al., *F. glabrifolia* M.Panahi & al. and *F. oopoda*) (Fig. 2, h). Only two species of Merwia; *F. alliacea* and *F. szowitsiana* contain furanucoumarins (FC; Fig. 2, i). When terpenoid coumarin (TC) was mapped on phylogenetic tree, it was occurred within Merwia, Scrodosma and Pachycarpa sections together with *F. hyrcana* (Fig. 2, j). Acetophenone derivatives (APD) were reported in three species of last genus *Dorema* including *F. glabrifolia*, *F. hyrcana*, and *F. michaelii* M.Panahi & al. (Fig. 2, k) and also diterpenes (DIT) were reported from two species *F. ammoniacum* and *F. glabrifolia*. Organosulphur compounds (SO) have characteristically concentrated in the species *F. foetida* from sect. Scrodosma and the members of Merwia. That's the reason Disulphides (DS) as one group of Organosulphur compounds, responsible for the evil odor of aforementioned species, *F. latisecta* Rech.f. & Aellen, *F. foetida*, and *F. assa-foetida* (Fig. 2, L). *F. foetida* is a unique species that contain Tiophene derivatives and Polyacetylene (TD, PCT Table 2). In Table S2 the whole chemical constituents of Ferulinae members in Iran have been ascertained with chemical formula.

Table 1 Typology of phytochemical constituents with the numbers species contains each component.

Char. No.	Major compounds	Chemical compounds	Abb.	No. species
1	Terpenes	Monoterpenes	MT	28
2		Monoterpene Hydrocarbons	MH	26
3		Oxygenated Monoterpenes	OM	16
4		Monoterpene Esters	ME	1
5	Sesquiterpenes		S	23
6		Sesquiterpenes Simple	SQ	1
7		Sesquiterpenes Hydrocarbons	SH	18
8		Oxygenated Sesquiterpenes	OS	15
9		Sesquiterpene Esters	SE	7
10		Sesquiterpene Daucane Esters	SED	2
11		Sesquiterpene Eudesmane Esters	SEE	1
12		Sesquiterpene Germacrane Esters	SEG	3
13		Sesquiterpene Guaiane Esters	SEU	1
14		Sesquiterpene Humulane Esters	SEH	2
15		Sesquiterpene Lactones	SL	4
16		Sesquiterpene Daucane Lactones	SLD	1
17		Sesquiterpene Eudesmane Lactones	SLE	1
18		Sesquiterpene Germacrane Lactones	SLG	1
19		Sesquiterpene Guaiane Lactones	SLU	2
20	Diterpenes		DIT	2
21	Sterols		ST	4
22	Phenolic compounds		P	10
23		Phenols (simple)	PH	4
24		Phenolic Acids	PA	4
25		Chromen Derivatives	CHD	1
26		Flavonoids	FV	7
27	Coumarins		C	13
28		Simple Coumarins	CM	6
29		Furanucoumarins	FC	2
30		Terpenoid Coumarins	TC	10
31	Arylic compounds		AR	13
32		Phenylethanoids	PE	1
33		Phenylpropanoids	PP	10
34		Safrole Derivatives	SDV	4
35		Acetophenone Derivatives	APD	3
36		Sesquiterpene Acetophenone Derivatives	SQ-AC	1
37	Polyacetylene		PCT	1
38	Organic Sulphur Compounds		SO	9
39		Disulphide	DS	8
40		Tiophene Derivatives	TD	1

Table 2 Specific *Ferula* L. species that contain one chemical constituent

Chemical Constituent	Species
ME	*F. persica* var. *persica*
PE	*F. szowitsiana*
SQ	*F. ammoniacum*
SED	*F. ovina*
	F. orientalis
SEE	*F. flabelliloba*
SEG	*F. orientalis*
	F. karakalensis
	F. persica var. *persica*
SEH	*F. haussknechti*
	F. rigidula
SEU	*F. karakalensis*
SLD	*F. diversivittata*
SLE & CHD	*F. oopoda*
SLG	*F. orientalis*
SLU	*F. alliacea*
	F. oopoda
SQ-AC	*F. hyrcana*
PCT & TD	*F. foetida*

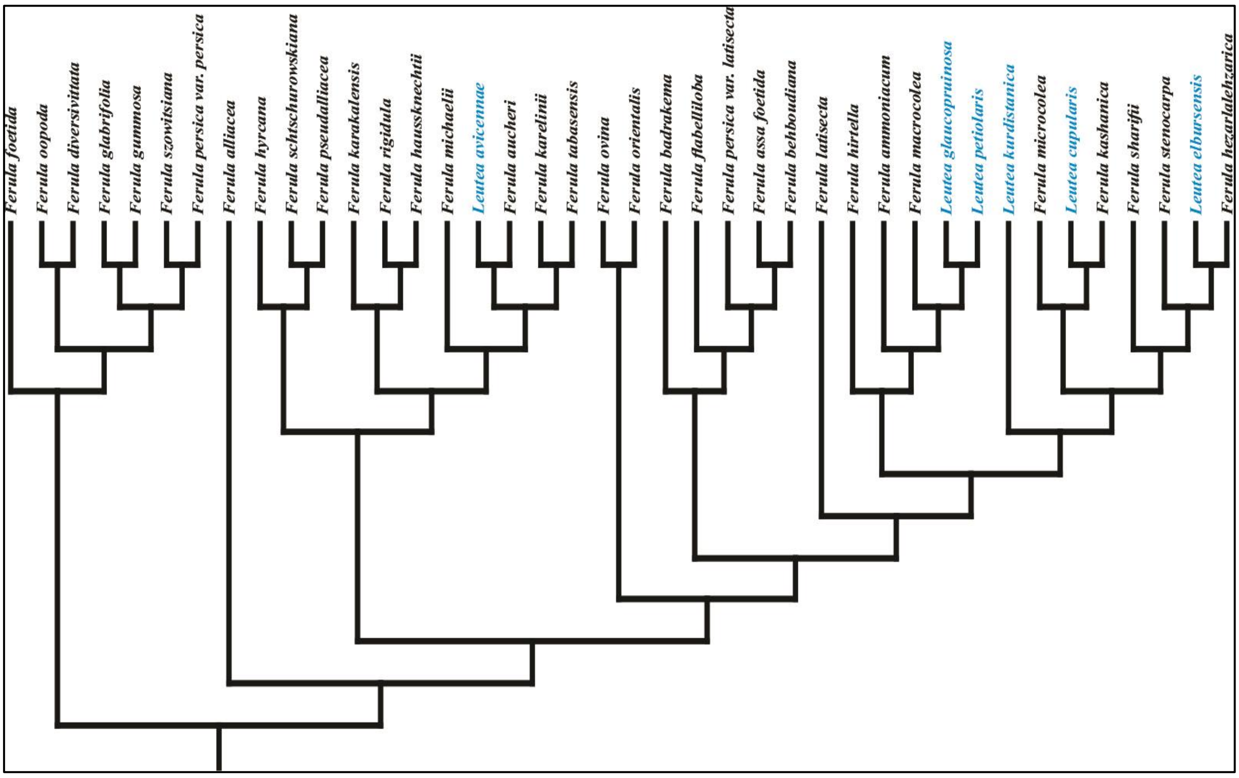

Fig. 1 Unrooted tree from UPGMA cluster analysis of phytochemical data in *Ferulinae* members of Iran. The position of *Leutea* species colored in blue.

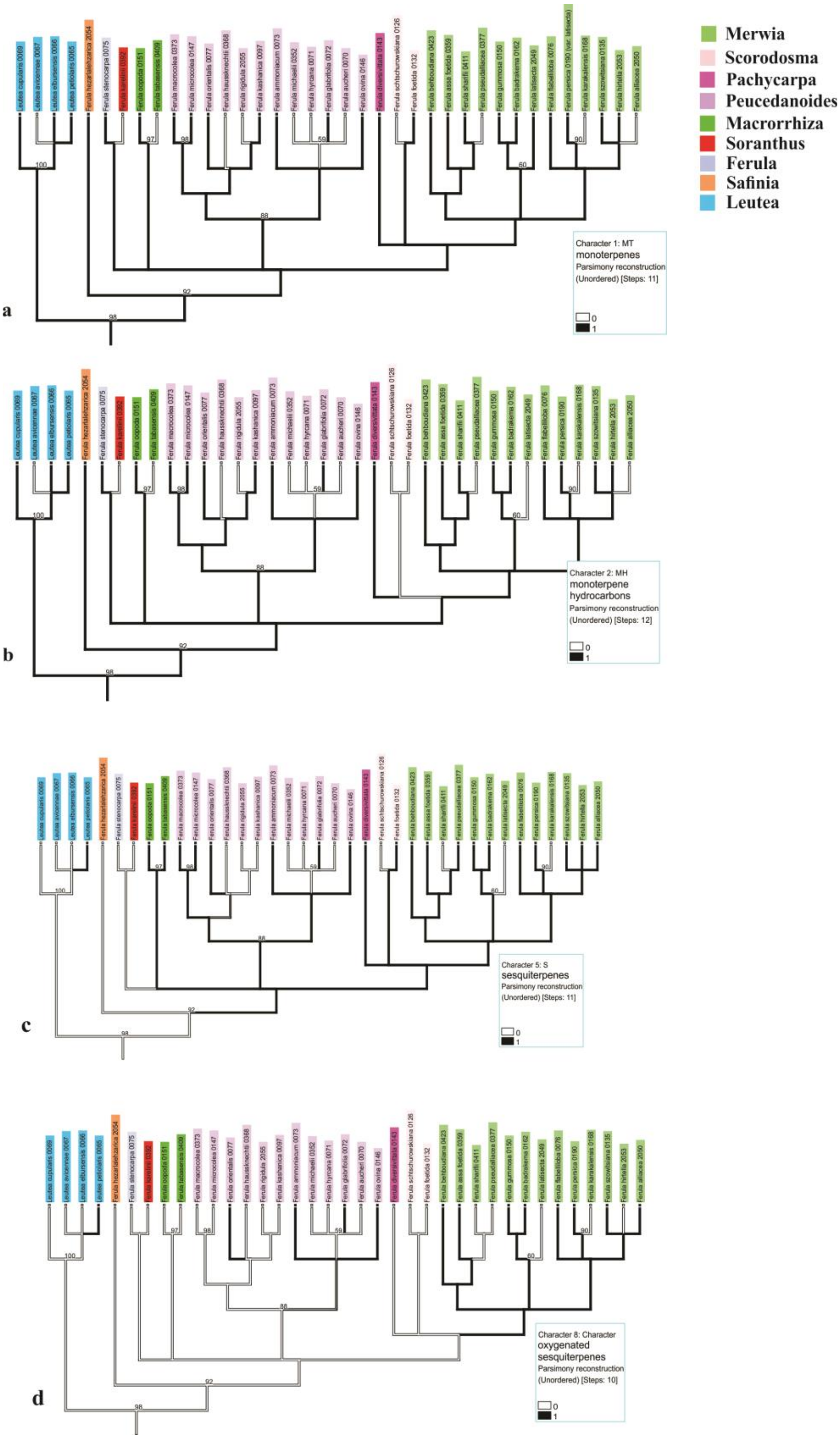

Fig. 2 Mapping phytochemical data on phylogenetic tree pruned from last phylogenetic analyses. a (MT); b (MH); c (S); d (OS) trees (For abbrev. see Table 1.). The legend refers to sections of *Ferulinae* in Iran [24].

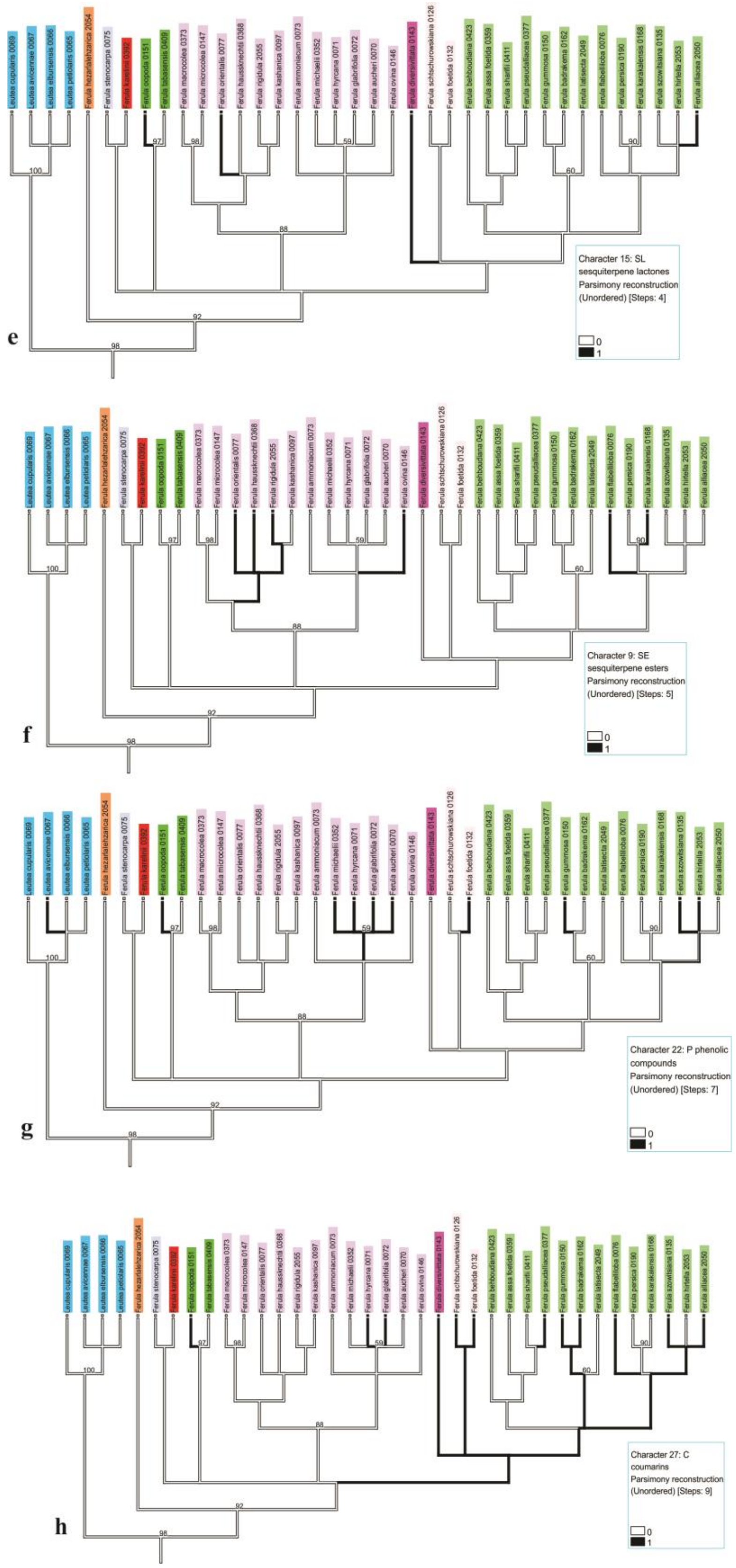

Fig. 2 Continued, e (SL); f (SE); g (P); h (C) trees (For abbrev. see Table 1.).

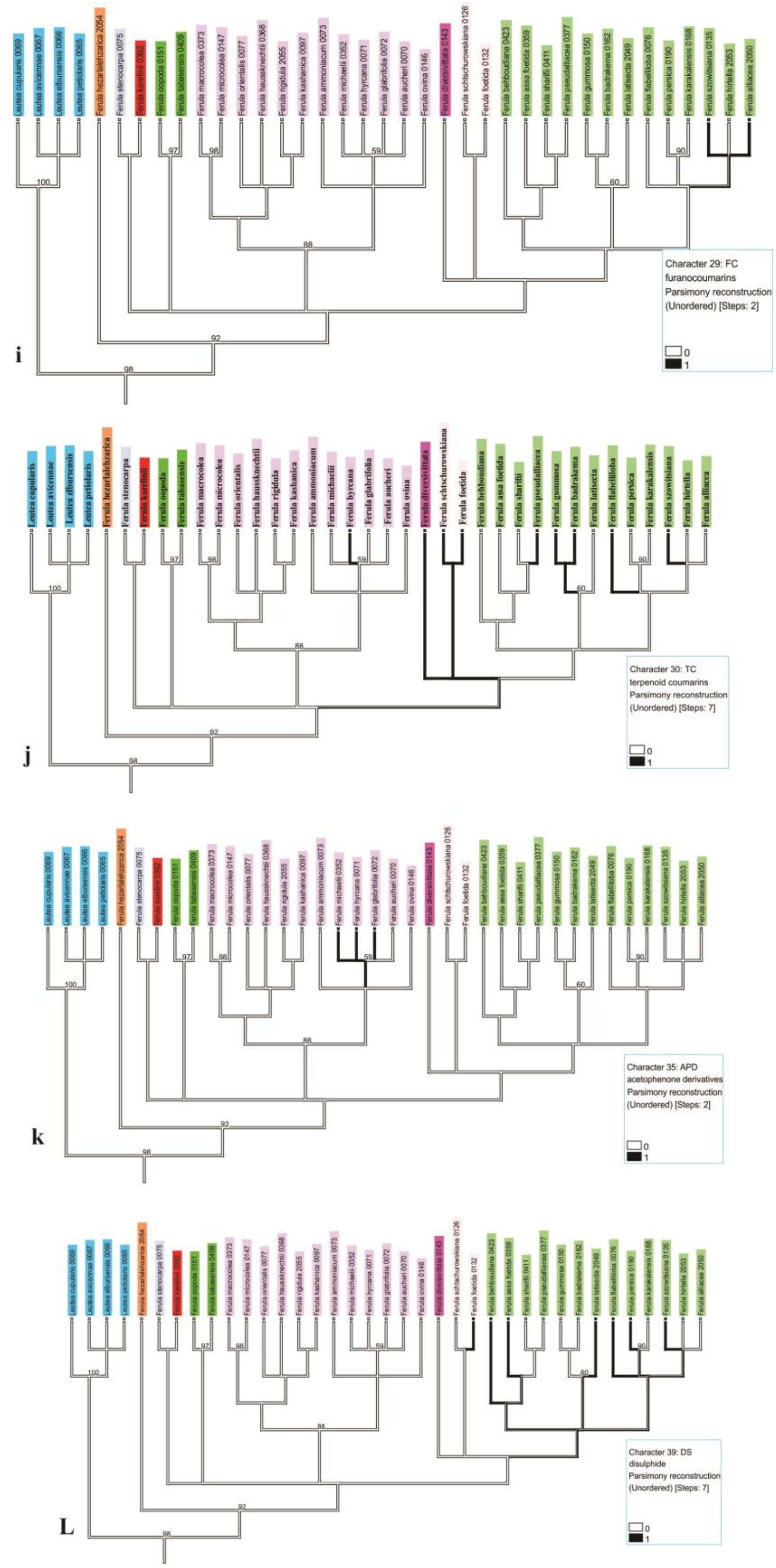

Fig. 2 Continued. I (FC); j (TC), k (APD); L (DS) trees (For abbrev. see Table 1.).

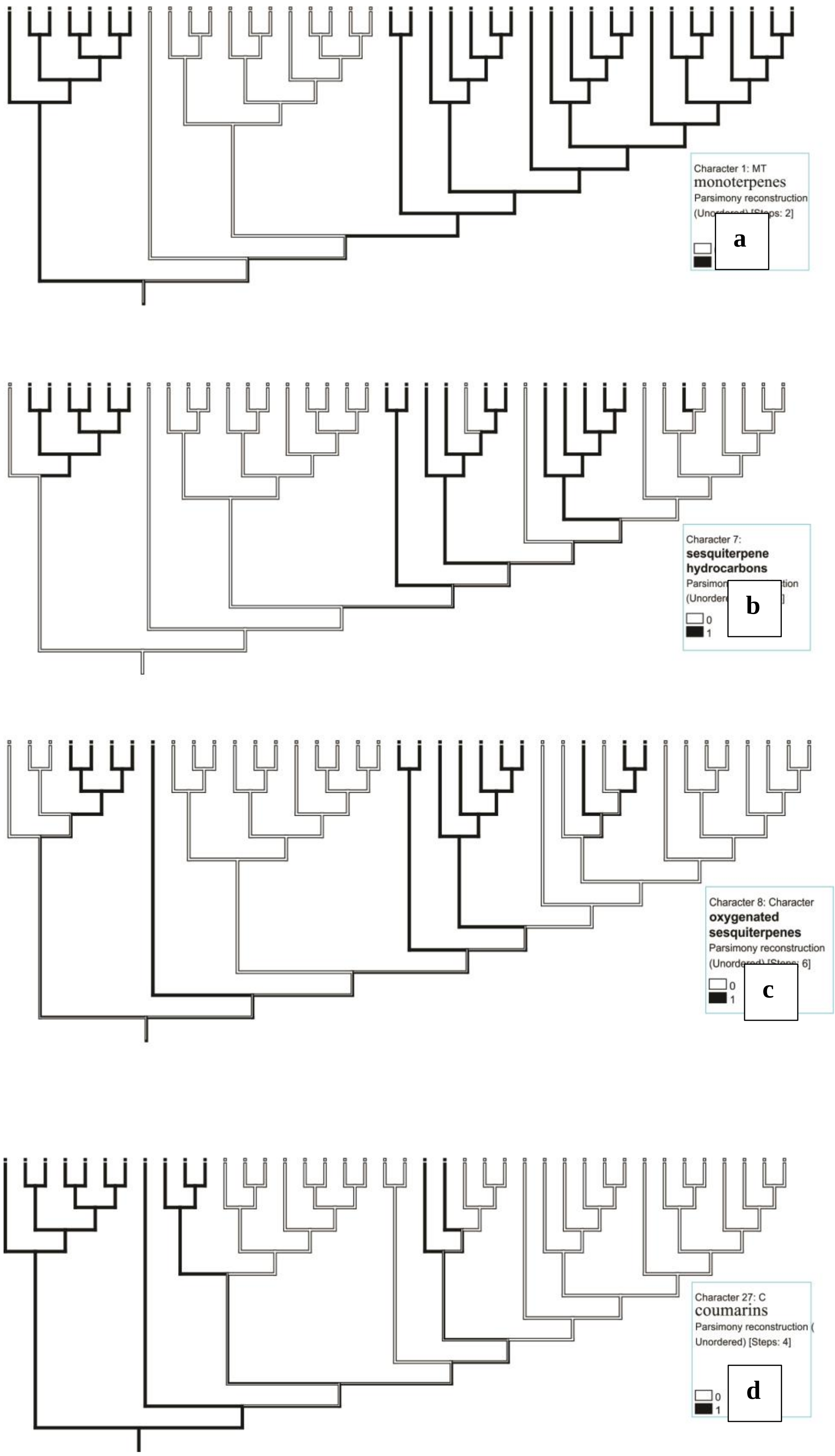

Fig. 3 Phytochemical trees after tracing the characters over cluster tree. The name of species as the same as in Fig.1 that omitted here.

Table 3 Phytochemical characters for sections of *Ferula* that shows major types of chemical components (For abbrev. see Table 1.).

Ferula	MT	MH	OM	S	SH	OS	SE	SL	DIT	ST	P	PA	PH	FV	C	CM	FC	TC	AR	PP	SDV	APD	SO	DS	TD
sect. Merwia	●	●	●	●	●	●	●	●		●	●	●	●	●	●	●	●	●	●	●	●		●	●	
Scrodosma	●		●	●							●			●	●			●	●	●			●	●	●
Pachycarpa	●	●	●	●	●			●							●	●		●	●	●					
Peucedanoides	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●		●	●	●	●	●			
Macrorrhiza	●	●	●	●	●			●			●		●		●	●			●		●				
Soranthus														●											
Stenocarpa (subgen. Ferula)	●	●																							
subgen. Safinia	●	●																							
Leutea	●	●	●	●	●	●					●	●		●											

Discussion

Phytochemistry in the Iranian species of *Ferula*

Numerous species of *Ferula*, particularly those producing oleo-gum-resins, were subject to phytochemical studies. These plants are particularly rich in coumarins, sesquiterpene coumarins, monoterpenes etc. (Table S1 and Table S2). Although some of the chemical compounds occurring in some species of *Ferula* was recorded as informative characters such as Coumarins, flavonoids and phenylpropanoids that show sufficient variation [43] but they were not surveyed widely enough to be potentially useful phylogenetically. Some coumarins, e.g. farnesiferol A, are characteristic for *Ferula* [44]. The presence of non-volatile sesquiterpenoids, for example sesquiterpene lactones like guaianolides and germacranolides, seems to be characteristic for some umbellifer genera including *Ferula* and *Laserpitium* L. [7].

For six species of *Leutea* which chemical components were detected now, different components have been represented but none of chemical constituents is not characterized in the genus level (Table 3, S1). Mostly they contain monoterpene hydrocarbons with highest percentage. Within the *L. avicennae* Mozaff., caffeic acid as a phenolic compound and a key intermediate in the biosynthesis of lignin, and also astragalin as flavonoid has been reported while they are not reported from another species of *Leutea* (Table S1, [1]). Occasionally the percentage of some compounds would be important within a part of plant for extraction e.g. monoterpene hydrocarbons mostly concentrated within the flowers of *L. cupularis* (Boiss.) Pimenov than in the stem which is richest part in oxygenated monoterpenes and α-terpinyl isobutyrate (Table S1, [2]), or in the aerial parts of *L. kurdistanica* Mozaff., phenylpropanoids are the major compounds (Table S1, [6]). Therefore it is clear that the species of *Leutea* mostly contain three type chemical components including Monoterpenes, Sesquiterpenes groups and Phenolic compounds (Table 3).

The last phytochemical studies on 18 species of *Ferula* in Iran revealed that monoterpene hydrocarbons constituted the principle fraction of the oils of most species of *Ferula* [45] as it is ascertained here (Table 3, S1; Fig. 2.). Based on the typology of phytochemical constituents (Table 2), Monoterpenes are indicated in the chemical matrix as three groups; monoterpene hydrocarbons (MH), Oxygenated monoterpenes (OM) and monoterpene esters (ME) that the two earliest components have been represented as the major fraction of oils of the most sections of *Ferula* and specially OM compounds concentrated in five sections indicated as subgen. Narthex (Table 3) while ME only have reported from *F. persica* var. *persica* (Table 2, S1). As an example in *F. ovina*, a widespread *Ferula* species in Iran, the essential oil chemical compositions collected from different regions mostly contain monoterpene hydrocarbons (Table S1) with different qualitatively amounts that comprise mostly α-pinene, β-pinene, limonene and myrcene as monoterpene fraction isolated compounds. In the last investigation it was defined that *F. ovina* oils showed considerable chemical consistency at the flowering stage, since all populations analyzed had a similar chemical profile [45]. When compare the oils of fresh and dry plant of *F. ovina*, the percentages of α-pinene and limonene found in the oils of both stages are different. Contrary to the oil of dried aerial parts, fresh stage oil contained the lower percentage of α-pinene, germacrene D and sabinene and the content of spathulenol in dry plants oil reached 9.6% but it was not identified in the fresh plants oil as a main components [46].

Moreover, Kanani *et al*. [45] confirmed that non-terpene compounds, i.e. organosulfur, aliphatic and phenylpropanoid derivatives would be characteristic for some *Ferula* species and as interesting chemotaxonomic markers such as the high amounts of aliphatic hydrocarbons in *F. orientalis* L. and *F. microcolea* (Boiss.) Boiss. According to our results, organosulfur characterized in Merwia and Scorodosma sections and phenylpropanoid derivatives concentrated in the four sections (Merwia and Scorodosma, Pachycarpa, Peucedanoides, Table 3). Also in the essential oil of *F. foetida*, the combination of high amounts of organosulfur compounds and phenylpropanoids have been found to be considering as a chemotaxonomic marker for this species that confirm here (organosulfur compounds indicated as SO, DS and TD in Table 3). Based on our results, most of the chemical components such as Monoterpenes, Sesquiterpenes, Phenolic compounds and Coumarins have been concentrated in the five sections of *Ferula* (Merwia, Scorodosma, Pachycarpa, Peucedanoides and Macrorrhiza) that has been classified in subgen. Narthex (Table 3) [24].

By considering the other investigations on *Ferula* species, it seems that several variables can influence the differences in oil constituents, such as the environmental (geographical sites) and climatic conditions of the plant and the choice of the extraction method and antimicrobial test (Table S1, [47, 48]). These results showed that the four most remarkable compounds found in the oils of *F. gummosa* were: β-pinene, α-pinene, δ-3-carene and limonene which two first compounds have significant antibiotic activity and also the samples collected from tropical regions showed better percentage and type of flavoring combinations than samples from cold regions [48]. The variation of phytochemicals was not only found among samples of different regions but also among samples of one region with different altitude, reflecting the effect of environment on essential oil components. In contrast, samples from different regions but the same altitude showed different compositions, reflecting the genetic variability among samples [48]. Franz [49]. demonstrated that compositional variation within a species can be affected by (1) individual genetic variability, (2) variation among different plant parts and different developmental stages and (3) modifications due to the environment [49]. Understanding these factors can make the difference between a good yield of high-quality oil and a poor yield of undesirable oil.

The composition of the seed oils and the leaf oils of the two species *F. oopoda* and *F. badkhysi* Koso-Pol. (from Zarand, Kerman) showed significant similarity for the percentages of the main components that confirm the opinion about taxonomic position of two species as synonymous [13,50]. However, the existence of chemotypes in the *Ferula* species has been suggested in some studies, for instance some compounds isolated from *F. communis*, showed poisonous effects to cattle and sheep due to the presence of prenylcoumarins [41].

Considering the chemical structures of the majority of the *Ferula* secondary metabolites and the proposed biogenesis [51], it is evident that the biogenetic pathways involving terpenoids (sesquiterpenes) and phenylpropanoids are particularly active. These are also interacting among them to synthesize compounds with mixed biogenetic origin, thus it is most probable that new metabolites possibly isolated in future studies might exhibit these structural features. The chemical composition of essential oil can be highly affected by ecological conditions and genetic structure. The investigation on secretary system of four endemics of *Ferula* (*F. foetida*, *F. varia* Trautv., *F. kyzylkumica* Korovin and one species of last genus *Dorema*; *D. sabulosum* Litw.) from Uzbekistan, indicated that these species with growing in various habitats have a secretory system represented with terpenoid keeping schizogenous secretory ducts with developed secretory system with larger ducts producing more terpenoids adapted as desert plants. However, the taproots of monocarpic desert species (*F. foetida*, *F. varia*, *D. sabulosum*) have well developed in phloem tissue with a larger number of secretory ducts than the underground organs of polycarpic species *F. kyzylkumica* that cause to accumulate large amount of terpenoids and other biologically active compounds which are necessary for plant survival and reproduction in the arid environment [52].

Biological Properties

Since antiquity, essential oils of aromatic plants have been widely used for their biological activities such as antimicrobial, anti-fungicidal, anti-inflammatory, sedative and anesthetic remedies. At present, approximately 3000 essential oils are known at least 300 of which are commercially important especially for the pharmaceutical, agronomic, food, cosmetic and perfume industries [5]. It has indicated that different species of *Ferula* genus have been used in traditional medicine and also in food as spices for many centuries. Based on recent studies on chemical composition of different species of *Ferula* and their medicinal effect, we summarized some important compositions with their biological effects in Table S1. These differences in chemical composition within the species yield the chemotypes which partially dependent on the environment, grown in different localities then could have different biological activity such as mutagenic and anti-mutagenic activities of essential oils for example those reported in *F. orientalis* [53].

In the following paragraphs we try to explain some examples from Ferulinae members with emphasis on biological activities in recent researches. Umbelliprenin, is one of the most interesting bioactive constituents extracted from the genus *Ferula* that first reported as sesquiterpene coumarin synthesized in *F. persica*. The most interesting properties of umbelliprenin were its anti-inflammatory and cancer chemopreventive activities [54]. It has also been found that the cancer chemoprevention of umbelliprenin is comparable with curcumin, a well-known cancer chemopreventive agent [35]. Another activity of umbelliprenin is its anti-proliferative effect although it is not cytotoxic on all cell lines. Furthermore, it seems that umbelliprenin, as a prenylated coumarin, showed various biological activities and it might be an outstanding compound for designing and synthesizing new derivatives with higher potency and more safety. It suggests that *F. persica*, as a candidate to focus future research on anti-diabetic and anti-viral activities [55], confirming its traditionally usage as antispasmodic, antibacterial and anti-hypertensive.

Based on recent investigations, those essential oils rich in oxygenated monoterpenes are potent antimicrobial agents for example, the essential oil from stem of *Leutea cupularis* inhibited the growth of all test bacteria than essential oils of flower and leaf parts [56]. It has been shown that monoterpene could cease ion transport processes in bacterial cell membrane and finally destroy cellular integrity. Moreover, Limonene, γ-terpinene and elemicin compounds have been demonstrated with strong antimicrobial and antioxidant activity from *Leutea kurdistanica* (Table S1) [57]. Through the recent investigation on antimicrobial and cytotoxic activity of *F. gummosa*, it has indicated that this species is a cytocompatible solution and has a favorable antimicrobial effectiveness against endodontic pathogens [58]. The observed differences between extracted compositions of *F. assa-foetida* may be probably due to using of different parts of plants for analysis, different environmental and genetic factors, different chemotypes and the nutritional status of the plants as well as other factors that can influence the oil composition [59]. Recently, the essential oil from *F. assa-foetida* oleo-gum-resin, was compared to the essential oil extracted from its seeds with significantly stronger antibacterial effect (the antibacterial activity measured against four oral bacteria *Streptococcus* species and *Lactobasillus rhamnosus*) [60].

Nearly, more than 60% of clinically approved anticancer drugs are derivatives of medicinal plants. The growing incidence of cancer and high cost, various limitations in the conventional therapy including high cost and high toxicity of present anticancer drugs has faced a severe challenge to all the researches to design and develop an alternative, eco-friendly, biocompatible and cost-effective strategy in a greener way. Under this scenario, phytomolecules are expected to revolutionize cancer treatment in the next decade [62, 63]. The results activity of ferutinin extracted from *F. ovina* indicate that ferutinin as a phytoestrogen, have selective cytotoxic effects and induce apoptosis *in vitro* [61]. Through a review on cytotoxic activity of the genus *Ferula,* it was assumed that the most prominent biological features of the genus are their cytotoxic effects [39] and much effort needs to identify potent and effective *Ferula* compounds that could be appropriate and used in medicine.

It is considered that a wide number of the newly described metabolites from *Ferula* species have been tested for their biological activities (Table S1, Table S2). Besides the quite common antioxidant characteristics, some of these compounds have showed a wide range of activities such as antimicrobial, antiviral (HIV), antibacterial and antiprotozoal, thus offering new potentially useful compounds for the therapeutic treatment of various diseases. It should be noticed that these compounds particularly the new described ones, only are extracted in little amounts as natural sources so for species conservation need to further studies for improving the yields with good and effective doses [64]. Interestingly, to develop the bioactivity potential of the numerous metabolites isolated from *Ferula* species, it is necessary simultaneous studies of their pharmacokinetics and *in vivo* tests to obtain the real therapeutic and toxicological aspects as having attention increased to the genus and its wide effectiveness in traditional medicine.

Conclusion

Ferula species as a member of Apiaceae family, are monocarpic and only once produce flowers during the life cycle and reproduce through seed so excessive harvest of roots and flowers of these species are dangerous, and must be avoided, especially in the case of endemic and endangered species. Then heavily and excessive collection of these plants has caused a notable decrease in populations of the plant in the area that necessary to be controlled. With the conservation respect, special consideration should be given to protect from extinction of these renewable resources for the future.

The phytochemical patterns recognized for the *Ferula* species are varied. These include different classes of natural products, i.e. monoterpenes, coumarins, sesquiterpenes, phenylpropanoids, sulfur-containing compounds and steroids (Table 3, Table S2). The sesquiterpenoids are also considered as chemotaxonomic markers in the Apiaceae, and the genus *Ferula* showed a widespread presence of compounds of several families of sesquiterpene lactones, including derivatives containing the cadinane, daucane, germacrane, guaiane, and eudesmane backbones. All these compounds could be useful taxonomic markers within the genus, but they also provide evidence of the systematic proximity among various genera in the Apiaceae family itself. The main metabolic feature, which may be observed by considering the wide list of compounds and chemical structures reported in this review, is the presence of a huge number of metabolites of mixed biosynthetic origin, such as monoterpenes and sesquiterpene coumarins, sesquiterpene hydrocarbons or oxygenated, furanucoumarins and Acetophenone Derivatives. Concerning these compounds, the species of the *Ferula* genus resulted to be very efficient producer of these rare phytoconstituents. The occurrence of these secondary metabolites seems to be restricted to a few species within the Apiaceae, the Asteraceae and the Rutaceae families [65]. Last but not the least, the sulfur-containing secondary metabolites, present as different derivatives such as thiophenes, disulfides and trisulfides , found in both the volatile fraction and organic solvents extracts, are an additional distinctive chemical trait of the *Ferula* species which confer the characteristic smell to several species of the genus specifically in the sect. Merwia and Scorodosma. It is clear that for *Leutea* there is not considered any characteristically chemical components at the genus level but for *Ferula* genus defined five sections of sungen. Narthex containing the most typical constituents that could result from the similar metabolic pathway during their evolution.

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