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Intitulé

**Secondary metabolites and pharmacological  
properties of *Ferula* genus**

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## *Dedication*

This dedication is a humble tribute to the love, wisdom, and joy you have brought into my world.

« To my parents << **Lemmoui Derradji , Sabi Amel** >> whose love has been the foundation of my existence, I am forever grateful. Your unwavering support and belief in my dreams have been a guiding light and propelling me forward . I am forever indebted to you ».

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I dedicate this work  
to my family, who gave me a dignified education.  
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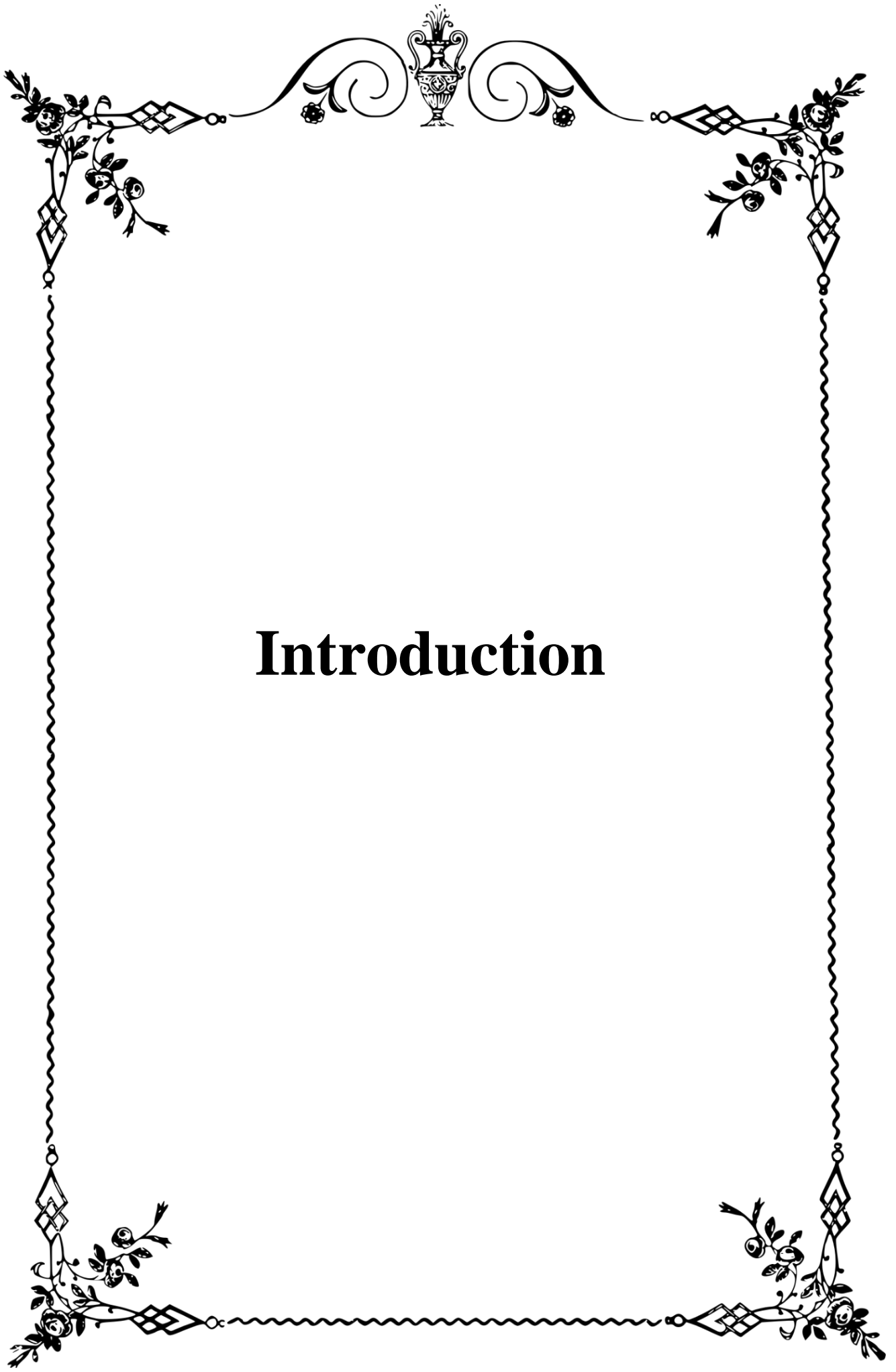
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## List of abbreviation

<b>%</b>	Percentage
<b>A. flavus</b>	Aspergillus flavus
<b>AFNOR</b>	Association Française de Normalisation ( the standards organization of France)
<b>AGS</b>	Aicardi-Goutières syndrome
<b>AIDS</b>	Acquired immunodeficiency syndrome
<b>APG III classification</b>	Angiosperms Phylogeny Group
<b>C</b>	Carbon
<b>C. albicans</b>	Candida albicans
<b>Caco-2</b>	Colon ancer
<b>CAT</b>	Catalase
<b>Cm</b>	Centimetre
<b>Cont.</b>	Continued
<b>E. coli</b>	Escherichia coli
<b>E. faecalis</b>	Enterococcus faecalis
<b>ER stress</b>	Endoplasmic Reticulum Stress
<b>Etc.</b>	<i>et cetera</i>
<b>GSH</b>	Glutathione
<b>H1N1</b>	h(aemagglutinin type)1 and n(euraminidase type) 1. ( <i>type of influenza A</i> )
<b>HeLa</b>	Henrietta Lacks
<b>HepG2</b>	Hepatoblastoma cell line
<b>HIV</b>	Human immunodeficiency viruses
<b>HL-60</b>	Human promyelocytic leukemia cell line
<b>HSV-1</b>	Herpes simplex viruses
<b>IPP</b>	isopentenyl diphosphate
<b>K562</b>	the first human immortalised myelogenous leukemia cell line to be established
<b>L. major promastigotes</b>	Leishmania major promastigotes
<b>M</b>	Meter
<b>MCF-7</b>	Michigan Cancer Foundation -7.
<b>P. aeruginosa</b>	Pseudomonas aeruginosa
<b>S. aureus</b>	Staphylococcus aureus
<b>SKOV-3</b>	ovarian cancer cell line
<b>SMs</b>	Secondary metabolites
<b>SOD</b>	Superoxide dismutase
<b>SSR</b>	Simple sequence repeats



# Introduction

Medicinal and aromatic plants represent an inexhaustible source of traditional and effective remedies due to the active principles they contain: alkaloids, flavonoids, terpenoids, is associated with the development of civilization. Around the world, these plants have played a role in traditional medicine and in culinary preparations .Currently, between 20,000 and 25,000 plants are used in pharmacology. The majority of these drugs are of plant origin and contain at least one active molecule (**Tabak *et al.*, 2022**).

Superior and aromatic plants have been traditionally used in preserving food and folk medicine. Essential oils, complex and concentrated liquid mixtures, are responsible for their beneficial properties. Aromatic plants synthesize these oils as secondary metabolites and enacted as a part of their defense system against pathogens and pests. These oils contain volatile components that offer antimicrobial, antiviral, antifungal, and insecticidal properties.

The history of the application of essential oils comes back to ancient times, being utilized mainly for their flavoring, sanitary and medicinal properties. Over the past decades, thousands of aromatic plants have been subjected to phytochemical analysis for their volatile components, and results unveiled the great qualitative and quantitative diversity that exists in the composition of essential oils. Most of the essential oil components are small and lipophilic molecules which mainly belong to the monoterpene and sesquiterpene classes of compounds. Many of these phytochemicals are bioactive and therefore confer valuable therapeutic potentials to the essential oils, with the antimicrobial and antioxidant properties being among the most well-known (**Sahebkar & Iranshahi, 2011**).

Secondary metabolites are organic compounds that are produced by plants and other organisms. Unlike primary metabolites, which are essential for basic life functions, secondary metabolites are not directly involved in growth or development. Instead, they serve various specialized functions, such as defense against predators, the attraction of pollinators, and communication between organisms. One fascinating genus that exhibits a rich diversity of secondary metabolites is *Ferula*. Which is known for its aromatic and medicinal properties.

In recent years, *Ferula* plants have gained increasing attention from researchers due to their potential therapeutic properties. Many studies have focused on the bioactive compounds found in *Ferula* Species, particularly their antioxidant, anti-inflammatory, and anticancer activities. The essential oils of *Ferula* species have also been extensively studied for their antimicrobial properties, with several species showing promising results against various pathogenic microorganisms.

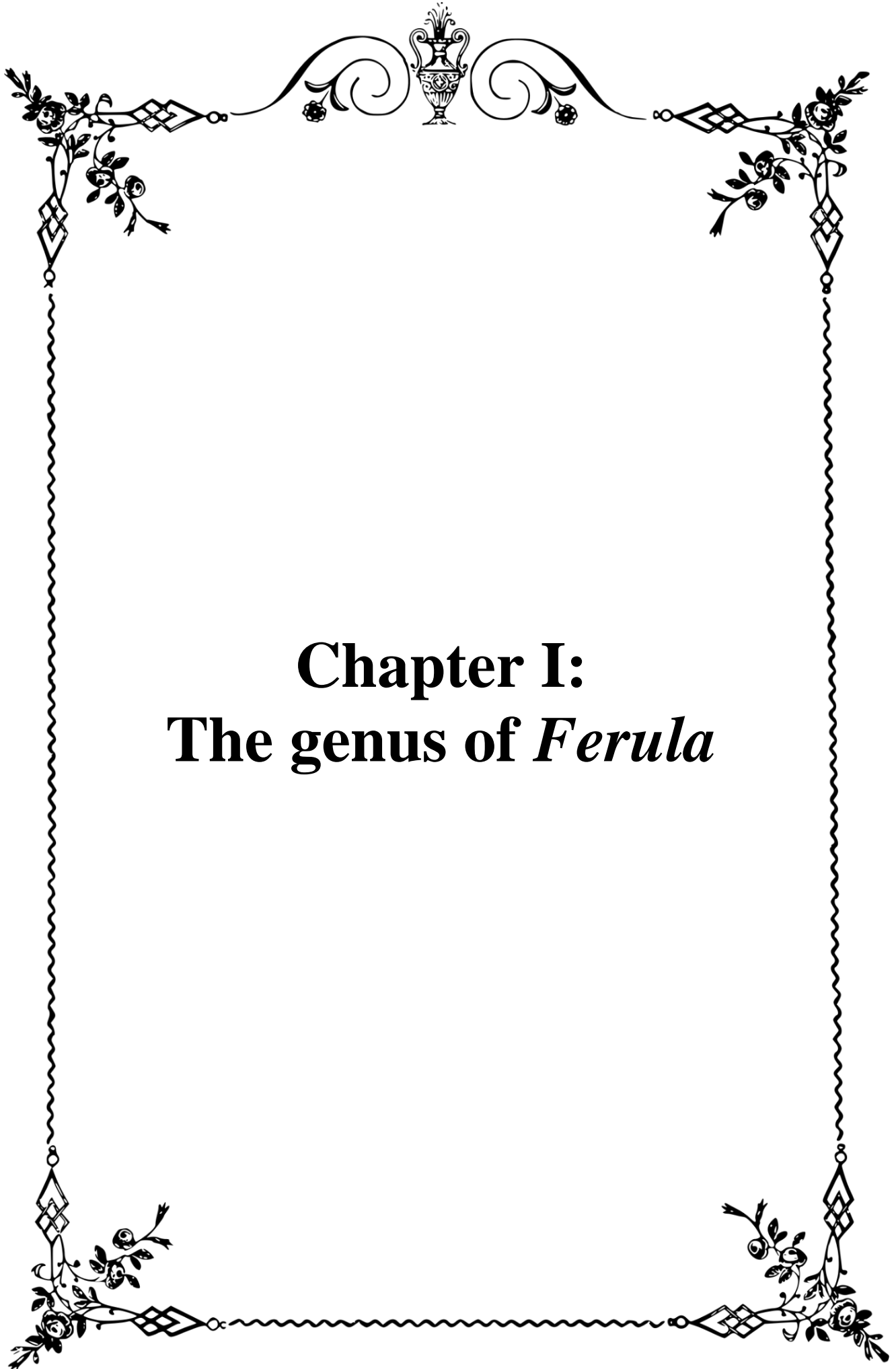
Many of the *Ferula* species have been historically known as a rich source of aromatic resins. The chemical constituents of plants in the genus *Ferula* have been fairly

thoroughly studied, with the most common compounds being sesquiterpenes and sesquiterpene coumarins. As such, many members of the genus have been used in China for the treatment of rheumatoid arthritis and stomach diseases (**Baser *et al.*, 2021**).

Considering the pharmacological and phytochemical significance of the constituents of the genus *Ferula* in traditional medicine, we focused on the phytochemical study and determination of secondary metabolites of the *Ferula L.* genus, belonging to the Apiaceae family, originating from different parts of the world and also in Algeria. Additionally, we evaluated the medicinal properties (biological activities) of the plant extract.

This work is largely divided, in the form of a bibliographic synthesis, and consists of two chapters:

- **The first chapter** we provide detailed botanical study, geographical distributions, chemical compositions, uses, and therapeutic properties of the Apiaceae family and the genus *Ferula*.
- **The second chapter** consists of three main titles:
  - ✓ Secondary metabolites of plants, particularly of the genus *Ferula*.
  - ✓ Chemical compounds of *Ferula* essential oils.
  - ✓ Review of phytochemical study and pharmacological activity of *Ferula* genus.
- We conclude this work with a general conclusion.



**Chapter I:**  
**The genus of *Ferula***

## 1. The genus of *Ferula*

### 1.1. Apiaceae family: Generality

One of the most significant families of flowering plants, the Apiaceae family has 3780 species in 434 genera and was formerly known as the Umbelliferae family (Umbelliferae). It is distributed throughout the world, mostly in the northern temperate regions and high altitudes in the tropics. The main common features of Apiaceae species are aromatic herbaceous nature, alternate leaves with sheathing bases, hollow stems, small flowers, inflorescences determined in simple or compound umbel, and indehiscent fruits or seeds with oil ducts (Sayed-Ahmad *et al.*, 2017).

This large family is a well-known producer of essential oil with therapeutic properties, namely antibacterial, antioxidant, and antifungal activities. Therefore, it is used as a natural preservative for food products (Elghwaji *et al.*, 2017).

This family is also characterized by its richness in secondary metabolites, such as flavonoids, coumarins, iridoids, sterols, acetylenic compounds and lactones, sesquiterpenes, diterpenes, and triterpenes (Tabanca *et al.*, 2006).

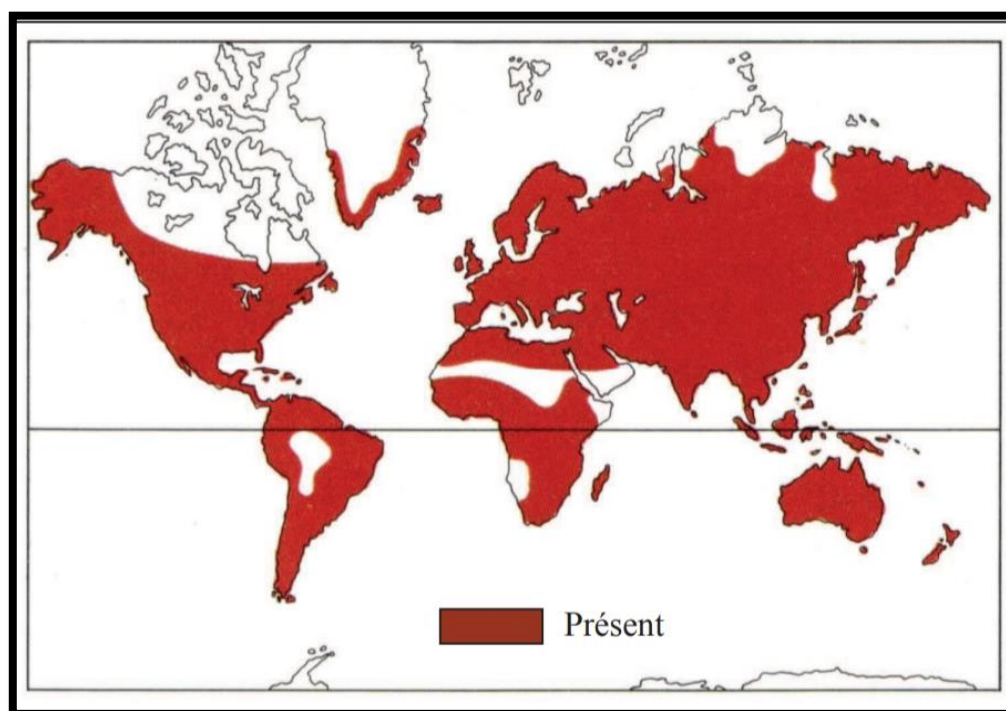


**Figure 1:** Plant of Apiaceae family.

### 1.1.1. Geographic distribution

The Apiaceae family occupies an important place in the Algerian flora where it is represented by 56 genera, 130 species (including 24 endemics), and 26 subspecies (**Quézel & Santa, 1963**).

The species of this family are present worldwide (**figure 2**). But it is most diverse in temperate climatic areas, such as Eurasia and North America. It is quite rare in tropical humid regions where it is limited to high mountains. Mediterranean and arid climatic conditions favor high species diversification (**Reduron, 2021**).



**Figure 2** : Global geographic distribution of Apiaceae (**Djarri, 2011**).

The main genera are *Eryngium*, with 230 species, *Bupleurum*, with 180 species, *Ferula*, with 170 species, *Pimpinella*, with 150 species, *Peucedanum*, with 120 species, *Hydrocotyle*, with 120 species, *Angelica*, with 100 species, *Lomatium*, with 70 species, *Heracleum*, with 65 species and *Apium*, with 25 species (**Bouderdara, 2013**).

The genera are distributed among continents (**Table 1**), with predominance for the Asian continent (**Halimi, 2020**).

**Table 1:** Global distribution of Apiaceae genera (Heywood *et al.*, 1996).

Continent	Genera	Endemic
Africa	126	50
America	197	52
Asia	265	159
Australia	36	11
Europe	139	29

### 1.1.2. Classification

The systematic position of the Apiaceae family according to the Cronquist classification (Cronquist, 1981), is as follows:

<b>Kingdom</b>	Plantae
<b>Subkingdom</b>	Tracheobionta
<b>Division</b>	Magnoliophyta
<b>Class</b>	Magnoliopsida
<b>Subclass</b>	Rosidae
<b>Family</b>	Apiaceae

### 1.1.3. Botanical description

#### 1.1.3.1. Vegetative organs

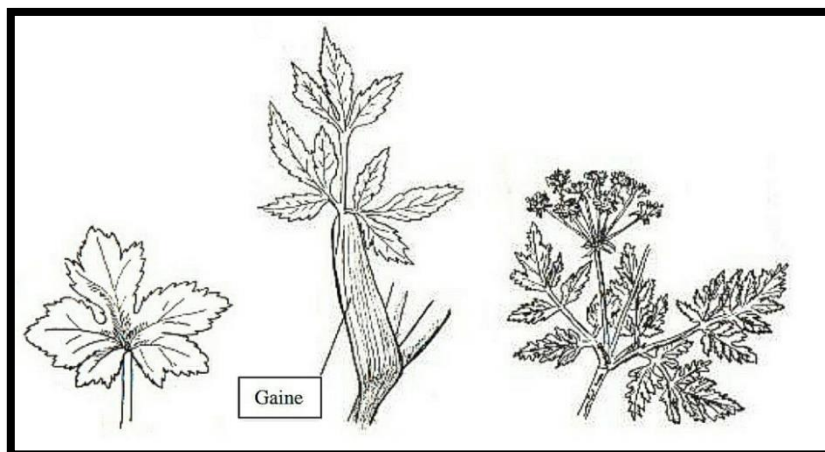
Plants of the Apiaceae family are primarily herbaceous plants that can be annual, biennial, or mostly perennial (Filliat, 2012).

##### 1) The stems

Stems with often hollow internodes; with secretory ducts, containing essential oils resins, triterpene saponins, coumarins, polyacetylenes, monoterpenes and sesquiterpenes monoterpenes and sesquiterpenes; umbelliferose (a trisaccharide) as a reserve material. These stems have lengthwise grooves on the outside (fluted stems) (Djarri, 2011).

## 2) The leaves

The leaves are alternate, compound pinnate or palmate, deeply incised or lobed, entire or serrated. The venation is pinnate to palmate, with petioles that may partially enclose the stem, stipulate, or exstipulate. This type of leaf is referred to as pinnatisect (**Judd *et al.*, 2002**).



**Figure 3 :** Vegetative organs of Apiaceae plants (**Filliat, 2012**).

### 1.1.3.2. Reproductive organs

#### 1) Inflorescence

Inflorescence includes one or more compound umbels, either terminating the stem or terminal, or lateral and opposite the leaves. The inflorescence is rarely reduced to a simple umbel or a capitulum (**Leurquin, 2007**).

#### 2) The flowers

The flowers are usually white and rarely yellowish, greenish, or pink. The simplicity and regularity characterize *Apiaceae*. Therefore, they always have the same floral formula: the calyx consists of five sepals (5S), and the corolla consists of five free petals (5P) of the actinomorphic type. The androecium is composed of five stamens, and the gynoecium or pistil is composed of two carpels (2C) anteroposteriorly fused to the floral cup and forming an inferior ovary. After fertilization, the inferior ovary becomes a diakene or double mericarp (**Aliouche & Aouadj, 2019**).

### 3) Fruits

Fruits are formed by two mericarps attached to a central axis (each mericarp has two faces: commissural (flat) and dorsal (convex)). The dorsal side bears at least five ribs separated by four valleculae containing short secretory ducts (strips) (Coste & Flahault, 1906).

### 4) Ovary

Inferior ovary with generally axial placentation; styles more or less swollen at the base, forming a nectariferous organ (the stylopod) at the apex of the ovary; stigmas generally 2 to 5, reduced, capped to truncated, or elongated (Djarri, 2011).

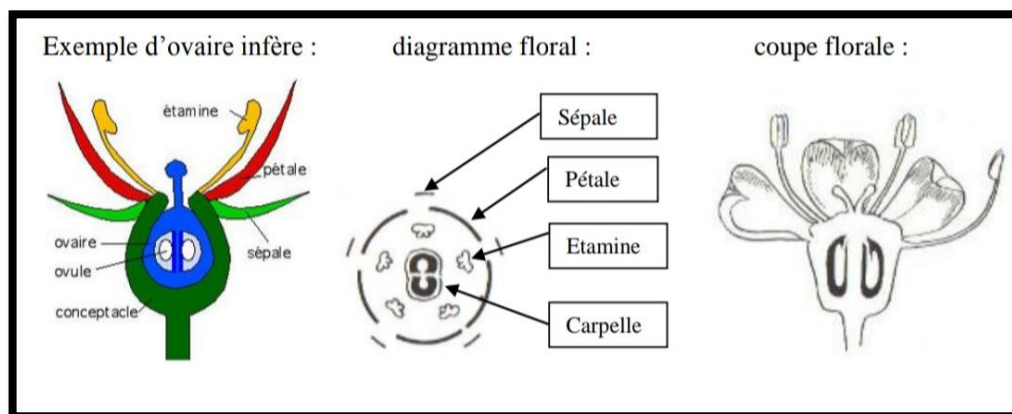


Figure 4 : Reproductive organs of Apiaceae plants (Filliat, 2012).

#### 1.1.4. Utilization of Apiaceae family

The Apiaceae family includes aromatic plants that have significant economic importance. These plants are widely utilized for various purposes such as food, flavoring agents, ornamental plants, medicinal applications, and in industries like food, perfume, pharmaceuticals, cosmetics, and cosmeceuticals. Many Apiaceae plants are spices that have been used for flavoring, seasoning, coloring, and even as preservatives for centuries, particularly in regions like India, China, and Southeast Asian countries (Thiviya *et al.*, 2021).

The Apiaceae family has a rich history of traditional medicinal use, with many species being commonly used in households to treat various health issues. Recent studies have highlighted that several species within this family contain bioactive phytochemicals that possess strong antioxidant, antibacterial, antibiotic, antimicrobial, and anti-inflammatory properties. Additionally, these species have shown potential effects in managing conditions

such as diabetes, cancer prevention, cardiovascular protection, and reducing blood glucose and lipid levels (Thiviya *et al.*, 2021).

Different parts of the Apiaceae plants are generally consumed as vegetables or spices, such as leaves (carrot, fennel, dill, celery, parsley, and coriander), seeds (caraway, cumin, anise, dill, fennel, celery, angelica, and coriander), root (carrot, angelica), and leaf stalks (fennel). Aromatic spices have been traditionally used for the preparation of herbal teas, salads, and flavouring agents in stewed, boiled, grilled, or baked dishes, meat and fish dishes, and ice cream. Some spices from Apiaceae are used as preservative agents in food due to their antioxidant components. Apiaceae is largely produced for its application in foods, pharmaceuticals, perfumes, and cosmetic products (Thiviya *et al.*, 2021).

### 1.1.5. Chemical composition of Apiaceae family

The Apiaceae family is known for its great diversity in secondary metabolites, especially those found in their essential oils. The collection of results from the literature identifies a wide range of coumarins, sesquiterpenes, acetylenic compounds, essential oils, flavonoids, and sesquiterpene lactones for this family. These active principles are the main secondary metabolites of this family. The presence of chromones, chalcones, saponins, and alkaloids has been reported in some species of this family (Bouderdara, 2013).

**Table 2 :** Chemical composition of some Apiaceae species (Thiviya *et al.*, 2021).

Apiaceae	Plant Part Used	Uses	Important Chemical Constituents
Anise ( <i>Pimpinella anisum</i> )	Grains	Condiment or flavor	Phenolic acids including anisic acid, chlorogenic acid isomers, caffeoylquinic acid, flavonoids including rutin, luteolin-7-glucoside, apigenin-7-glucoside, disorienting, other components trans-anethole, estragole, anise ketone caryophyllene, anisaldehyde, linalool, limonene, pinene, acetaldehyde, p-cresol, creosol, hydroquinine, farnasene, camphene, eugenol, acetanisole.
Dill ( <i>Anethum graveolens</i> )	Leaves Grains	vegetale condiment or flavor	Phenolic acids: chlorogenic and benzoic acids, flavonoids: quercetin, kaempferol, myricetin, catechins, isorhamnetin, others carvone, limonene, geraniol, $\alpha$ -phellandrene, p-cymene

Table 2: cont.

Apiaceae	Plant Part Used	Uses	Important Chemical Constituents
Caraway ( <i>Carum carvi</i> )	Root Leaves Grains	Condiment or flavor	Phenolic acids including chlorogenic, p-coumaric, caffeic, and ferulic acid, flavonoids including kaempferol, quercetin, 3-glucuronide, isoquercitrin, volatile compound including limonene, carvone, sesquiterpene, aromatic aldehydes, terpene esters, terpenol, terpenal, terpenon, safranal, tannin.
Parsley ( <i>Petroselinum crispum</i> )	Leaves	Vegetale Condiment or flavor	Phenolic acids: chlorogenic acid, p-coumaric acid, caffeic acid, gallic acid, vanillic acid flavonoids: apigenin, luteolin, kaempferol, myricetin, rutin, quercetin.
Cumin ( <i>Cuminum cyminum</i> )	Grains	Vegetale condiment or flavor	Phenolic acids including quercetin, p-p-coumaric, rosmarinic, vanillic and cinnamic acids, and trans-2-dihydrocinnamic acid others cuminal, cuminaldehyde, linalool, cymene and $\gamma$ -terpenoids, thymoquinone, 3-carene-10-al, $\gamma$ -terpinene, p-cymene and $\beta$ -pinene, pinocarveol, carotol, resorcinol, tannin
Coriander ( <i>Coriandrum sativum</i> )	Leaves Grains	Vegetale condiment or flavor	Phenolic acids including p-coumaric, ferulic, vanillic, chlorogenic, caffeic, and gallic acid, flavonoids including quercetin, kaempferol, acacetin, rutin other linalool, borneol, geraniol, terpineol, cumene, pinene, $\gamma$ -terpinene, limonene, myrcene, camphene, tocopherols, pyrogallol, p-cymol, n-decylaldehyde, acetic acid esters
Fennel ( <i>Foeniculum vulgare</i> )	Leaves Grains	Vegetale condiment or flavor	Phenolic acids: p-coumaric acid, ferulic, quercetin, rosmarinic, tannic, caffeic, gallic, cinnamic, vanillic, ellagic, chlorogenic, and acid, flavonoids: rutin, quercetin, kaempferol, others vitamin C and E, oleoresins, $\beta$ -carotene, $\beta$ -sitosterol, campesterol, eugenol, carnosil, limonene, camphene, $\beta$ -pinene, fenchyl alcohol, anisaldehyde, myristicin, dillapiole

## 1.2. The genus of *Ferula*: Generality

The genus *Ferula* L. belongs to family Apiaceae (Umbelliferae) (Yaqoob & Nawchoo, 2016). These species are used, among other things, as tranquillizers, antispasmodics, or to treat digestive disorders and fertility problems. They are aromatic, like the majority of Apiaceae. Their essential oils are responsible for some of their biological activities. And also, which are used in perfumery and in the food industry (Benmansour, 2020).

Plants of the *Ferula* genus are rich in biologically active secondary metabolites that specifically include sesquiterpene derivatives of daucane types and coumarin sesquiterpenes. In addition, they are known for their richness in gum-oleoresins possessing several biological activities, such as antioxidant, antiviral, antifungal, and antidiabetic activities (Benmansour, 2020).

### 1.2.1. Geographic distribution

The *Ferula* genus comprises nearly 180 species growing worldwide, mainly in arid regions. A total of 130 species are common to the Mediterranean basin and Central Asia where it represents the most abundant genus (177 species) (Pimenov & Leonov, 2004). The endemic and indigenous species of the *Ferula* in the flora of some countries, of which the data are available (Table 3), are listed below (Mohammadhosseini, 2019).

**Table 3:** Some endemic and indigenous species of the genus *Ferula* growing wild in different parts of the world (Mohammadhosseini, 2019).

Country flora	Number	Name
Italy	3	<i>Ferula arrigonii</i> Bocchieri, <i>F. communis</i> L. and <i>F. glauca</i> L.
Iran	15	<i>F. pseudalliacea</i> Rech.f., <i>F. gabriellii</i> Rech.f., <i>F. kashanica</i> Rech.f., <i>F. persica</i> Wild., <i>F. macrocolea</i> (Boiss.) Boiss., <i>F. microcolea</i> (Boiss.) Boiss., <i>F. stenocarpa</i> Boiss. & Hausskn, <i>F. tabasensis</i> Rech.f., <i>F. behboudiana</i> Rech. f. & Esfand, <i>F. lutensis</i> Rech.f., <i>F. assa-foetida</i> L., <i>F. sharifii</i> Rech.f., <i>F. serpentinica</i> Rech.f., <i>F. flabelliloba</i> Rech. f. & Aell. and <i>F. xylorhachis</i> Rech.f.
Turkey	9	<i>F. amanicola</i> Hub.-Mor. Et Pesmen, <i>F. anatolica</i> (Boiss.) Boiss., <i>F. drudeana</i> Korovin, <i>F. halophila</i> Pesmen, <i>F. huber-morathii</i> Pesmen, <i>F. longipedunculata</i> Pesmen, <i>F. lycia</i> Boiss., <i>F. parva</i> Freyn et Bornm. and <i>F. tenuissima</i> Hub.-Mor. et Pesmen

**Table 4:** cont.

Country flora	Number	Name
Tunisia	4	<i>F. communis</i> L., <i>F. tingitana</i> L., <i>F. tunetana</i> Pomel ex Batt. and <i>F. lutea</i> (Poir.) Maire
Pakistan	15	<i>F. assa-foetida</i> L., <i>F. baluchistanica</i> , <i>F. communis</i> L., <i>F. costata</i> , <i>F. hindukushensis</i> , <i>F. jaeschkeana</i> Vatke, <i>F. kokanica</i> Rgl. et Schmalh., <i>F. lehmannii</i> Boiss., <i>F. microloba</i> Boiss., <i>F. narthex</i> (Falc.) Drude, <i>F. oopoda</i> (Boiss. Et Buhse) Boiss., <i>F. ovina</i> Boiss., <i>F. reppiae</i> , <i>F. rubicaulis</i> , and <i>F. stewartiana</i>
Saudi Arabia	4	<i>F. communis</i> var. <i>communis</i> L./var. <i>glauca</i> (L.) Rouy and Camus, <i>F. ovina</i> (Boiss.) Boiss., <i>F. rutbaensis</i> C.C. Townsend. And <i>F. sinaica</i> Boiss
India	3	<i>F. narthex</i> (Falc.) Drude, <i>F. thomsoni</i> and <i>F. jaeschkeana</i> Vatke

Algeria, in turn, has several species of *Ferula* (**Table 4**). The most common species in northern Algeria is *F. communis* (**Dehak, 2012**).

**Table 4 :** Species of the genus *Ferula* found in Algeria (**Dehak, 2012**).

Species	Biotops
<i>F. communis</i>	Tell Atlas
<i>F. cossoniana</i>	Highlands
<i>F. lutea</i>	Tell Atla
<i>F. Tingitana</i>	Northern Sahar
<i>F. vesceritensis</i>	Eastern part of Saharn Atlas and Northern sahara of Mzab
<i>F. assafoetida</i>	Highlands
<i>F. sulcata</i>	Kabylia ( <b>new Species</b> )
<i>F. loscossii</i>	Southern part of south Algeria ( <b>new Species</b> )

### 1.2.2. Systematic position of the genus *Ferula* (APG III classification, 2009)

The APG III classification (2009), or phylogenetic classification, is the third version of the botanical classification of angiosperms established by the Angiosperms Phylogeny Group. The position of the Apiaceae family, including the genus *Ferula*, in this classification system is as follows:

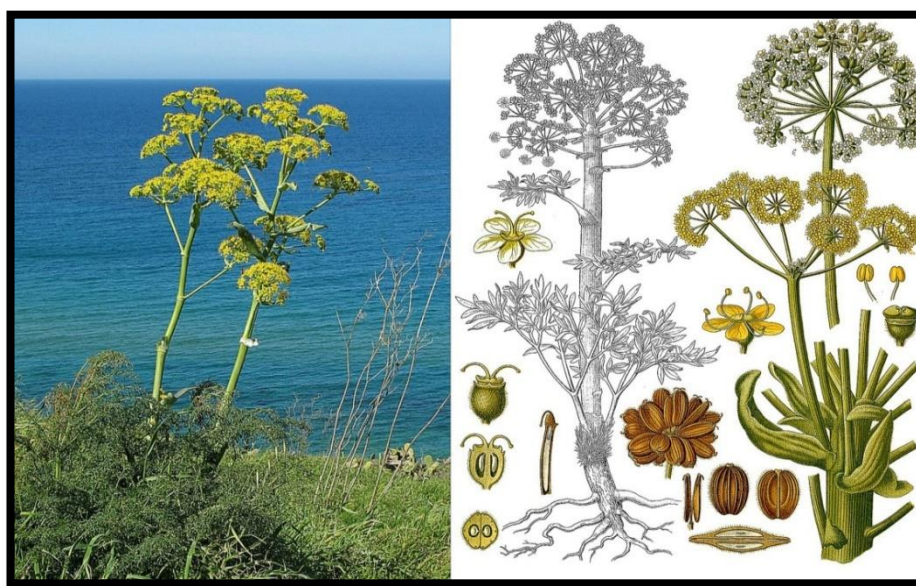
<b>Phylum</b>	Angiosperms
<b>Class</b>	Eudicots
<b>Subclass</b>	Asterids
<b>Superorder</b>	Campanulids
<b>Order</b>	Apiales
<b>Family</b>	Apiaceae
<b>Genus</b>	<i>Ferula</i>

### 1.2.3. Botanical description

*Ferula* plant is a perennial shrub that can reach up to two meters in height, with very rapid growth: (in a matter of weeks), a stem erect 1-3 m (Quézel & Santa, 1963).

The fruit is oval or oblong, flattened on the back, smooth, and surrounded by a flat border; the mericarps have five ribs, the three dorsal ones thin and equal, the two marginal ones expanded into a flattened wing; the vittae are made up of several small strands, the carpophore is free, bifid, and the seeds have a flat commissural face (Coste & Flahault, 1906).

The leaves are all composed of linear strips. The flowers are yellow, arranged in umbels with 5-40 rays, with the lateral ones smaller than the central one and often sterile. The involucre is absent or consists of several leaflets. The calyx has 5 teeth, and the petals are oval, pointed, entire, with an upward or inwardly curved tip. The styles are spreading or reflected (Alkhatib, 2010).



**Figure 5 :** Natural and schematic pictures of *Ferula* species (Sahebkar & Iranshahi, 2010).

### 1.2.4. The species of *Ferula* genus

#### 1.2.4.1. *Ferula Communis* L.

Common *Ferula* is a perennial, glabrous plant, with a stem very robust, wide (3-7 cm. in diameter), Full, finely striated and can grow to 2 to 3 metres high .Its soft leaves are divided into multiple narrow leaflets: the lower leaves are petiolate, measuring up to 60 cm in length, and the upper leaves have a large boat-shaped sheath. The fruit, which appears in July-August and is dark brown at maturity, is formed by two mericarps measuring 10 to 15 mm in length, flattened and each traversed by five non-prominent filiform ridges. The terminal fertile umbel is large and composed of 20 to 40 rays. The flower is bright yellow, *Ferula communis* is widespread in Algeria (Lamnauer & Batanouny, 2005; Hammiche *et al.*, 2013).



Figure 6 : *F. communis* L (<https://www.phrygana.eu>).

#### 1.2.4.2. *Ferula Vesceritensis*

A perennial plant that can grow over 1 meter tall under favorable climatic conditions (Chehma, 2019). In summer, it is represented only by a rigid hollow stem. Leaves with elongated, straight divisions. Green flowers with wide petals bearing hairs on their dorsal nerves. Oval fruits with pointed tips and carried by peduncles shorter than themselves (Bouchouka, 2016).



**Figure 7:** *F. vesceritensis* Coss. Et DR (Chehma, 2019).

#### 1.2.4.3. *Ferula Lutea*

*Ferula Lutea* (Poir.) Maire is a herbaceous plant with highly divided leaves (in leaflets) that have a sheathing base and a blade. The mericarps have non-prominent filiform ribs, and the pedicels of the ripe fruits are approximately twice their length (2-3 cm). The leaves are finely and shortly divided, linear and pointed, ash-green, rough, and slightly hispid. The flowers are yellow, like all umbellifers, hermaphrodite and always very small, generally grouped at the apex in a very characteristic inflorescence that gave its name to the entire family, the “umbel”. The flower itself bears five sepals, five petals, and five stamens, two carpels that give rise, at maturity, to a “diachaine”, or double fruit, very recognizable by its stem reaching 1-3 meters. The umbels have 10 to 15 rays (Rahmouni, 2021).



**Figure 8 :** *F. lutea* (Poiret) Maire (Rahmouni, 2021).

#### 1.2.4.4. *Ferula Tingitana*

Also known as the “Tangier *Ferula*,” *Ferula tingitana* is a biennial herbaceous plant with a stem that can reach up to 3 meters high, and its leaves are divided into leaflets cut approximately like those of parsley site. The fruits have very short pedicels (**Quézel & Santa, 1963**).



**Figure 9:** *F. tingitana* L. (<http://www.freenatureimages.eu>).

#### 1.2.4.5. *Ferula Cossoniana*

This name is a synonym of *Ferula longipes* *cos*, perennial, the stems of 5-12 decimeters, highly branched with long, divergent branches; the pedicels of ripe fruits are about twice their length (2-3 cm). Its leaves are ash green, scabrous, and shortly hispid, with very short linear divisions (**Quézel & Santa, 1963**).



**Figure 10 :** *F. Cossoniana* Batt. Et Trab. (<https://www.teline.fr>).

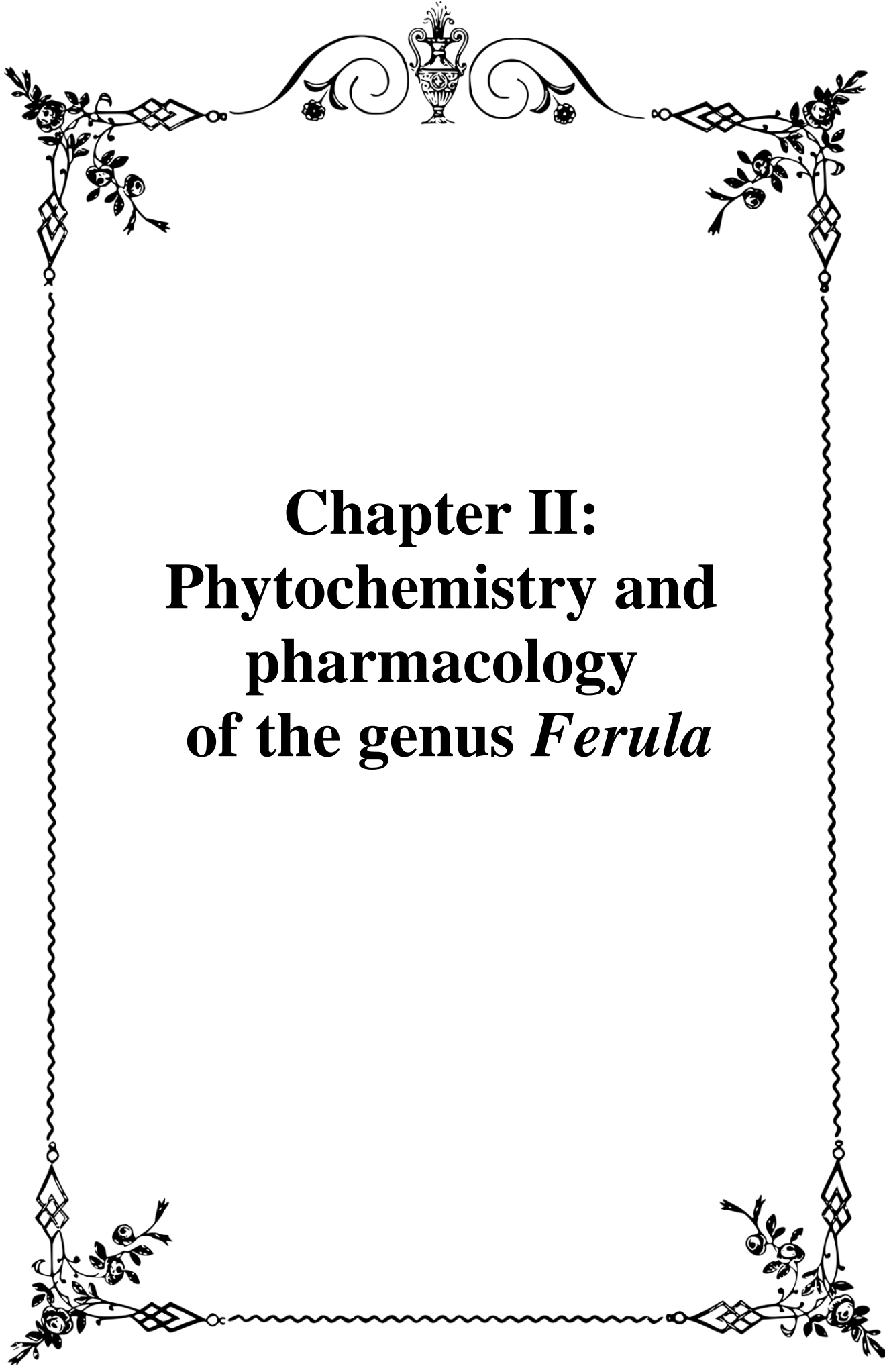
#### 1.2.4.6. *Ferula Assafoetida* L.

*Ferula assafoetida* L. Is a medicinal plant belongs to the Apiaceae family, and is a herbaceous perennial with an unpleasant odor that grows to about 2 m in height. The oleo-gum resin is often obtained by incision of the roots or removal of the stems (**Iranshahy & Iranshahi, 2011**).

*F. assafoetida* have a circular mass of 30-40 cm leaves. The stem leaves have wide sheathing petioles. Flowering stems are 2.5-3 m High and 10 m thick and hollow. These flowering stems have several schizogenous ducts in the cortex containing resinous gums. The flowers are small and dirty yellow colored produced in large compound umbels. Fruits of this plant are oval, thin, flat, reddish brown and Contain a milky substance. Roots are thick, massive and pulpy. The foul odor comes from the resin gum extracted from the stems and roots (**Kareparamban et al., 2012**).



**Figure 11:** *F. assa-foetida* L. (<https://www.teline.fr>).



**Chapter II:**  
**Phytochemistry and**  
**pharmacology**  
**of the genus *Ferula***

## 2. Phytochemistry and pharmacology of the genus *Ferula*

### 2.1. Secondary metabolites

#### 2.1.1. Definition

Plants synthesize organic molecules that play no role in nutrient assimilation or the growth and development of the plant. These compounds are called secondary metabolites (Hopkins, 2003).

Secondary metabolites are present in all higher plants (Wink, 2003), they are natural substances produced in small quantities in plants (Ali *et al.*, 2013). And microorganisms such as bacteria and fungi (Troppens *et al.*, 2013).

These compounds are important not only because of their role in plants but also for their biological properties such as antioxidant, antimicrobial, and anticarcinogenic effects, as well as their therapeutic effects against several diseases, including hypertension, diabetes, and obesity (Aires *et al.*, 2013).

#### 2.1.2. Classification

Secondary metabolites extracted from plants are subdivided into three major classes: phenolic compounds, terpenoids, and alkaloids (Kabera *et al.*, 2014).

Each of these classes contains a wide variety of compounds that possess a broad range of activities in human biology. They have significant economic value, particularly for the pharmaceutical and cosmetic industries (Behih & Ben Amrouche, 2017).

##### 2.1.2.1. Phenolic Compounds

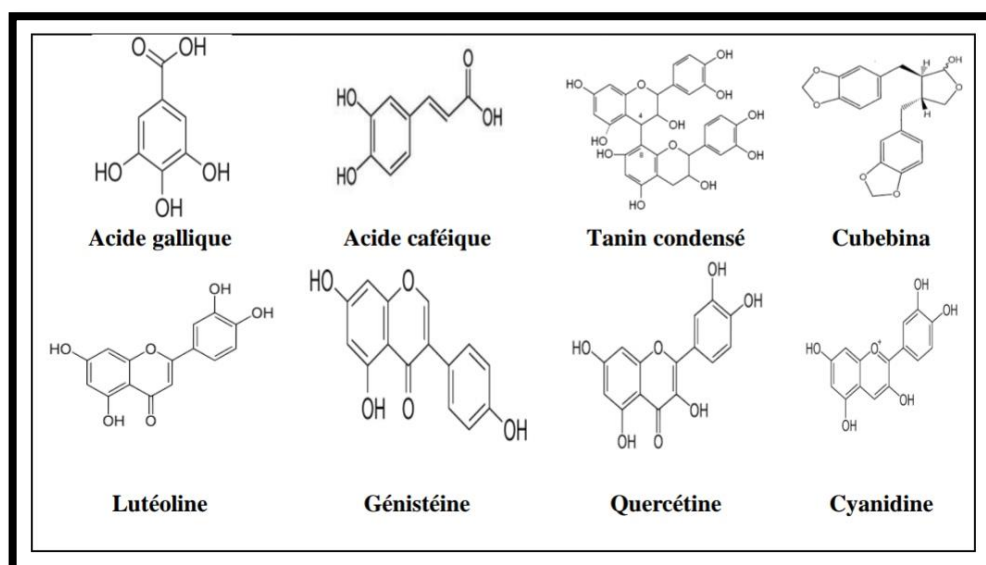
Phenolic compounds (polyphenols) constitute a vast group of substances that are difficult to define simply. The fundamental structural element that characterizes them is the presence of at least one benzene ring directly linked to at least one hydroxyl group, either free or engaged in another function such as ether, ester, glycoside, etc. (Bruneton, 2009).

Phenolic compounds have many beneficial effects on health, mainly due to their antioxidant, antimicrobial, and anticancer properties (Djedida, 2017).

Phenolic compounds present in the plant kingdom are classified into three families based on their aromatic skeleton: phenolic acids, coumarins, and flavonoids. These compounds are further categorized into groups based on the number of carbon atoms in the molecule (Vermeris & Nicholson, 2006).

**Table 5 :** Classification of phenolic compounds (Vermerris & Nicholson, 2006).

Structure	Class
C6	Simple phenolics
C6 – C1	Phenolic acids and related compounds
C6 – C2	Acetophenones and phenylacetic acids
C6 – C3	Cinnamic acids, cinnamyl aldehydes, cinnamyl alcohols
C6 – C3	Coumarins, isocoumarins, and chromones
C15	Chalcones, aurones, dihydrochalcones
C15	Flavans
C15	Flavones
C15	Flavanones
C15	Flavanonols
C15	Anthocyanidins
C15	Anthocyanins
C30	Biflavonyls
C6-C1-C6, C6-C2-C6	Benzophenones, xanthenes, stilbenes
C6, C10, C14	Quinones
C18	Betacyanins
Lignans, neolignans	Dimers or oligomers
Lignin	Polymers
Tannins	Oligomers or polymers
Phlobaphenes	Polymers



**Figure 12:** Structure of phenolic compounds of plants (Latri *et al.*, 2022).

### 2.1.2.2. Terpenoids

Terpenoids constitute a large family of phytoconstituents of little functional and structural common ground. They are composed of the most important group of active compounds in plants with over 23,000 known structures (Kabera *et al.*, 2014). Terpenoids are the hydrocarbons of plant origin of the general formula  $(C_5H_8)_n$  as well as their oxygenated, hydrogenated and dehydrogenated derivatives (Yadava *et al.*, 2014).

The number of isoprene units defines the different classes of terpenes: monoterpenes (C<sub>10</sub>), sesquiterpenes (C<sub>15</sub>), diterpenes (C<sub>20</sub>), sesterterpenes (C<sub>25</sub>), triterpenes (C<sub>30</sub>), and tetraterpenes (C<sub>40</sub>). Simple terpenes with C<sub>10</sub> and C<sub>15</sub> are likely to have appeared later in evolution and are characteristic of vascular plants that have developed secretory structures. They can be classified based on the value of n or the number of carbon atoms present in the structure (Yadava *et al.*, 2014).

**Table 6 :** Classification of terpenoid (Yadava *et al.*, 2014).

Class	Value of n	Number of carbon atoms
Monoterpenoids (C <sub>10</sub> H <sub>16</sub> )	2	10
Sesquiterpenoids (C <sub>15</sub> H <sub>24</sub> )	3	15
Diterpenoids (C <sub>20</sub> H <sub>32</sub> )	4	20
Sesterpenoids (C <sub>25</sub> H <sub>40</sub> )	5	25
Troterpenoids (C <sub>30</sub> H <sub>48</sub> )	6	30
Tetraterpenoids (C <sub>40</sub> H <sub>64</sub> )	8	40
Polyterpenoids (C <sub>5</sub> H <sub>8</sub> ) <sub>n</sub>	>8	40

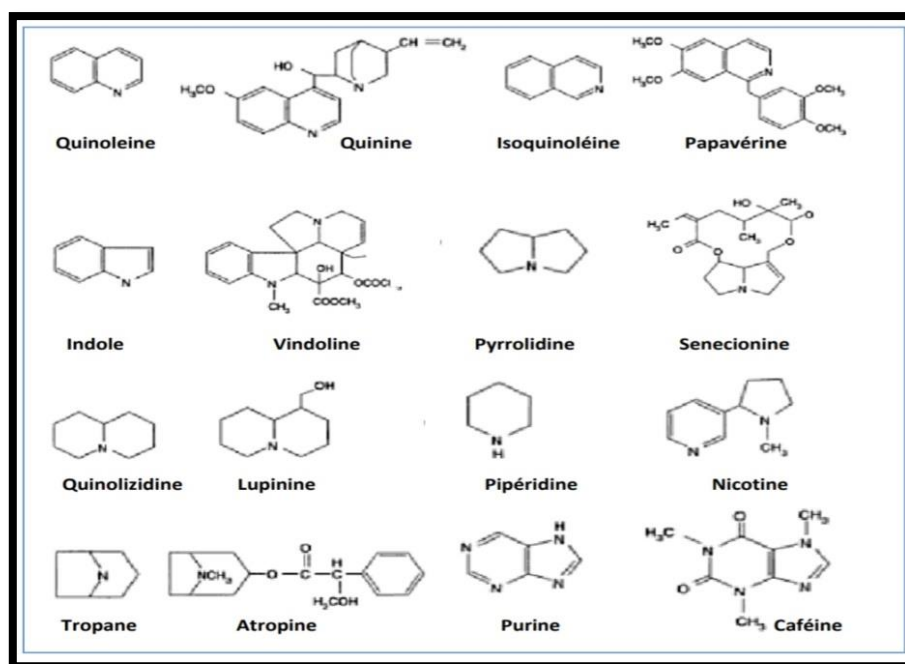
### 2.1.2.3. Alkaloids

An alkaloid is a naturally occurring compound, typically of plant origin, that is nitrogenous and more or less basic. Alkaloids have limited distribution and exhibit biological activity at low doses. Their classification as alkaloids is confirmed by common precipitation reactions with general alkaloid reagents (**Djermane, 2014**).

Most alkaloids, which represent the active principles of many medicinal or toxic plants, are used in several medications (morphine, quinine, cocaine, atropine, codeine, caffeine, ephedrine, etc.). They also have remarkable physiological effects on the nervous system (antispasmodic, mydriatic, local anesthetic) (**Zenk & Juenger, 2007**).

There are three main categories of alkaloids:

- **Pseudoalkaloids:** They do not contain intr-acyclic nitrogen, and nitrogen incorporation into the structure occurs in the final phase. An example is the coniine.
- **Protoalkaloids:** Nitrogen is not included in a heterocyclic system. They are derived from amino acids. Examples include mescaline, hordenine, and colchicine.
- **True alkaloids:** They are classified based on their cyclic structure. The nitrogen atom is included in a heterocycle. True alkaloids are formed through the biosynthesis of amino acids and possess significant pharmacological activity (**Djermane, 2014**).



**Figure 13:** Classes and exemples of alkaloids (**Djermane, 2014**).

## 2.2. Essential oils

### 2.2.1. Definition

Numerous authors have attempted to define essential oils. AFNOR (French Association for Standardization) provides the following definition (Standard NF T 75-006): « Essential oil is the product obtained from a plant-based raw material, either by steam distillation, or by mechanical processes from the epicarp of citrus fruits, or by ‘dry’ distillation. The essential oil is then separated from the aqueous phase by physical processes » (Afnor, 2000).

Essential oils are important aromatic components of herbs and spices, and their biological activities have been known and utilized since ancient times in perfumery, food preservation, flavoring, and medicine. The antimicrobial activities of essential oils indicate their unique antibacterial, antifungal, and antiviral properties (Herman, 2019).

These volatile compounds have the property of solubilizing in oils and grease, which is why they have empirically been given the name « essential oil. » The term « oil » emphasizes the viscous and hydrophobic nature of these substances, while the term « essential » refers to the plant’s main characteristics expressed through its exhalations (Menaceur, 2015).

### 2.2.2. Localization of essential oils in the plants

Essential oils are often located on or near the surface of the plant. They can be stored in various plant organs:

- Flowers (Orange, rose, lavender, mint)
- Leaves (Eucalyptus, mint, thyme, bay leaf, sage, pine needles, basil)
- Underground organs: roots, rhizomes (Ginger)
- Fruits (Fennel, pepper, citrus peels)
- Seeds (Nutmeg, coriander)
- Wood and bark (Cinnamon, camphor, rosewood) (Bounab, 2020).

### 2.2.3. The physico-chemical properties of essential oils

Essential oils form a relatively homogeneous group in terms of their physical properties:

- They are generally mobile liquids.
- They are volatile, which distinguishes them from greasy oils (« fixed oil »).

- The color ranges from colorless to light brown, except for Chamomile essential oil, which is blue-green, And Patchouli oil, which also has a similar color.
- The density is generally lower than that of water (ranging from 0.850 to 0.950), except for Cinnamon, Clove, and Sassafras essential oils. The dense is Wintergreen essential oil.
- The boiling point is always above 100°C.
- Essential oils are soluble in greases and non-polar solvents. Their solubility varies in different concentrations of alcohols, and they have very slight solubility in water, around 0.30 to 0.50%.
- They exhibit optical activity (rotatory power) and often have a high refractive index
- They oxidize in the presence of light and resinify as they absorb oxygen, causing changes in their odor, increased boiling point, and decreased solubility.
- They can absorb chlorine, bromine, and iodine with the release of heat. They can also combine with water to form hydrates.
- The lipophilicity of essential oils allows them to pass through physiological membranes, particularly through the skin. A famous experiment showed that applying Eucalyptol on the soles of the feet results in a smell of Eucalyptus on the breath shortly later (**Toulba, 2017**).

#### **2.2.4. The Chemical composition of essential oils**

The chemical composition of essential oils is complex and can vary depending on the plant organ, climatic factors, soil nature, cultural practices, and extraction method. Essential oils are a mixture of constituents belonging to three categories of compounds (**Chalabi, 2017**). In general, the constituents in essential oils are terpenes (monoterpenes and sesquiterpenes), aromatic compounds (aldehyde, alcohol, phenol, methoxy derivative, and so on), and terpenoids (isoprenoids) for diterpenes, triterpenes, and tetraterpenes, they have the larger molecule than monoterpenes and sesquiterpenes, but they are present at very low concentration in essential oils (**Tongnuanchan & Benjakul, 2014**).

##### **2.2.4.1. Terpenes**

Terpenes form structurally and functionally different classes. They are made from combinations of several 5-carbon-base (C<sub>5</sub>) units called isoprene. The biosynthesis of the terpenes consists of the synthesis of the isopentenyl diphosphate (IPP) precursor, repetitive addition of IPPs to form the prenyldiphosphate precursor of the various classes of terpenes, modification of the allylic prenyldiphosphate by terpene specific synthetases to form the

terpene skeleton and finally, secondary enzymatic modification (redox reaction) of the skeleton to attribute functional properties to the different terpenes. The main terpenes are the monoterpenes (C<sub>10</sub>) and sesquiterpenes (C<sub>15</sub>), but Hemiterpenes (C<sub>5</sub>), diterpenes (C<sub>20</sub>), triterpenes (C<sub>30</sub>) and tetraterpenes (C<sub>40</sub>) also exist. A terpene containing oxygen is called a terpenoid (**Bakkali *et al.*, 2008**).

### 1) Monoterpenes

These are molecules with 10 carbon atoms, and they exist in the form of simple hydrocarbons that can be acyclic (myrcene, ocimene), monocyclic (p-cymene,  $\alpha$ -terpinene), or bicyclic (camphene, pinene). In addition to hydrocarbons, various oxygenated derivatives are also found: aldehydes (linalool, geranial, etc.), alcohols (citronellol, geraniol, etc.), acids (linoleic acid, etc.), and even esters (linalyl acetate, etc.) (**Menaceur, 2015**)

### 2) Sesquiterpenes

They are formed by the assembly of three isoprene units (C<sub>15</sub>H<sub>24</sub>), and the extension of the chain increases the number of cyclizations, allowing for a wide variety of structures. Examples of plants containing these components are Angelica, Bergamot, Wild Celery, Celery, Lemongrass, Coriander, Eucalyptus, Geranium, Juniper, Lavender, Lemon, Mandarin, Mint, Peppermint, Petitgrain, Pine, Rosemary, and Thyme. They contain more than 3000 molecules, such as  $\beta$ -caryophyllene,  $\alpha$ -humulene,  $\alpha$ -bisabolol, and farnesol (**Boucekrit, 2018**).

#### 2.2.4.2. Aromatic Compounds

They are most commonly found in essential oils from the Apiaceae family (such as Parsley, anise, fennel, etc.) and are characteristic of essential oils like clove, vanilla, cinnamon, basil, Tarragon, etc. (**Laib & Megag, 2020**).

#### 2.2.4.3. Phenylpropanoids

These substances are very common in the Apiaceae and make up the majority of essential oils. Examples include Pimpinella anisum (anethole), Apium petroselinum (apiol) and Foeniculum vulgare (foeniculin), etc. (**Ould Beziou & Mechter, 2019**).

#### 2.2.4.4. Derive

Due to their extraction method, essential oils can contain various aliphatic compounds, usually of low molecular weight, that can be carried over during hydrodistillation. These compounds can be nitrogenous or sulfur-containing (**Chalabi, 2017**).

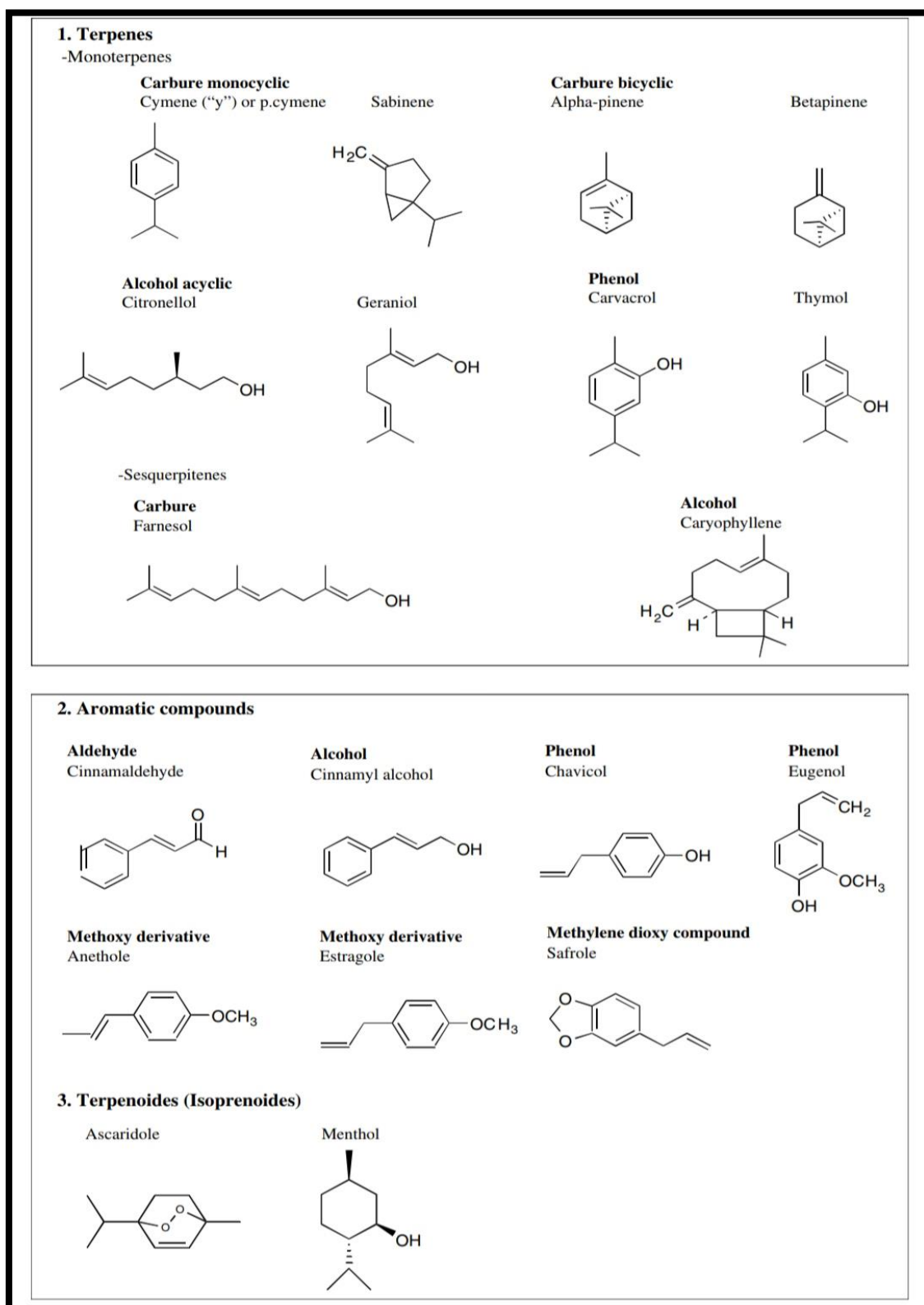


Figure 14: Chemical structures of selected components of essential oils (Bakkali *et al.*, 2008).

### 2.3. Secondary metabolites of *Ferula* genus

The genus *Ferula* has been studied for several years. Numerous studies have been conducted on the secondary metabolites synthesized by different parts of the species belonging to this genus (Youmbai, 2015).

The genus of *Ferula* is a rich source of coumarins, particularly sesquiterpene coumarins found in various species Such as *F. sinaica*, *F. sumbul*, *F. assa-foetida*, *F. persica*, *F. sinkiangensis*, *F. teterrima*, *F. Vesceritensis*, *F. sinaica*, *F. szowitsiana*, *F. latisecta*, *F. persica* Boiss, and *F. narthex* Bioiss (Salehi *et al.*, 2019).

Sesquiterpene coumarins found in the *Ferula* genus have been associated with various biological activities such as anti-HIV, anti-tumor promoting, urease inhibitory, cytotoxicity, antibacterial, antiviral, P-glycoprotein inhibitory, and anti-inflammatory effects. These coumarins have a common coumarin group and a sesquiterpene moiety in their structures (Salehi *et al.*, 2019).

*Asafoetida*, a commonly used *Ferula* species, contains resin, gum, and essential oil. The resin fraction consists of ferulic acid, coumarins, and sesquiterpene coumarins, while the gum contains sugars, polysaccharides, and glycoproteins. *F. assafoetida* roots have the highest accumulation of terpenoids, including  $\beta$ -pinene,  $\alpha$ -pinene,  $\gamma$ -elemene,  $\beta$ -maaliene, and  $\alpha/\beta$ -eudesmol. *Galbanum*, another *Ferula* Species, contains terpenes and gums. A study on genes involved in terpene biosynthesis could help to manipulate valuable industrial and pharmaceutical compounds of *Ferula* species (Salehi *et al.*, 2019).

#### 2.3.1. Coumarin derivatives

##### 2.3.1.1. Hemiterpene coumarins

Several coumarin derivatives were identified within a methanol extract obtained from the dried roots of *F. sumbul* (Kauffm.) Hook.F. These derivatives include two furanocoumarin esters, namely fesumtuorin A and fesumtuorin B, along with a bicoumarin known as fesumtuorin C. Additionally, the extract contained five spirobicoumarins: fesumtuorin D, fesumtuorin E, fesumtuorin F, fesumtuorin G, and fesumtuorin H. Furthermore, nineteen previously known coumarins were also present in the extract (Pandita & Pandita, 2021).

##### 2.3.1.2. Monoterpene coumarins

Monoterpenes, which are also referred to as C (10) isoprenoids, form a diverse group of natural compounds commonly found in aromatic plant essential oils and defensive

oleoresins. They are widely recognized for their presence in these substances. In another study conducted by **El-Razek et al. (2001)**, researchers successfully isolated two monoterpene coumarins, specifically ferulagol A and ferulagol B, from a dichloromethane extract derived from *F. ferulago L.*

### 2.3.1.3. Sesquiterpene coumarins

sesquiterpene coumarin is the characteristic bioactive composition of herbs from *Ferula* genus (**Li et al., 2018**).

From the ethyl acetate extract, a total of six sesquiterpenoids, namely pallidones A–F, were discovered. These sesquiterpenoids were accompanied by two previously identified sesquiterpenes, feselol and conferol, which have been previously observed in various *Ferula* species (**Su et al., 2000**).

The roots of *F. pallida* Korovin were used to extract compounds. The study also examined the potential biogenetic pathway of sesquiterpene coumarins, specifically pallidones A and B. It was proposed that a common biosynthetic precursor for pallidones A–F and other sesquiterpene coumarins is 2-hydroxy-4-methoxycinnamic acid. Two potential pathways were suggested: one involving cyclization to form the coumarin skeleton, and the other involving the addition of water to a double bond, followed by oxidation of the hydroxyl group to generate the appropriate intermediate. Both pathways involve condensation reactions with the corresponding sesquiterpene derivative. (**Su et al., 2000**).

### 2.3.2. Terpenoids

Terpenoids (or isoprenoids) are a large and diverse class of naturally occurring organic chemical compounds found in all classes of living things that can be assembled and modified in thousands of different ways; they are the most abundant group of natural products (**Ghosh, 2020**).

Terpenoid compounds make up the majority of *Ferula* secondary metabolites (SMs). *F. gummosa* and *F. assa-foetida* terpene biosynthesis genes were identified using a transcript profile study combined with metabolite analysis. These datasets are invaluable resources for metabolic engineering of *Ferula* species' terpene biosynthesis pathways. Several SSR motifs linked to unigenes putatively encoding terpene biosynthesis enzymes have been identified in *F. gummosa*, which are likely valuable genetic resources for future *Ferula* species research. In terms of terpene biosynthesis, the roots of *Ferula* species are more active than other organs, and the root tissues of *Ferula* species are a better host for endophytes than the leaf and stem tissues. As a result, the production of SMs using (**Kuete, 2013**).

### 2.3.3. Flavonoids

Flavonoids are naturally occurring polyphenolic compounds found in fruits, vegetables, grains, bark, roots, stems, flowers, tea, and wine. The health benefits of these natural products are well known, and efforts are being made to isolate the ingredients known as flavonoids. Flavonoids are now widely recognised as an important component in numerous nutraceuticals, pharmaceutical, medicinal, and cosmetic applications. This is due to their anti-oxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic properties, as well as their ability to modulate key cellular enzyme function (**Panche *et al.*, 2016**). They are plant extracts found in different parts of the plant. Flavonoids are low-molecular-weight phenolic compounds found throughout the plant kingdom. Vegetables use them for growth and defence. Plaques should be avoided. They are a distinct class of compounds found in higher plants (**Havsteen, 2002**).

Flavonoids are a type of secondary metabolite found in plants that are distinguished by their chemical structure, which consists of a 15-carbon skeleton with two aromatic rings (A and B rings) connected by a three-carbon bridge (C ring). Flavonoids differ due to variations in the substitution pattern and functional groups attached to the basic structure. Flavonoids are classified into two major groups based on the degree of central heterocyclic ring saturation (**Saini *et al.*, 2017**).

Some *Ferula* species may contain flavonoids; it is not a characteristic unique to the genus. The flavonoid content and composition can vary among different species within the *Ferula* genus and among different parts of the same plant. Therefore, it's important to consider specific species and sources when discussing flavonoids within the *Ferula* genus (**Deveci *et al.*, 2018**).

Within the *Ferula* genus, various species have been reported to contain flavonoids. Here are a few examples:

*Ferula gummosa*: A study published in the Journal of Essential Oils Research analyzed the chemical composition of *Ferula gummosa*, a species native to Iran. The researchers identified several flavonoids, including quercetin and kaempferol derivatives, as major constituents of the plant extract (**Hassanzadeh-Khayyat *et al.*, 2011**).

*Ferula communis*: In a study published in the official journal of the societa botanica italiana, the chemical composition of *Ferula communis*, a species found in the Mediterranean region and Asia, was examined. The researchers reported the presence of flavonoids, including quercetin and phenols (**Rahali *et al.*, 2018**).

*Ferula narthex*: A research article in the Journal of Herbs, Spices & Medicinal Plants investigated the flavonoid content of *Ferula narthex*, commonly known as *Asafoetida*. The study found the presence of various flavonoids, including quercetin and rutin (**Ozturk et al., 2013**).

#### 2.3.4. Sulfur compounds

Plant metabolites containing sulfur have a variety of structures, ranging from primary metabolites like sulfur-containing amino acids to secondary metabolites like glucosinolates. Only the genus *Ferula* has reported sec-Butyl disulfide derivatives (**Iranshahi, 2012**). Other *Ferula* species have also been found to contain sulfur-containing compounds:

Two studies analyzed the volatile oil composition of *F. assa-foetida* seeds from Iran and *assa-foetida* oleogum resin from Pakistan. In the seed analysis, 25 known components were identified, accounting for 94.0% of the total oil. Sulfur-containing compounds were the major group (53.5%), followed by monoterpene and sesquiterpene hydrocarbons. The main constituents included various disulfides and terpenes. In the resin analysis, 93 compounds representing 92.3% of the oil were identified, with sulfur-containing compounds (78.5%) being dominant. The main components were asa disulfides and pinenes (**Sahebkar & Iranshahi 2011**).

Sulfur-containing heterocyclic compounds, foetithiophene C, Foetithiophene D, foetithiophene E and foetithiophene F, were also obtained from the roots of *F. foetida* Regel (petroleum ether extract) (**Mohammadhosseini et al., 2019**).

Sulfur compound, persicasulfide A, B, C, F. was isolated from the roots of *Ferula persica* (**Iranshahi et al., 2009**).

#### 2.3.5. Sesquiterpenes

**Chen et al., (2000)** isolated five daucane-type sesquiterpenes, kuhistanicaol A, kuhistanicaol B, kuhistanicaol C, kuhistanicaol D and kuhistanicaol G from the methanol extract of the air-dried of stems and roots of *F. kuhistanica* Korovin. An eudesmanolide and a carotene derivative were isolated from a methanol-methylene chloride (1:1) extract from the leaves of *F. sinaica* Boiss. (**Ahmed et al., 2001**).

An oxygenated sesquiterpenoid, (1S,4S,5R,6S,7S,10S)-5,10,11-cadinanetriol, from a distinct Sardinian chemotype of *F. communis* L. was isolated from the acetone extract (**Appendino et al., 2001**).

## 2.4. Chemical compounds of *Ferula* essential oils

Extensive research has been conducted on the secondary metabolites produced by various parts of *Ferula* genus species through phytochemical studies. While *Ferula* species share some similarities in their volatile components, there are many compositional differences among them. The presence of sulfur-containing compounds is the most prominent measure used to categorize *Ferula* oils. Terpenoid compounds are almost always the most abundant components of *Ferula* oils, including  $\alpha$ -pinene,  $\beta$ -pinene, myrcene and limonene (among monoterpene hydrocarbons); linalool,  $\gamma$ -terpineol and neryl acetate (among oxygenated monoterpenes);  $\beta$ -caryophyllene, Germacrene B, germacrene D and  $\delta$ -cadinene (among sesquiterpene hydrocarbons) and caryophyllene oxide,  $\alpha$ -cadinol, guaiol and spathulenol (among oxygenated sesquiterpenes) (Sahebkar & Iranshahi, 2010; Rahmouni, 2021).

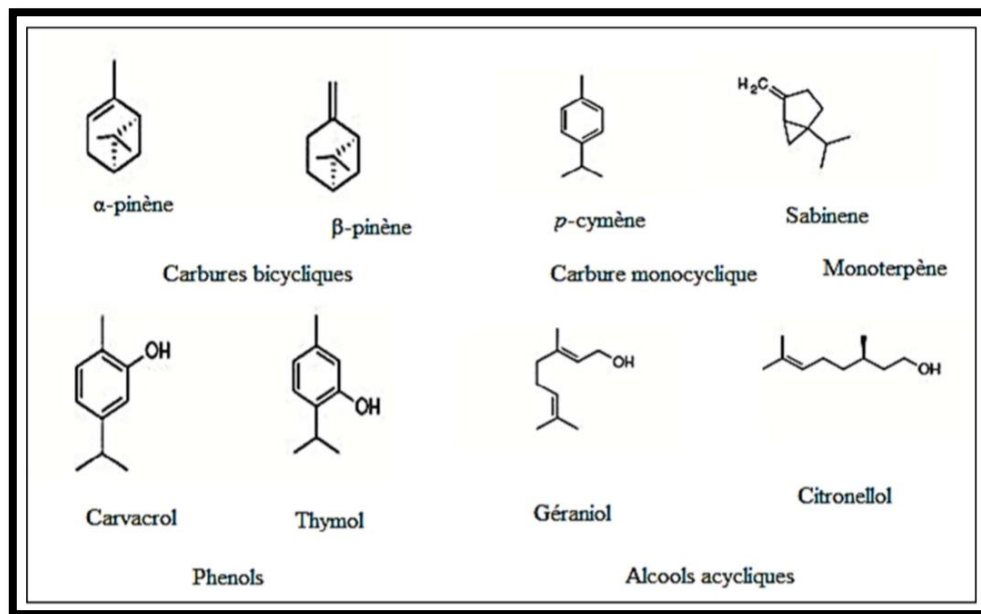


Figure 15 : Chemical structure of some monoterpenes (Rahmouni, 2021).

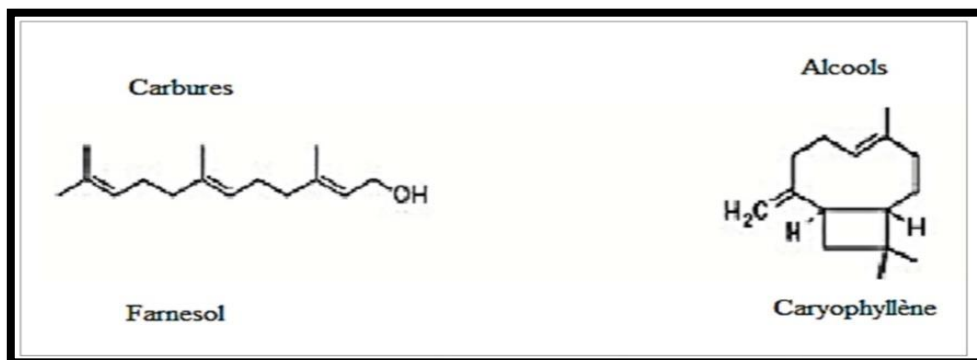


Figure 16: Chemical structure of some sesquiterpenes (Rahmouni, 2021).

The essential oils obtained from *Ferula* species In North Algeria were compared with previously reported oils. It was found that  $\alpha$ -pinene was commonly present in all oils, but the essential oil of *Ferula communis* L. had the highest concentration of  $\alpha$ -pinene.  $\beta$ -myrcene was only detected in the oils of *F. vesceritensis* and *F. communis*, where it was predominantly present in the latter. The essential oil of *F. vesceritensis* was found to have a unique composition, with high concentrations of  $\beta$ -pinene, limonene, and carotol, which were not found in the other Algerian *Ferula* oils. And *F. lutea* was found to have  $\alpha$ -pinene. This information was presented in (Table 7) of the research report (Bouratoua, 2014).

**Table 7** : Major components of essential oils of Algerian *Ferula* species (Bouratoua, 2014).

Ferula species	Major compounds ( $\geq 5\%$ )
<i>F. communis</i> L.	$\alpha$ -pinene $\beta$ -pinene $\beta$ -myrcene Limonene Carotol
<i>F. vesceritensis</i>	$\alpha$ -pinene $\beta$ -myrcene
<i>F. lutea</i>	$\alpha$ -pinene

The major constituents of essential oils are usually belonging to terpenoids, specifically sesquiterpene derivatives. In order to gain a better understanding of the diversity in composition of the essential oils of the *Ferula* genus, we present different classes of compounds and their diversity in the composition of the essential oils of species in this genus. The table below (Tab 8) shows the major compounds of the essential oils of *Ferula* species (Labeled, 2015).

**Table 8 :** Main components found in the essential oils of the *Ferula* genus (Labeled, 2015).

<b>Ferula species</b>	<b>Major compound (≥5%)</b>	<b>Origin</b>	<b>References</b>
<i>F. communis</i>	Myrcene Aristolene $\alpha$ -Pinène	France	(Ferrari <i>et al.</i> , 2005)
	Aristolene (E,E)-Farnesol $\beta$ -Gurjunene	Italy	(Rubiolo <i>et al.</i> , 2006)
<i>F. vesceritensis</i>	9, 9-Tetradecadiyne Germacrene D Farnesène $\alpha$ -Bisabolène	Algeria (Ghardaia)	(Zellagui <i>et al.</i> , 2012)
<i>F. gummosa</i>	$\beta$ -Pinene $\alpha$ -Pinene $\delta$ -3-Carène	Iran (Tehran)	(Sayyah <i>et al.</i> , 2001)
<i>F. gummosa</i> (Fruits)	$\beta$ -Pinene $\alpha$ -Pinene	Iran (Isfahan)	(Kouyakh <i>et al.</i> , 2008)
	$\beta$ -Pinene $\alpha$ -Pinene g-3-Carene Limonene	Several regions of Iran	(Kouyakh <i>et al.</i> , 2008)
<i>F. gummosa</i> (Latex)	$\beta$ -Pinene g-3-Carene $\alpha$ -Pinene	Iran	(Ghannadi & Amree, 2002)
<i>F. gummosa</i> (Oleo-gum resin)	Limonene $\alpha$ -Pinene Myrcene Terpinolene Linalool g-3-Carene g-Terpinene Phellandral	Iran	(Sadraei <i>et al.</i> , 2001)
<i>F. gummosa</i> (stems & roots)	$\beta$ -Pinene cis-Chrysanthenyl acétate (E)-Nerolidol	Iran	(Rustaiyan & Monfared, 2002)
<i>F. ovina</i> (Fruits)	$\alpha$ -pinene $\beta$ -phellandrene Isobornyl acetate $\alpha$ -Fenchene Myrcene	Iran (Khorasan)	(Iranshahi & Hassanzadeh-Khayya, 2008)

**Table 8:** cont.

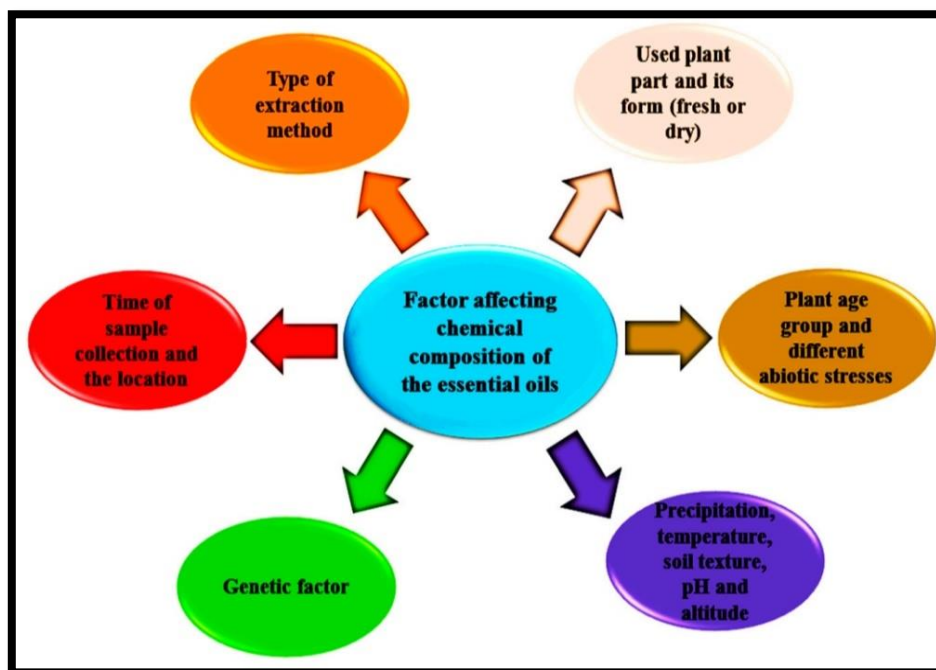
<b>Ferula species</b>	<b>Major compound (≥5%)</b>	<b>Origin</b>	<b>References</b>
<i>F. ovina</i> (Aerial parts)	Carvacrol α-Pinene Limonene Carotol	Iran (Khorasan)	<b>(Iranshahi &amp; Hassanzadeh-Khayya, 2008)</b>
	Carvacrol α-Pinene Géranyl isovalerate Géranyl propionate Limonène Carotol	Iran (Isfahan)	<b>(Ghannadi <i>et al.</i>, 2002)</b>
	α-Pinene Limonene β-Pinene α-Fenchyl acetate Bornyl acetate	Iran (Azerbaijan)	<b>(Rahmani <i>et al.</i>, 2008)</b>
<i>F. assafoetida</i>	(E)-1-Propenyl sec-butyl disulfide (Z)-1-Propenyl sec-butyl disulfide Germacrene B α-Pinene β-Pinene	Iran	<b>(Khajeh <i>et al.</i>, 2005)</b>
	sec-butyl-(E,Z)-1-propényl disulfide 1-(methylthio) propyl-(E,Z)-1-propényl disulfide	Pakistan	<b>(Takeoka, 2001)</b>
<i>F. persica</i>	Dill-apiole Elemicine	Iran	<b>(Javidnia <i>et al.</i>, 2005)</b>
<i>F. glauca</i> (leaves)	(E)-Caryophyllene Caryophyllene oxide α-Humulene	Italy	<b>(Maggi <i>et al.</i>, 2009)</b>
<i>F. glauca</i> (Flowers)	Germacrene D Myrcene α-Pinene β-Pinene	Italy	<b>(Maggi <i>et al.</i>, 2009)</b>
<i>F. glauca</i> (Fruits)	α-Pinene β-Pinene	Italy	<b>(Maggi <i>et al.</i>, 2009)</b>

**Table 8:** cont.

Ferula species	Major compound (≥5%)	Origin	References
<i>F. glauca</i> (Roots)	(E)-β-Farnesene Elemicine Myristicin epi-Zonarene δ-Cadinene β-Barbatene β-Bisabolene	Italy	(Maggi <i>et al.</i> , 2009)

**Table 8**, summarizes most of the bibliographic studies on essential oils obtained from different parts of *Ferula* species. The obtained results show significant differences in the chemical composition of the oils studied (Labeled, 2015).

The oil content In *Ferula* species is affected by environmental conditions, including soil texture, altitude, temperature, and precipitation rate. Studies have shown that the maximum accumulations of essential oils and sulfur compounds were found in *Ferula assa-foetida* L. genetic factors have a greater effect on the chemical constituents of essential oil than environmental factors. Decreasing temperature and increasing altitude have a negative correlation with the content of essential oils. The quality, quantity, and chemical profile of essential oils also vary according to the extraction methods used. Plant age and used plant part (flowers, seeds, leaves, stems, bark, fruits, or roots) (Sonigra & Meena, 2021).



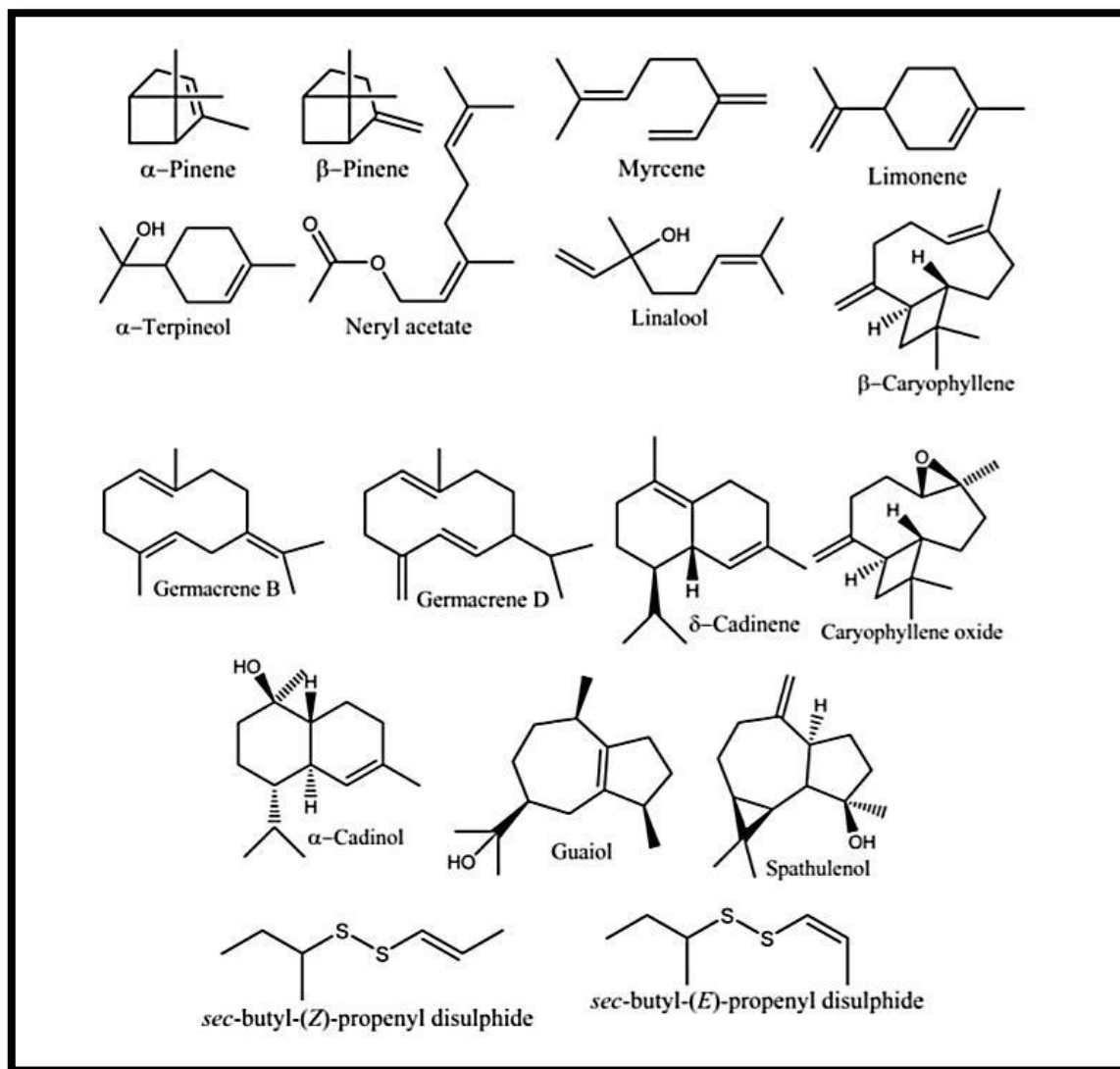
**Figure 17:** Factors affecting the chemical profile of essential oils of *Ferula* species (Sonigra & Meena, 2021).

Monoterpenes and sesquiterpene hydrocarbons constitute the majority of identified compounds in the essential oils extracted from different *Ferula* species, with a percentage of 5% or higher (Labeled, 2015):

- **$\alpha$ -pinene**, was found as the major component in the essential oils of 24 *Ferula* species, serving as the main component in the essential oils of 9 studied species: *F. badrakema*, *F. gluca*, *F. hutella*, *F. jaeschkeana*, *F. macrocolea*, *F. orientalis*, *F. ovina*, *F. stenocarpa* et *F. szowitsiana*
- **$\beta$ -pinene**, has been found as the major component in the essential oils of 12 species of *Ferula*, including as a principal component in *F. macrocolea* and *F. gummosa*
- **Limonene**, has been found as the major component in the essential oils of 9 species of *Ferula*, including as a principal component in *F. gummosa* and *F. jaeschkeama*.
- **Myrcene**, has been found as the major component in the essential oils of 5 species of *Ferula*, including *F. gluca*, *F. gummosa*, *F. ovina*, *F. szowitsiana*, and as a principal component in *F. communis*.
- **Germacrene D**, has been found as the major component in the essential oils of 3 species of *Ferula*, including *F. szowitsiana*, *F. vesciritensis*, and as a principal component in *F. gluca*
- **$\beta$ -Phellandrene**, has been found as the major component in the essential oils of 3 species of *Ferula*, including *F. ovina*, *F. szowitsiana*, and as a principal component in *F. orientalis*.

The most common monoterpene compounds found in *Ferula* genus are  $\alpha$ -pinene,  $\beta$ -pinene, myrcene, and limonene. Monoterpene oxygenated compounds include linalool,  $\alpha$ -terpineol, and neril acetate. Hydrocarbon sesquiterpenes include  $\beta$ -caryophyllene, germacrène B, germacrène D, and  $\delta$ -cadinene. Oxygenated sesquiterpenes include caryophyllene oxide,  $\alpha$ -cadinol, guaiol, and spathulenol. Finally, sulfur compounds are represented by sec-butyl-(Z)-propenyl disulfide, sec-butyl-(E)-propenyl disulphide (Rahmouni, 2021).

The chemical structures of the most common major components in the essential oils of the *Ferula* genus are summarized in (figure 18).



**Figure 18:** Chemical structure of the most frequent main components present in the essential oils of *Ferula* species (Sahebkar & Iranshahi, 2010).

## 2.5. The pharmacological properties of *Ferula* genus

*Ferula* is a genus of perennial herbs in the Apiaceae family, many *Ferula* species have historically been known as a rich source of aromatic resins and as natural remedies for a variety of disorders in traditional medicine. The most notable applications have been *F. assa-foetida*, *F. badra-kema*, *F. gummosa*, and *F. persica*. Essential oils are natural, complex, and concentrated liquid mixtures made up of various volatile components (Amiri, 2014). These volatile components are synthesised as secondary metabolites by aromatic plants and act as part of the herbal defence system against bacterial, viral, fungal, and insect attacks. The use of essential oils dates back to ancient times when they were primarily used for their flavoring, sanitary, and medicinal properties (Bakkali *et al.*, 2008; Barupal, 2019).

According to reports, the resins extracted from *Ferula* species are employed as a febrifuge and carminative agent for stomach disorders. Some species are also used to treat

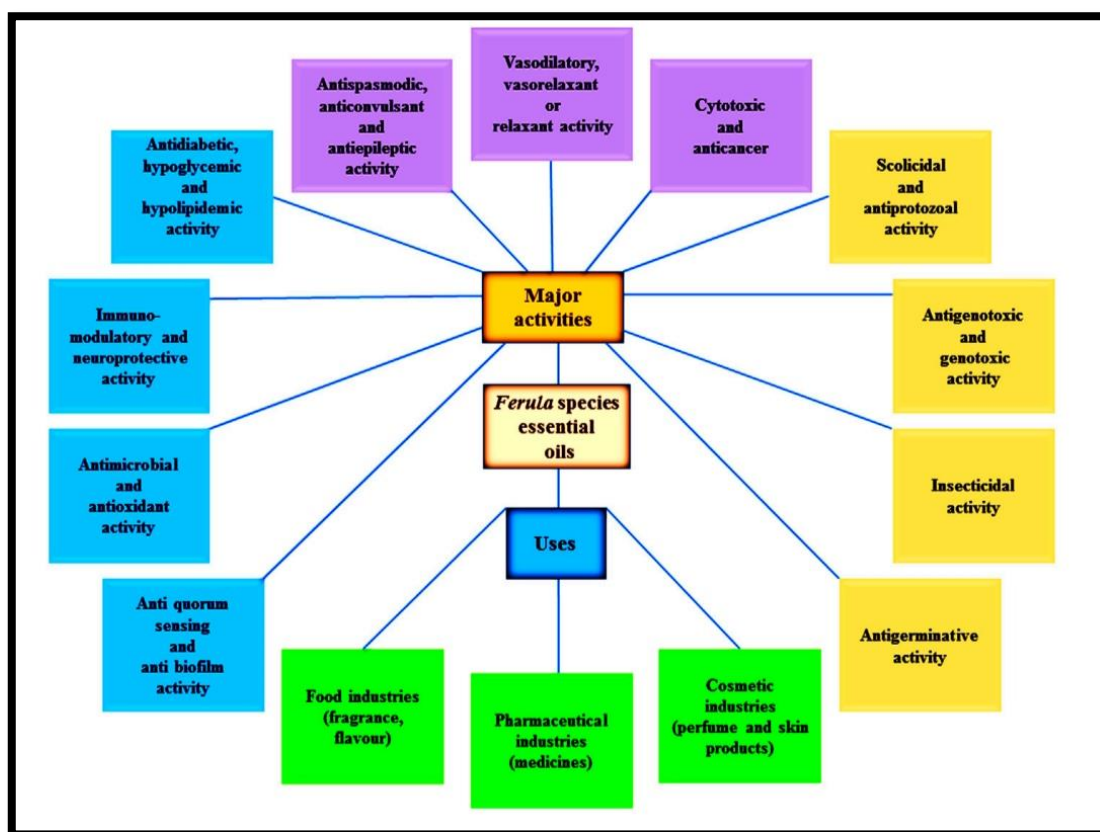
hysteria and skin problems in conventional therapy. In traditional medicine, several species from this genus have been used as sedatives and to treat digestive issues, rheumatism, headaches, arthritis, dizziness, and toothaches (**Boghrati & Iranshahi, 2018**).

It should be noted that the roots and resins of *Ferula* species (**Table 9**), are often the most commonly used parts in traditional medicine (**Rahmouni, 2018**).

**Table 9** : Properties of some species of the *Ferula* genus (**Dehak, 2012**).

Plante	Part Used	Use and properties
<i>F. assa-foetida</i>	Gum (latex)	Fragrant, expectorant, carminative, laxative, antispasmodic, emmenagogue, anthelmintic, sedative, aphrodisiac.
<i>F.persica</i>	Gum Roots	Antihysterical, stomachic, febrifuge, vermifuge, carminative, antidiabetic.
<i>F. communis</i> <i>Var. subsp</i>	Latex	Antihysterical, antidiabetic.
	Rhizomes Flowers	Antidysenteric, skin infections, antipyretic.
<i>Var.breviedia</i>	Part aerial	Toxic to humans and animals.
<i>F. szoswitziana</i>	gum	Antirheumatic, anticarcinogenic.
<i>F. tingitana</i>	gum	Antispasmodic.
<i>F. gummosa</i>	gum	Antispasmodic, expectorant, anticonvulsant, anticataract.
<i>F.kuhistanica</i>	Fruits	Skin diseases, wounds.
<i>F.hermonis</i>	Roots	Stimulant of the nervous system, aphrodisiac, antidiabetic.
<i>F. sinkiangensis</i>	Roots	Rheumatoid arthritis, stomachaches.
<i>F.teterrima</i>	Roots	Rheumatoid arthritis, stomachaches, scorpion stings.
<i>F. diversivittata</i>	Roots	Antihysterical, anticonvulsant.
<i>F.varia</i>	Roots	Intestinal antiparasitic, antipyretic, oral antiseptic
<i>F. fukanensis</i>	Roots	Anti-inflammatory, bronchitis and rheumatoid arthritis.

The *Ferula* species have been found to contain approximately 160 chemical compounds in their essential oils, which are responsible for their various biological activities and make them a suitable option for industrial applications (**Sonigra & Meena, 2021**). Several sesquiterpenes isolated from *Ferula* roots demonstrated antibacterial, antifungal, cytotoxic, antioxidant, and hormonal activities, as well as P-glycoprotein inhibitory and immunomodulatory properties (**Miski, 2013**).



**Figure 19:** Different bioactivities and uses of the *Ferula* species essential oils (Sonigra & Meena, 2021).

### 2.5.1. Cytotoxicity activity

Cytotoxicity studies are a useful initial step in determining the potential toxicity of a test substance, including plant extracts or biologically active compounds isolated from plants. Minimal to no toxicity is essential for the successful development of a pharmaceutical or cosmetic preparation and in this regard, cellular toxicity studies play a crucial role. The concept of basal cytotoxicity, where deleterious effects are noted on structures and functions common to all human cells, is relevant when considering the relationship between acute toxicity and cytotoxicity. The selectivity index is an important measure to identify substances with promising biological activity and negligible cytotoxicity. Various bioassays and a number of different cell lines have been used to assess cytotoxicity of African medicinal plants. Additionally, extracting solvents ranging in polarity have been used to extract different plant parts, contributing to the wide variety of cytotoxicity results of African plants (McGaw *et al.*, 2014).

The plant of *Ferula* is moderately toxic, and it remains toxic throughout all its vegetative stages. The chemical composition of the latex of *Ferula* plants varies depending on the region. Several studies have explained the absence of toxicity in certain biotypes.

*Ferula* plants dominated by the sesquiterpene compound ferutinine of the daucane type are considered "non-toxic," while those with ferulenol as the major compound have significant toxicity (Hammiche *et al.*, 2013).

Ferulenol, a prenylated 4-hydroxycoumarin isolated from *F.communis* (Table 10), exerted dose-dependent cytotoxicity against various human tumor cell lines. It stimulated tubulin polymerization in vitro, inhibited the binding of radio-labeled colchicine to tubulin, re-arranged cellular microtubule network into short fibres and altered nuclear morphology (Bocca *et al.*, 2002). In another study, the cytotoxicity of ferulenol on human breast cancer (MCF-7), colon cancer (Caco-2), ovarian cancer (SKOV-3) and leukemic (HL-60) cells was evaluated; based on the results, ferulenol showed significant cytotoxic effects against these cancer cell lines (Nazari & Iranshahi, 2011).

**Table 10 :** Overview of the cytotoxic activities of *Ferula* species (Iranshahi *et al.*, 2018).

Plant Name	Important Compound	Biological activity
<i>F. assa-foetida</i>	8-acetoxy-5-hydroxy Umbelliprenin	Cytotoxic
	Coumarin compounds	Cytotoxic
	Ferutinine	Cytotoxic
	Methanolic extract	Cytotoxic
<i>F. vesceritensis</i>	Lapiferin	Cytotoxic
<i>F. communis</i>	Ferulenol	Cytotoxic
<i>F. lutea</i>	Methyl caffeate	Cytotoxic
	n-butanol extract	Cytotoxic
<i>F. gummosa</i>	Sesquiterpenes, coumarins	Cytotoxic
	Ethanollic extract	Cytotoxic
<i>F. sinkiangensis</i>	Ethyl acetate Fraction	Cytotoxic
<i>F. szowitziana</i>	Auraptene Cytotoxic	Cytotoxic
<i>F. oopoda</i>	Dehydrooopodin	Cytotoxic

### 2.5.2. Anti-oxidant activity

The anti-oxidant system is a set of enzymes such as superoxide dismutase (SOD) and catalase (CAT), Biological macromolecule structures such as albumin, Ceruloplasmin, ferritin and other small molecules, molecules such as ascorbic acid, alpha-tocopherol, Carotenoids, polyphenols, ubiquinol-10, reduced Glutathione (GSH), methionine, uric acid, and bilirubin. The effects of *Ferula* plants on oxidative stress are discussed below (Ghasemi *et al.*, 2021).

Kamololol acetate extracted from *F. pseudalliacea* showed strong antioxidant activity against colorectal cancer cell lines (Mahaki *et al.*, 2019). Daucane sesquiterpenoid esters isolated from *F. hermonis* and *F. rigidula* exhibited antioxidant effects and inhibited oxidation and production of reactive substances. Essential oils from *F. vesceritensis*, *F. heuffelii*, and *F. tingitana* demonstrated antioxidant activity (Ghasemi *et al.*, 2021). Extracts from *F. caspica* had high antioxidant effects, particularly the chloroform and ethyl acetate extracts (Kahraman *et al.*, 2019).

### 2.5.3. Anti-inflammatory activity

The evaluation of the anti-inflammatory effects of *F. assafoetida*, a plant. The study conducted on mice showed that the antinociceptive effect of *F. assafoetida* seed essential oil and found it to be effective in reducing chronic and acute pain, possibly through anti-inflammatory mechanisms or by modulating central opioid pathways. Additionally, *F. assafoetida* and its extracts exhibited dose-dependent cytotoxic effects, with some revitalizing effects observed at lower concentrations (Ghasemi *et al.*, 2021).

The anti-inflammatory effects of three main compounds from *F. hermonis* root oil namely, ferutin, teferin, and eferidin on carrageenan-induced edema were evaluated in rats. Both ferutin and teferin showed anti-inflammatory effects at a certain dose (Geroushi *et al.*, 2011).

Coumarin and warfarin, which are constituents of *Ferula*, have been reported to possess anti-inflammatory activities. coumarins have been shown to decrease inflammation. In conditions like post-mastectomy lymphedema by inhibiting the pro-inflammatory enzyme 5-lipoxygenase (Hoult & Payá, 1996).

### 2.5.4. Immunomodulatory activity

The main task of the immune system is to defend against pathogens. The first line of defense in this system are: lymphocytes, neutrophils, and monocytes/macrophages which are known as phagocytes. Other functions of phagocytic cells are chemotaxis and degradation of biological pathogens. Some molecules derived from medicinal plants alter the

Immunomodulatory activity of these phagocytic cells. Essential oils derived from these plants can increase or decrease the activity of the immune system based on their chemical composition. Some of such compounds are terpenes and several other natural agents present in essential oils of *Ferula* species which have shown Immunomodulatory properties (Oüzek *et al.*, 2017).

A study on the essential oil extracted from *Ferula iliensis* Krasn. Ex Korovin plant material. The essential oil demonstrated the ability to stimulate calcium ion mobilization and reactive oxygen species production in certain immune cells (Oüzek *et al.*, 2017).

A study on the effects of *Ferula akitschkensis* essential oils on human neutrophil cells. They identified the primary components of the oils and found that certain components stimulated calcium mobilization in neutrophils (Schepetkin *et al.*, 2016).

## 2.5.5. Antimicrobial activity

### 2.5.5.1. Antibacterials activity

The antibacterial effects of aromatic and medicinal plants and their products including extracts, essential oils and oleoresins have been recognized since antiquity, while attempts to characterize these properties in the laboratory date back to the early 1900s (Boghrati & Iranshahi, 2019).

It was shown that a number of *Ferula* species exhibited antibacterial activity. In 2010, it was found that *Ferula lycia* essential oil had an effective antibacterial activity especially against Haemophilus influenza (Boghrati & Iranshahi, 2019).

The essential oils from *Ferula glauca* were evaluated for their antibacterial and antifungal activities. The oils showed sensitivity against Gram-positive bacteria *Bacillus subtilis* and moderate inhibitory activity against other bacteria. The oils derived from leaves and fruits exhibited the highest activity and contained compounds such as  $\epsilon$ -caryophyllene,  $\alpha$ - and  $\beta$ -pinenes known for their antibacterial properties (Maggi *et al.*, 2009).

A study evaluate the antibacterial activity of different extracts (petroleum ether, hexane, hot water, cold water, and ethanol extracts) of *Ferula assa-foetida*. The disc diffusion method was used to assess the activity. All extracts of *F. assa-foetida* exhibited strong antibacterial activity against various bacterial strains, including *E. coli*, *S. aureus*, *E. faecalis*, *Shigella flexneri*, and *Klebsiella pneumonia* (Bhatnager *et al.*, 2015).

sesquiterpene coumarins from *Ferula communis* rhizome exhibited strong antibacterial activity against different strains, comparable to streptomycin sulphate antibacterial (Al-Yahya *et al.*, 1998).

The antibacterial activity of the essential oil extracted from the leaves of *F. vesceritensis* was investigated. The results revealed that the oil exhibited inhibitory effects against all tested microorganisms, including *E. coli*, *K. pneumonia*, *S. aureus*, and *P. aeruginosa*. However, the study did not delve into the identification of specific phytochemicals responsible for the observed antibacterial activity (Zellagui *et al.*, 2012).

The essential oil derived from the flowers and leaves of *F. tingitana L.* exhibited a moderate effect against the tested bacteria. However, it did not show any inhibitory effect against the fungi *A. flavus* and *C. albicans*. The oil extracted from the leaves displayed higher potency in comparison to the standard antibiotic tetracycline. The author attributed this antimicrobial activity to the presence of phenolic compounds in the oil (Elghwaji *et al.*, 2017).

#### 2.5.5.2. Antifungal activity

*F. assa-foetida* is a rich source of polysulfides (sulfur-Containing compounds), which apparently play a role in the antifungal activity of *F. assa-foetida* (Boghrati & Iranshahi, 2018). In a study investigated the antifungal activity of the essential oils obtained from *F. assa-foetida* oleo-gum-resins in culture of fungal strains in the presence of serial dilution of essential oils. According to Kavooosi and his coworkers, the essential oil significantly reduced the growth of *C. albicans* and *Aspergillus niger* (Kavooosi & Rowshan, 2013).

The chloroform extract of *F. persica.var. persica* showed antifungal activity. Through fractionation, the active components were identified as sulfur-containing compounds, persicasulfide A and persicasulfide B. These compounds exhibited potent antifungal activity (Mirjani *et al.*, 2005).

Dividing *Ferula* species into two groups including polysulfide-containing species and those have a little or no sulfur-containing compounds, the former group with the high content of sulfur-containing compounds have shown the most significant antifungal activities to date. Probably, Polysulfides play a role in the antifungal activity of *Ferula* species, similar to those of allicin and its derivatives (isolated from *Allium* species) reported so far. However, some daucane sesquiterpenes including ferutin and teferidin, exhibited promising antifungal activities (Boghrati & Iranshahi, 2018).

#### 2.5.5.3. Antiparasitic activity

Leishmaniasis is a parasitic infection caused by *Leishmania* parasites, primarily found in tropical and subtropical regions. Current treatment options are limited and often

ineffective. Researchers have isolated coumarin derivatives from *Ferula narthex Boiss* and found promising leishmanicidal activity. Another study identified similar compounds but did not evaluate their activity against leishmaniasis. These findings suggest the potential of coumarin derivatives as future drugs for treating leishmaniasis, but further research is needed (Zhou *et al.*, 2017).

sesquiterpene coumarins were isolated from the roots of *Ferula szowitsiana* that have antileishmanial activity against *L. major* promastigotes (Iranshahi *et al.*, 2007). In another study showed that *F. assa-foetida* oleo gum resin have Antileishmanial activity against *L. major* promastigotes (Bafghi *et al.*, 2014).

*F. aasafoetida* exhibited inhibitory effects on the growth of *Blastocystis* sp. An anaerobic protozoan parasite that infects the intestines and leads to gastrointestinal symptoms. *Asafoetida* demonstrated a significant inhibitory effect on *Blastocystis* sp., with a 100% inhibition rate, at a certain concentrations (El Deeb *et al.*, 2012).

### 2.5.6. Antiviral activity

To date, very promising antiviral compounds have been isolated from *Ferula* species, some of which are active against dangerous viral infections including AIDS and influenza H1N1 (Boghrati & Iranshahi, 2019).

In (2009), isolated 30 compounds from the chloroform-soluble extract of *F. assa-foetida*. These compounds, including 5'-hydroxy umbelliprenin, methyl galbanate, galbanic acid, farnesiferol C, and others, were screened for their anti-influenza A (H1N1) viral activity. Nine compounds exhibited higher potency than the positive control amantadine. The structural similarities among these compounds suggest their potential as lead compounds for developing new drugs against influenza A (H1N1) viral infection (Lee *et al.*, 2009).

In (2014), three sesquiterpene coumarins, namely badrakemin acetate, Samarcandin diastereomer, and kellerin isolated from the gum resin of *F. assa-foetida*. The researchers investigated the antiviral activity of these coumarins against HSV-1 using a plaque-forming assay. Among the three isolated compounds, kellerin demonstrated the highest efficacy against HSV-1. Albeit being less potent than the reference compound acyclovir (Ghannadi *et al.*, 2014).




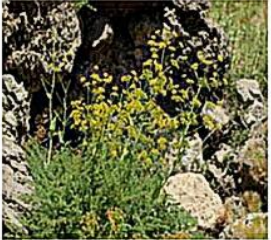

### 2.5.7. Anticancer activity

*Ferula sinkiangensis* is a significant member of the genus *Ferula*, primarily found in the Xinjiang Uygur autonomous region of China. It has been traditionally used as a folk medicine for treating rheumatoid arthritis and stomach disorders. In a study, researchers

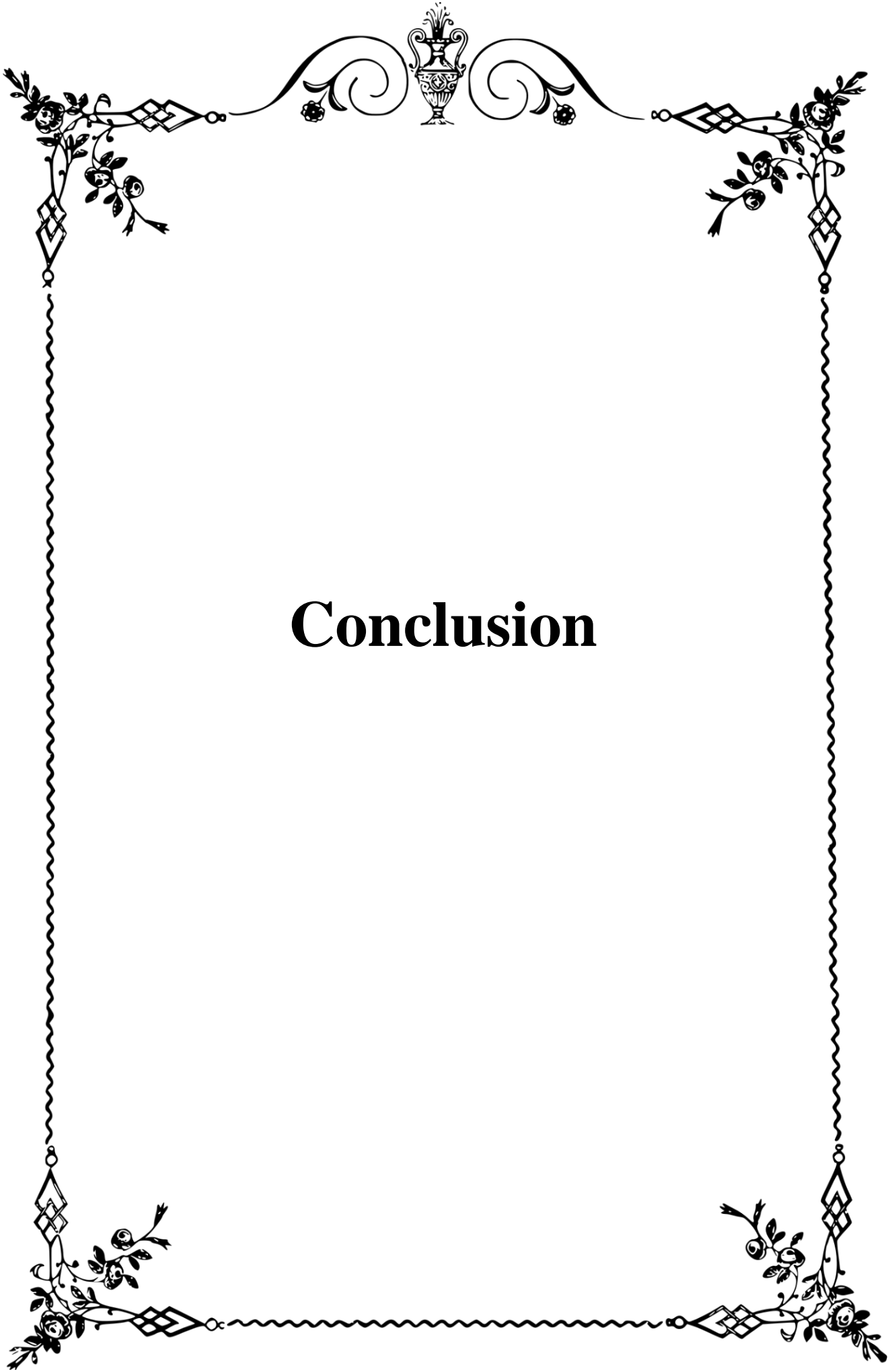
isolated six sesquiterpene coumarin ethers from the seeds of *F. sinkiangensis* (compounds 17-22). These coumarins were tested against AGS, HeLa, and K562 human cancer cell lines, and demonstrating cytotoxic activities. The results indicated that the isolated coumarin derivatives exhibited selective cytotoxicity against HeLa and AGS cancer cell lines (**Zhou et al., 2017**).

*Ferula ferulaeoides* is a species belonging to the genus *Ferula* that has been traditionally used for the treatment of spasm, digestive diseases, and arthritis. Researchers conducted studies to identify potential anti-cancer compounds from this species. They isolated sixteen sesquiterpene-coupled coumarins (compounds 26-41) from the root of *F. ferulaeoides* and evaluated their cytotoxicity against HepG2, MCF-7, and C6 cancer cell lines. Among the isolated compounds, compound 29, which is a derivative of sesquiterpene coumarin, exhibited the highest potency against HepG2, MCF-7, and C6 cells. Respectively, the researchers speculated that the presence of a furan ring or a methoxy group in the structure of compound 29 (also known as DAW22) could potentially inhibit its cytotoxic activity (**Zhou et al., 2017**).

In order to explore the mechanisms of DAW22- Induced cell death in cancer cells, DAW22-induced apoptosis in C6 Glioma cells. They found that DAW22 could inhibit C6 Glioma cell growth by death-receptor-mediated and mitochondrial apoptosis and ER stress. These findings support further evaluation of this compound as a potentially novel anti-neoplastic drug lead in Glioma cancer therapy (**Zhou et al., 2017**).

<i>Ferula</i> spp.	Most important active compounds	Pharmacological activity
 <i>Ferula asafoetida</i>	Umbelliferone Luteolin Ferulic acid $\alpha$ -Pinene	Antioxidant and anti-inflammation Antimicrobial and anti biofilm Anti-hyperglycemia Neuroprotective Anti tumor
 <i>Ferula communis</i>	Non-toxic chemotype: Ferutinin ferulenol	Anti-inflammatory Anti-platelet & Anticoagulant Antibacterial Cytotoxic
	Toxic chemotype: Ferulenol ferprenin	
 <i>Ferula gummosa</i>	$\beta$ -pinene and $\alpha$ -pinene Bulnesol $\alpha$ -eudesmol $\alpha$ -bisabolol	Anti-seizure Antimicrobial Anti-inflammatory Antinociceptive Spasmolytic
 <i>Ferula hermonis</i>	Ferutinin Teferin Teferidin	Aphrodisiac Anti-inflammatory Anti diabete Estrogenic activities Osteoporosis prevention Anti-microbial
 <i>Ferula szowitsiana</i>	Galbanic acid Umbelliprenin $\beta$ -pinene ferulic acid	Anti-genotoxic Anti-bacterial Anti oxidant Anti nociceptive

**Figure 20:** Bioactive components of some important *Ferula* species and their pharmacological effects (Sabzehzari *et al.*, 2020).



# Conclusion

Aromatic and medicinal plants play a significant role in various cultures and traditional practices worldwide. These plants possess unique aromatic compounds and bioactive substances that have been utilized for their therapeutic properties for centuries. They have been employed in herbal remedies, traditional medicine systems, and even modern pharmaceuticals. Their diverse chemical composition and biological activities make them valuable resources for drug discovery, nutraceuticals, and natural health products.

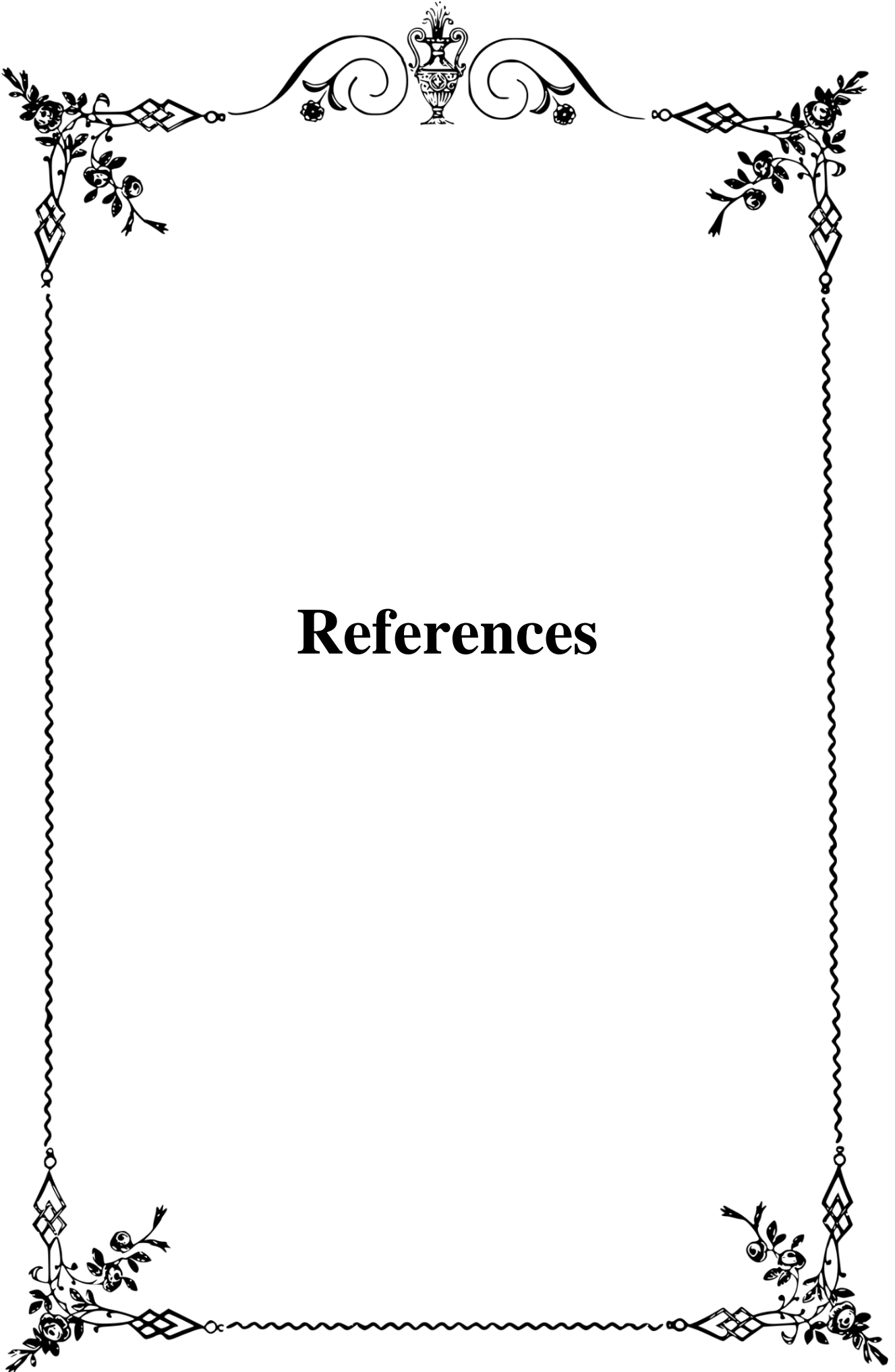
*Ferula* is a genus of plants that encompasses a diverse group of species. These plants are known for their aromatic properties and have been utilized for centuries in various traditional healing practices. With a rich history in herbal medicine, *Ferula* plants have gained attention for their potential pharmacological benefits and are being studied for their therapeutic properties. And that is why we have focused on studying the genus *Ferula*.

The main objective of our research work was to conduct a phytochemical evaluation of the secondary metabolites and volatile constituents, the pharmacological properties of a genus belonging to the Apiaceae family: *Ferula*, which found in the Algerian flora and in different parts of the world.

The chemical composition of *Ferula* plants is diverse and varies depending on the species and plant part. Many *Ferula* species contain bioactive compounds such as terpenoids, coumarins, flavonoids, and phenolic acids, which are responsible for the plants medicinal properties. The essential oils of *Ferula* plants are also rich in terpenes such as limonene,  $\beta$ -pinene,  $\alpha$ -pinene and Myrcene which contribute to their distinct aroma and flavour.

Pharmacological studies conducted by different research teams have successfully demonstrated and rationalized the multiple activities attributed to *Ferula* genus, such as: anti-oxidant, anti-inflammatory, immunomodulatory, antimicrobial, and anticancer. This study was designed to identify the chemical constituents and pharmacological effects of *Ferula*. The medicinal properties of the plant are due to its various chemical compounds.

The pharmacological properties of the *Ferula* genus make it a fascinating subject of study, and its utilization in traditional medicine provides a strong foundation for further exploration and potential therapeutic applications in the future.



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## **Abstract** -----

The main objective of this work is to study the secondary metabolites and pharmacological properties of a genus of the Apiaceae family: alkkelakh "*Ferula*" which is a diverse group of plants that have been traditionally used in many cultures for their medicinal properties.

*Ferula* plants are typically characterized by their tall and robust stems, large compound leaves, and numerous yellow flowers that bloom in umbels.

A theoretical search of species of the genus *Ferula* revealed their richness and diverse phytochemical composition. The plants of this genus contain various classes of secondary metabolites that contribute to their medicinal properties but some of these compounds can also be toxic to human and animal health. These secondary metabolites include coumarins, Terpenes, flavonoids, alkaloids.

*Ferula* plants are known for their essential oils, which are volatile organic compounds that are responsible for their characteristic aroma. Include limonene,  $\alpha$ -pinene,  $\beta$ -pinene, and  $\beta$ -caryophyllene, among others. Studies have shown that the essential oil extracted from various species of the *Ferula* genus possesses a wide range of biological activities: antimicrobial activity, antioxidant activity, anti-inflammatory activity, anticancer activity, and antifungal activity.

**Key words:** secondary metabolites, *Ferula*, essential oils, pharmacological properties, coumarin, ferulenol.

## المخلص

الهدف الرئيسي لهذا العمل هو دراسة الأيضيات الثانوية والخصائص الدوائية لجنس من عائلة الخيميات: الكلخ *Ferula*، وهو مجموعة متنوعة من النباتات التي استخدمت تقليدياً في العديد من الثقافات بسبب خصائصها العلاجية. تتميز نباتات الكلخ *Ferula* عادةً بسيقانها الطويلة والقوية، وأوراقها المركبة الكبيرة، والزهور الصفراء العديدة التي تتفتح في حزم.

أظهر البحث النظري لأنواع جنس الكلخ *Ferula* غناها وتنوع تركيبها النباتي. تحتوي نباتات هذا الجنس على فئات مختلفة من الأيضيات الثانوية التي تساهم في خصائصها العلاجية، ولكن بعض هذه المركبات قد تكون سامة أيضاً لصحة الإنسان والحيوان. تشمل هذه المركبات الثانوية الكومارينات، والتربينات، والفلانويدات، والقلويدات.

تعرف نباتات الفيروولا بزيوتها الأساسية، والتي هي مركبات عضوية طيارة المسؤولة عن رائحتها المميزة. تشمل هذه الزيوت الأساسية اليمونين، ألفا-بينين، بيتا-بينين، وبيتا-كاريوفيلين، وغيرها. أظهرت الدراسات أن زيت الكلخ *Ferula* المستخلص من مختلف أنواعها، يمتلك مجموعة واسعة من الأنشطة البيولوجية: نشاط مضاد للميكروبات، ونشاط مضاد للأكسدة، ونشاط مضاد للالتهابات، ونشاط مضاد للسرطان، ونشاط مضاد للفطريات.

**الكلمات المفتاحية :** الأيضيات الثانوية، الكلخ، الزيوت الأساسية، الكومارين، الخصائص العلاجية، الفيروولينول.

## Résumé -----

L'objectif principal de ce travail est d'étudier les métabolites secondaires et les propriétés pharmacologiques d'un genre de la famille des Apiaceae : l'alkkelakh "*Ferula*", qui est un groupe diversifié de plantes utilisées traditionnellement dans de nombreuses cultures pour leurs propriétés médicinales.

Les plantes de la *Ferula* sont généralement caractérisées par leurs tiges hautes et robustes, leurs grandes feuilles composées et leurs nombreuses fleurs jaunes qui s'épanouissent en ombelles.

Une recherche théorique des espèces du genre *Ferula* a révélé leur richesse et leur composition phytochimique diversifiée. Les plantes de ce genre contiennent différentes classes de métabolites secondaires qui contribuent à leurs propriétés médicinales, mais certains de ces composés peuvent également être toxiques pour la santé humaine et animale. Ces métabolites secondaires comprennent des coumarines, des terpènes, des flavonoïdes, des alcaloïdes.

Les plantes de la *Ferula* sont connues pour leurs huiles essentielles, qui sont des composés organiques volatils responsables de leur arôme caractéristique. Elles comprennent notamment le limonène, l' $\alpha$ -pinène, le  $\beta$ -pinène et le  $\beta$ -caryophyllène. Des études ont montré que l'huile essentielle extraite de différentes espèces du genre *Ferula* possède une large gamme d'activités biologiques : activité antimicrobienne, activité antioxydante, activité anti-inflammatoire, activité anticancéreuse et activité antifongique.

**Mots clés :** métabolites secondaires, *Ferula*, les huiles essentielle, coumarine, propriétés pharmacologiques, férulénol.