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Coumarins of genus *Ferula* L. (*Apiaceae* Lindl.)

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Abstract

The biologically active coumarins from *Ferula* L. species of the family *Apiaceae* Lindl. for the period 1970 to 2022 have been reviewed. The phytochemical investigation of different parts of *Ferula* L., including gum resin, leaves, fruits, seeds, roots, rhizomes, and resins led to the separation of different types of coumarins. Nearly 185 coumarins were isolated from 35 species of *Ferula* L. growing in different countries. Coumarins are represented mainly by umbelliferone (7-O-hydroxycoumarin) derivatives substituted in the C-7 position of aglycone, furanocoumarins and metabolites have terpene fragments, esters and glycosides. Umbelliferon is found as a taxon for the genus *Ferula* L. Some «unusual» metabolites have a furan fragment attached to the pyrone ring. Coumarins are of the psoralen type, containing a furan ring in the C-6 and C-7 positions of the primary skeleton. The rare coumarins with terpene fragments (hemiterpene, monoterpen, sesquiterpene) were reported. The biological activities of some extracts and individual metabolites such as antiinflammatory, cytotoxicity, antibacterial, antileishmanial, antiviral, antigenotoxic, antitumor, anticoagulant, antioxidant, antimycobacterial, inhibition a-glucosidase, antileishmanial were found.

1. Introduction

Biologically active substances obtained from plants serve as starting products for the synthesis of effective medicinal substances. Since natural compounds and drugs from them have some advantages over synthetic ones since they have less toxicity and higher efficiency in the treatment of various diseases.

The genus *Ferula* Linnaeus of the *Apiaceae* Lindl. the family is a promising source of biologically active substances and new highly effective drugs that have a wide range of pharmacological properties. Since ancient times, ferules have been used in folk medicine in various countries (Central Asia, Iran, China, and India) for the treatment of scabies, wounds, tumors, syphilis, tuberculosis, seizures, hysteria, the gastrointestinal tract, and as an antiparasitic remedy [1].

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Plants of the genus *Ferula* L. are widely distributed in Central Asia, Western Siberia, the Caucasus, the Mediterranean, North Africa, Asia Minor, Iran, Afghanistan, China, and India. Currently, the genus *Ferula* L. is represented by 185 species. 96 species are described in the Flora of the USSR, and 50 species are found on the territory of Kazakhstan, 20 of which are endemic [2].

In the annotated list of medicinal plants of Kazakhstan, Grudzinskaya L.M. supplemented species of the genus *Ferula* L. The most common and widely used in local folk medicine are 15 species: *Ferula foetida* (Bunge) Regel, *F. caspica* M. Bieb., *F. Diversivittata* Regel et Schmalh., *F. ferulaeoides* (Steud.) Korov., *F. Iliensis* Krasn.ex Korov., *F. karelinii* Bunge, *F. pallida* Korov., *F. penninervis* Regel et Schmalh., *F. sumbul* (Kauffm.) Hook. fil., *F. songarica* Pall. ex Spreng., *F. teterrima* Kar. et Kir., F. *transiliensis* (Herd.) M. Pimen., F. *tschimganica* Lipsky ex Korov., *F. tenuisecta* Korov., *F. varia* (Schrenk) Trautv [3].

The genus *Ferula* L. contains a rich biologically active complex and has a wide range of pharmacological activity. It is known that essential oils, sesquiterpene terpenoids, polyphenolic compounds, glycosides, carbohydrates, steroids, and organic acids have been isolated and identified mainly from these plants [4–11].

The main objective of this review is to focus on coumarins from various *Ferula* L. species growing in Central Asia, Turkey, Mongolia, Japan, and other countries, reported from 1970 to 2022.

The phytochemical investigation of different parts of *Ferula* L. species, including gum resin, leaves, fruits, seeds, roots, rhizomes, and resins led to the separation of different types of coumarins by the mean of diverse chromatographic tools. Their structure characterization was performed using various spectral techniques (UV, NMR, MS, X-ray analyses) and chemical means. A total of 184 coumarins were reported from *Ferula* L. species.

The biological activities of metabolites from genus *Ferula* L. antiinflammatory, cytotoxicity, antibacterial, antileishmanial, antiviral, antigenotoxic, antitumor, anticoagulant, antioxidant, antimycobacterial, inhibition a-glucosidase, antileishmanial and others were shown [12–15].

2. Coumarins

Ferula L. species are rich sources of coumarins, such as ordinary coumarins, furanocoumarins, coumarins which contain terpenoid fragments (hemiterpene, monoterpen, sesquiterpene), their esters and glycosides.

The common coumarins umbelliferone **(1)** and scopoletin **(2)** were described in the 1970s and 1980s. Umbelliferon is found in most of the species of *Ferula* L. and is a taxon. Khayat et al. and Taghinia et al. mentioned isolation herniarin **(3)** and 6,7-dihydroxy coumarin (esculetin) **(4)** as well [15, 16].

Coumarins are represented by umbelliferone derivatives prenylated in the C-7 position of aglycone. For extraction of coumarins methanol and water, n-hexane, dichloromethane, ethyl acetate, and chloroform were used. The discovery of prenylated coumarins **(5-8)** was mentioned in the early works of Batirov et al., Nabiev et al., Ermatov et al., and Kurbonov et al. [13–15, 17–22].

Zhou et al. isolated from the methanol extract of the dried roots of *F. sumbul* and characterized new prenylated coumarins osthol **(9)**, auraptenol **(10)** and meranzin hydrate **(11)** [23].

Iran scientists described diversion **(12)** from roots of *F. diversivitata* Regel et Schmalh, which using a comet assay. Scientists claim that diversion could be introduced as an antigenotoxic agent that prevents chemically induced DNA damage, in vitro. This coumarin could be valuable as an anti-tumour promoter or as a lead compound for new anti-cancer drug development [15, 24].

8-acetoxy-5-hydroxyumbelliprenin **(13)**, and asacoumarin **(14)** along with others from the methanol extract of the resin *F. foetida* have been isolated [25]. Kurbonov et al. mentioned the content of 0.06–0.11% coumarins in fruits [16], from which a new aureptan was isolated **(15)**, but the structure of the compound was not found in the literature.

The monoterpene coumarins namely ferulagol A **(16)** and ferulagol B **(17)** from a dichloromethane extract of *F. ferulago* L. have been reported. Recently ferusinkin A **(18)**, a rare new monoterpene coumarin and known analogs auraptene **(19)** and diversion (12) were purified and identified by Liu et al. of methanol extract from the aerial parts [14, 15].

Khayat et al. reported that sesquiterpene coumarins **(20-26)** are representing the major metabolites produced by *F. sinkiangensis* K.M. Shen [15]. Another sesquiterpene coumarins **(27-29)** discovered a group of natural products that are medicinally important because have considerable activity against the influenza A virus (H1N1) [12].

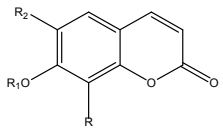
In a related study, coumarin esters, 7-O-(4,8,12,16-tetrahydroxy-4,8,12,16-tetramethylheptadecanoyl)-coumarin, ferulone A **(30)**, and 7-O-(4-hydroxy-4,8,12-trimethyl-trideca7,11-dienoyl)-coumarin and ferulone B **(31)** were obtained from the non-polar (n-hexane) fraction of extracts of roots of *F. orientalis* L. These two coumarin esters were isolated by a combination of vacuum liquid chromatography (VLC) and preparative thin-layer chromatographic (PTLC) and were characterized using spectroscopic methods. A coumarinyl ester ferulone C [7-O-(4,8,12-trihydroxy4,8,12-trimethyl-tridecanoyl)-chromen-2-one] **(32)** was isolated from an n-hexane extract of the roots of *F. persica* Wild [14].

In review, Nazari et al. mentioned prenyl fragmentation in C-3 position coumarins ferulenol **(33)** from *F. communis* and three of its derivatives 12′-benzoyloxyferulenol **(34)**, 12′-hydroxyferulenol **(35)**, 12′-acetoxy ferulenol **(36)** and KT 23 **(37)** from *F. pallida* and *F. penninervis* Rgl. et Schmalh., respectively, which demonstrated anticoagulant, antioxidant and antimycobacterial activities [12].

The isolation of two sesquiterpene coumarins derivatives from an 80% aqueous methanol extract of the roots of *F. fukanensis* K.M. Shen fukanemarin A **(38)** and fukanemarin B **(39)** were described by Motai and Kitanaka [14].

The structures of coumarins are shown in Fig. 1 (a), Fig. 1 (b), and Fig. 2.

Fig. 1 (a). Coumarins isolated from *Ferula* L.



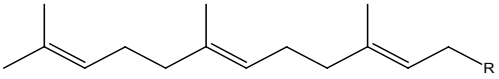
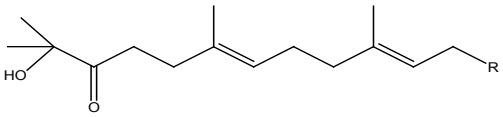
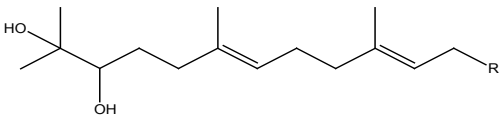
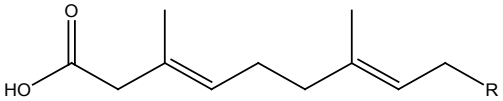
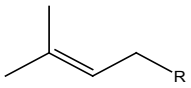
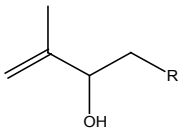
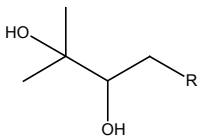
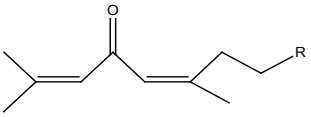
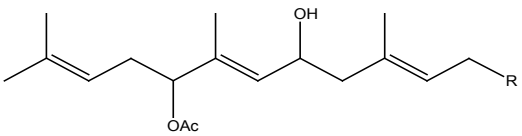
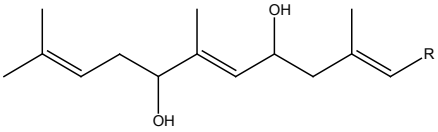
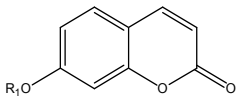
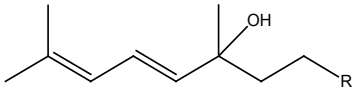
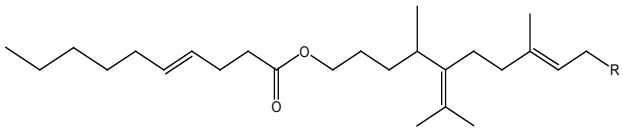
Constituents	R	R_1	R_2
Umbelliferone **(1)**	–	H	-
Scopoletin **(2)**	–	H	OMe
Herniarin **(3)**	–	Me	–
Esculetin **(4)**	OH	H	–
Umbelliprenin **(5)**	–		–
Karatavicin **(6)**	–		–
Karatavicinol **(7)**	–		–
Karatavic acid **(8)**	–		–
Osthol **(9)**		Me	–
Auraptenol **(10)**		Me	–
Meranzin hydrate **(11)**		Me	–
Diversin **(12)**	–		–
8-acetoxy-5-hydroxyumbelliprenin **(13)**	–		–
Asacoumarin **(14)**	–		–

Fig. 1 (b). Coumarins isolated from *Ferula* L.

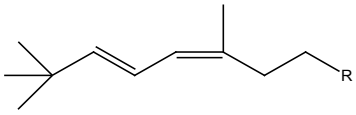




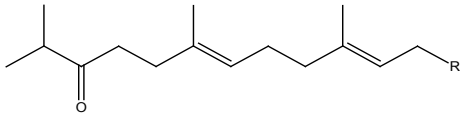
Ferulagol A **(16)**



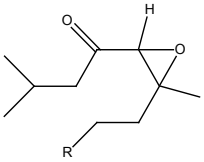
Ferusingensine D **(25)**



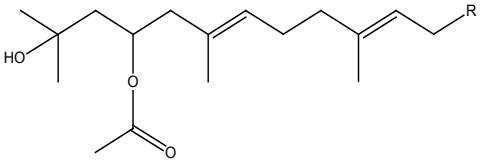
Ferulagol B **(17)**



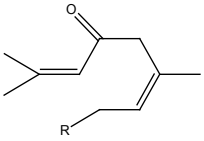
Ferusingensine E **(26)**



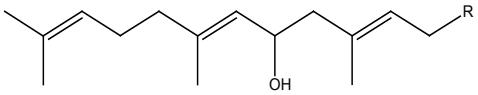
Ferusinkin A **(18)**



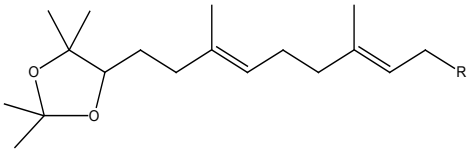
10′-R-acetoxy-11′-hydroxyumbelliprenin **(27)**



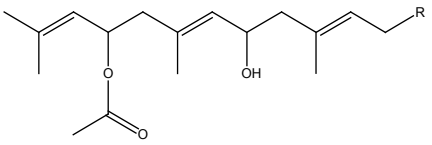
Auraptene **(19)**



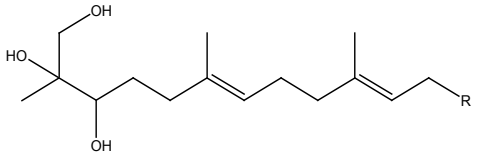
5′-shydroxyumbelliprenin **(28)**



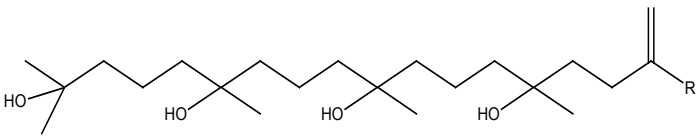
Karatavicinol A **(20)**



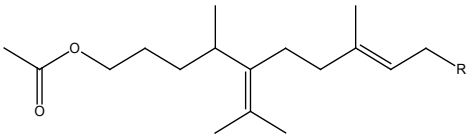
8′-acetoxy5′-S-hydroxyumbelliprenin **(29)**



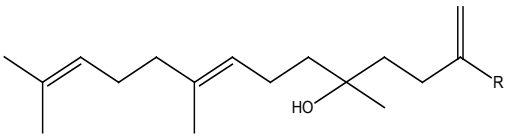
12’-Hydroxy-karatavicinol **(21)**



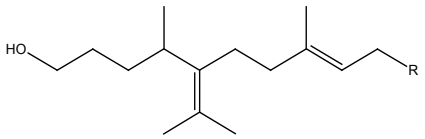
Ferulone A **(30)**



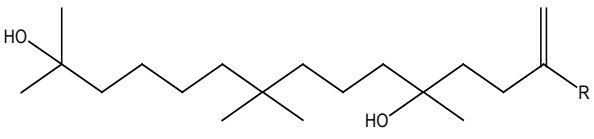
Ferusingensine A (**22**)



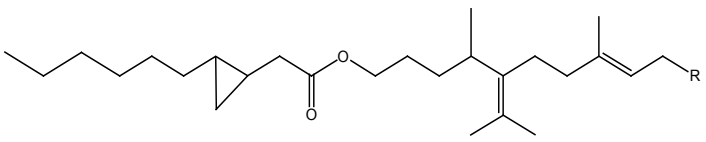
Ferulone B **(31)**



Ferusingensine B **(23)**

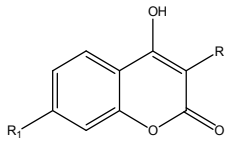


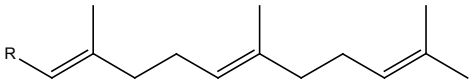
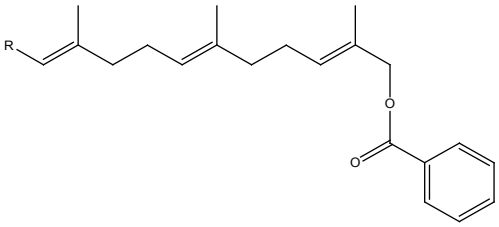
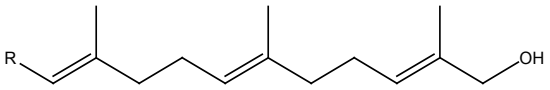
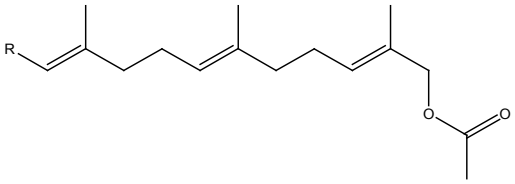
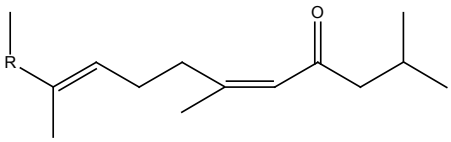
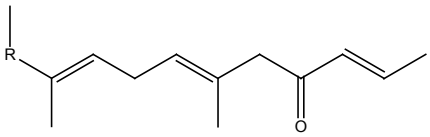
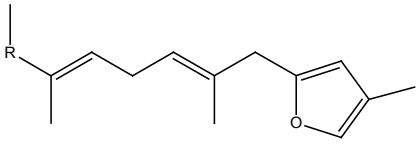
Ferulone C **(32)**



Ferusingensine C **(24)**

Fig. 2. Coumarins isolated from *Ferula* L.



Constituents	R	R_1
Ferulenol **(33)**		–
12′-benzoyloxyferulenol **(34)**		–
12′-Hydroxyferulenol **(35)**		–
12′-acetoxy ferulenol **(36)**		–
Kt23 **(37)**		OMe
Fukanemarin A **(38)**		OH
Fukanemarin B **(39)**		OMe

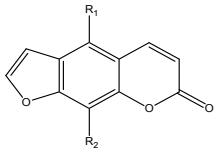
2.1. Furanocoumarins

Forty-eight furanocoumarins **(40-88)** have been determinate by foreign researches. Known metabolites **(40-49)** containing a furan ring with coumarin at C-6 and C-7 positions (psoralen type) from the methanol extract of the dried roots of *F. sumbul* determinated. New isomeric compounds fesumtuorin A-H **(53-60)** and rivulobin D **(61)** have a rare complex structures [23]. In early studies, similar compounds imperatorin **(50)**, isoimperatorin **(51)** and isopimpinellin **(52)** were isolated from the roots of *F. mogoltavica* Lipsky ex Korovin [26].

Analysis of the dichloromethane soluble fraction of a methanolic extract from the roots of *F. lutea* (Poir.) Maire afforded an inseparable mixture of two isomeric dihydrofuranocoumarin esters with senecioic and angelic acids, respectively, (−)-5-hydroxyprantschimgin **(62)** and (−)-5-hydroxydeltoin **(63)** [14].

The structures of coumarins are shown in Fig. 3 (a), Fig. 3 (b), Fig. 3 (c).

Fig. 3 (a). Psoralen type of coumarins isolated from *Ferula* L.



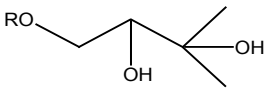
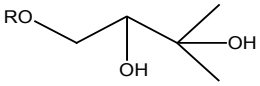
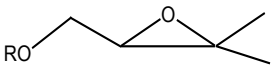
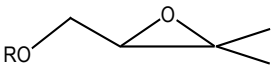
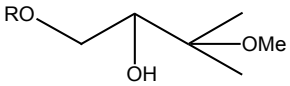
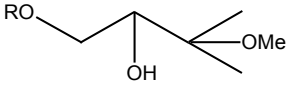
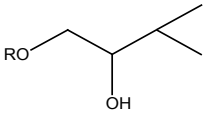
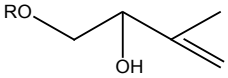
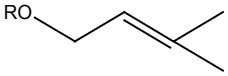
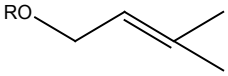
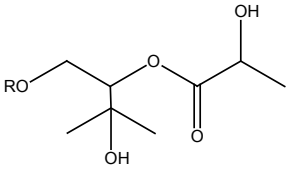
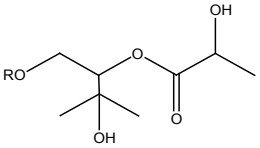
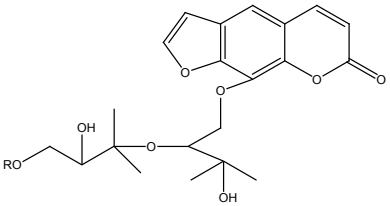
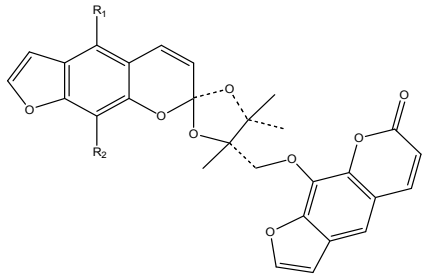
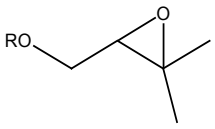
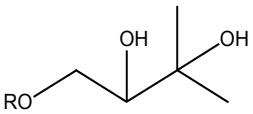
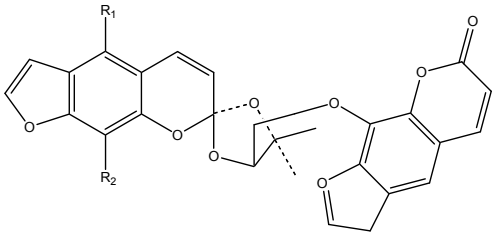
Constituents	R_1	R_2
Xanthoxol **(40)**	–	OH
Xanthotoxin **(41)**	–	OMe
Oxypeucedanin hydrate **(42)**		–
Heraclenol **(43)**	–	
Oxypeucedanin **(44)**		–
Heraclenin **(45)**	–	
Oxypeucedanin methnolate **(46)**		–
Heraclenol 3'-Methyl ester **(47)**	–	
Pranferol **(48)**		–
Pabulenol **(49)**		–
Imperatorin **(50)**	–	
Isoimperatorin **(51)**		–
Isopimpinellin **(52)**	OMe	OMe
Fesumtuorin A **(53)**		–
Fesumtuorin B **(54)**	–	
Fesumtuorin C **(55)**		–

Fig. 3 (b). Psoralen type of coumarins isolated from *Ferula* L.



Constituents	R_1	R_2
Fesumtuorin D **(56)**	–	
Fesumtuorin F **(58)**		–



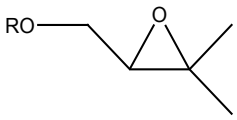
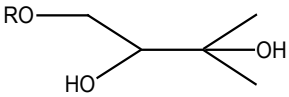
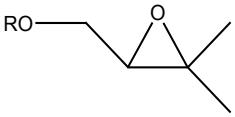
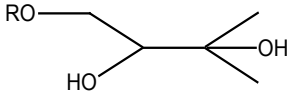
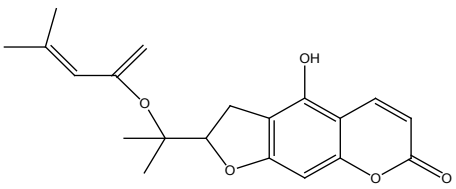
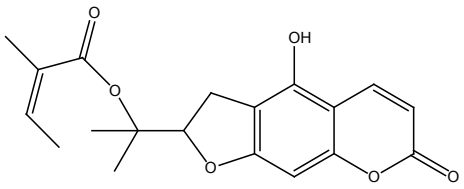
Constituents	R_1	R_2
Fesumtuorin E **(57)**	–	
Fesumtuorin G **(59)**		–
Fesumtuorin H **(60)**		–
Rivulobin D **(61)**	–	

Fig. 3 (c). Psoralen type of coumarins isolated from *Ferula* L.

	
(−)-5-hydroxyprantschimgin **(62)**	(−)-5-hydroxydeltoin **(63)**

Twelve furanocurarines are described in which the furan ring is attached to the pyrone ring of coumarin. The compounds are rarely found in plants and are described in Kahraman et al., Kojima et al., Motai et al. [8, 27, 28] as "unusual" metabolites.

Furanocoumarins with a sesquiterpenoid fragments 2,3-dihydro-7-hydroxy-2,3-dimethyl-2-[4′,8′-dimethyl-3′,7′-nonadienyl]-furo[3,2,c] coumarin **(64)** 2,3-dihydro-7-hydroxy-2,3-dimethyl-3-[4′,8′-dimethyl-3′,7′-nonadienyl]-furo [3,2,c]coumarin **(65)** were found. The structures were determinated by difference spectroscopic methods. Chloroform and ethyl acetate extracts containing these phenolic metabolites showed the highest antioxidant capacity and antimicrobial activities [8].

Analogous isomeric compounds of four novel prenyl-furocoumarin type sesquiterpenoid derivatives **(65a-68)** have been described Kojima et al., which isolated from an ethyl acetate extract obtained by fractional extraction of total methanol of *F. feruloides* [27].

Six sesquiterpene coumarin derivatives which are of special interest as it represents a new metabolites series fukanefuromarin J **(69)**, fukanefuromarin K **(70)**, fukanefuromarin L **(71)**, fukanefuromarin M **(72)**, fukanefuromarin H **(73)**, fukanefuromarin I **(74)** were isolated from an 80% aqueous methanol extract of the roots of *F. fukanensis*. The structures were established on the basis of spectroscopic methods, particularly heteronuclear multiple-bond connectivity (HMBC) and high-resolution mass spectroscopy (MS). The derivatives inhibited nitric oxide (NO) and inducible NO synthase, in terleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) gene expression in a murine macrophage-like cell line (RAW264.7) [28]. Motai and Kitanaka identified other derivatives of fukanefuromarins A-G **(75-81)** [14].

It was reported that baigene C **(82)** and O-methyl baigene C **(83)** from *F. mongolica* inhibit a-glucosidase, which is an enzyme responsible for the cleavage of glucose from disaccharides and oligosaccharides [12, 29].

New sesquieterpene coumarin, namely latisectin **(84)** together with one known compound, kopetdaghin C **(85)** were reported from the root of *F. latisecta* [30].

The phytochemical characterization of the aqueous-ethanol (5:95, v/v) extract of the roots of *F. ferulaeoides* (Steud.) Korov led to the separation of three terpenoid coumarins, series ferulin A-C **(86-88)** [14].

The structures of furanocoumarins are given in Fig. 4 (a), Fig. 4 (b), and Fig. 4 (c).

2.2. Other coumarins

There are also thirty nine coumarins **(89-128)**, a distinctive feature of which is the site of attachment of the terpenoid fragment at the C-7 position of the aglycone.

Some of the common terpenoid coumarins found in the roots and fruits of *Ferula* L. species are samarcandin **(89)** and samarcandin acetate **(90)**, samarkandone **(91)**, gummosin **(92)**, feselol **(93)**, conferone **(94)**, conferol **(95)** [12–15, 17, 18, 31–34].

Derivatives of the conferoside **(96)** and cauferoside **(97)** were identified in *F. conocaula* Korovin [19]. Previously, Bagirov et al., described the tavikone **(98)** from the kazakh specie *F. karatavica* Rgl. et Schmalh. Feselol **(93)** and conferol **(95)** are found in eleven species *F. juniperina* Korovin, F. sumbul (Kauffm.) Hook. fil., F. conocaula Korovin. *F. sinkiangensis* K.M. Shen, *F. vesceritensis*, *F. drudeana*, *F. tenuissima*, *F. huber-morathii*, *F. duranii*, *F. assa-foetida* L., *F. narthex* Boiss. [12, 17, 19, 23, 32–35].

Kuliyev et al., reported ferocolin **(99)**, ferocolinin **(100)**, ferocolidin **(101)**, ferocolicin **(102)**, kauferin **(103)**, kauferidin **(104)**, conferdione **(105)**, feterin **(106)**, kualozide **(107)** which obtained from the roots and fruits of *F. conocaula* Korovin [19].

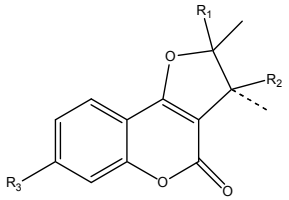
A series of terpenoid coumarins mogoltadin derivatives (7-[(6-hydroxy-5,5,8a-trimethyl-2-methylidene-decahydronaphthalen-1-yl)methoxy]-2H-chromen-2-one) **(108)**, mogoltavidin **(109)**, mogoltavinin **(110)**, mogoltavin **(111)**, mogoltavicin **(112)**, mogoltacin **(113)**, mogoltadone **(114)**, mogoltavin **(115)** were isolated from the roots of *F. mogoltavica* and *F. lithophila* Pimenov [27, 32].

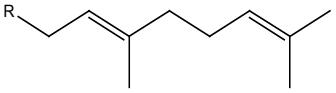
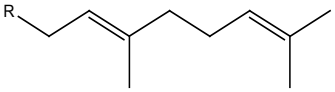
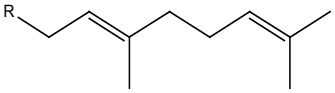
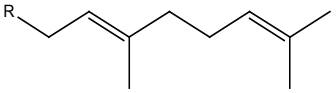
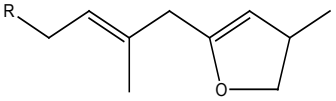
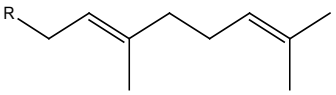
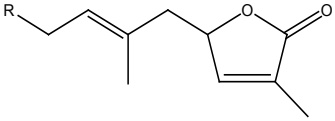
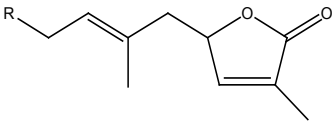
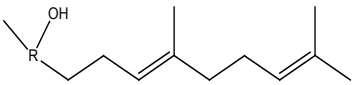
The isolations of new natural metabolites as antitumor agents tadzhiferin **(116)**, farnesiferol B **(117)**, and tavimolidine **(118)** and **(119-124)** reported in [13, 22, 32, 36–38].

Abd El-Razeket et al. established the structure of colladonin **(123)**, which coincides with farnesiferol A **(119)** [13, 22, 25]. However farnesiferol C **(120)** was isolated from species *F. sinkiangensis* K.M. Shen and *F. vesceritensis* [12, 33].

Batirov et al., and Babekov et al., found galbanic acid **(125)** in the leaves and root system of *F. kokanica*, while Ermatov et al., isolated two new terpenoid coumarin: a ketone and an alcohol from the roots of *F. penninervis* Rgl. et Schmalch., which have been named kamolone **(126)** and kamolol

Fig. 4 (a). Furanocoumarins isolated from *Ferula* L.



Constituents	R_1	R_2	R_3
2,3-dihydro-7-hydroxy-2,3-dimethyl-2-[4′,8′-dimethyl-3′,7′-nonadienyl]-furo[3,2,c]coumarin **(64)**	–		OH
2,3-dihydro-7-hydroxy-2,3-dimethyl-3-[4′,8′-dimethyl-3′,7′-nonadienyl]-furo [3,2,c]coumarin **(65)**		–	OH
2,3-dihydro-7-hydroxy-2S*,3R*-dimethyl-3-[4,8-dimethyl-3(E),7-nonadienyl]-furo[3,2-c]coumarin **(65a)**		–	OH
2,3-dihydro-7-hydroxy-2R*,3R*-dimethyl-3-[4,8-dimethyl-3(E),7-nonadienyl]-furo[3,2-c]coumarin **(66)**	–		OH
2,3-dihydro-7-hydroxy-2S*,3R*-dimethyl-3-[4-methyl-5-(4-methyl-2-furyl)- 3(E)-pentenyl]-furo[3,2-c]coumarin **(67)**	–		OH
2,3-dihydro-7-methoxy-2S*,3R*-dimethyl-3-[4,8-dimethyl-3(E),7-nonadienyl]-furo]3,2-c]coumarin **(68)**	–		MeOH
Fukanefuromarin J **(69)**		–	OH
Fukanefuromarin K **(70)**		–	OH
Fukanefuromarin L **(71)**		–	OH

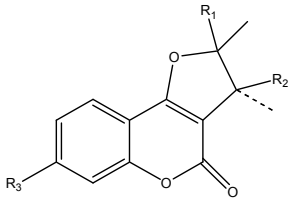
(127), respectively. Galbanic acid together with umbelliprenin shown inhibitory activities against promastigotes of *L. major* (antileishmanial activity) [12, 14, 15, 18, 21, 22, 37]. New metabolite reoselin **(128)** obtained from the roots of *F. juniperina* Korovin, along with other coumarins [17].

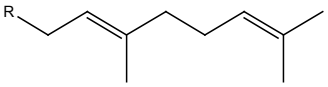
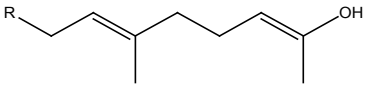
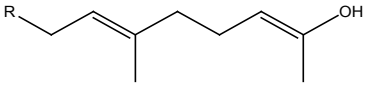
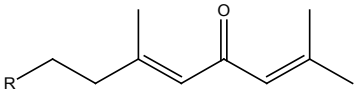
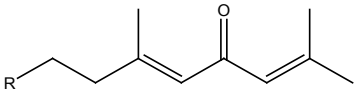
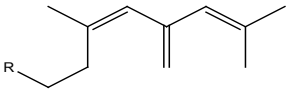
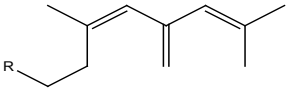
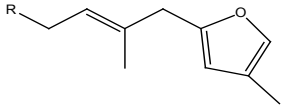
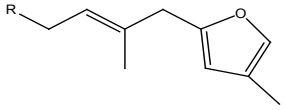
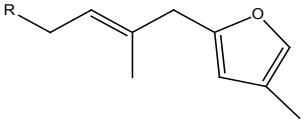
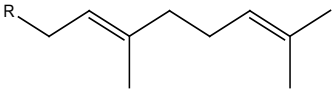
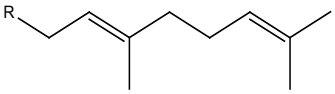
The structures of terpene coumarins are shown in Fig. 5 (a) and Fig. 5 (b).

The investigation of different parts of *F. sinkiangensis* K.M. Shen, led to the separation of series sinkiangenol A-E **(129-133)** [15].

Four known compounds farnesiferol A **(119)**, farnesiferol B **(117)**, badrakemone **(134)**, gummosin **(92)** and a new farnesiferone A **(135)** from the roots of *F. persica* Willd., and badrakemone **(134)**, farnesiferone A **(135)** with farnesiferol A **(119)** from the aerial parts were also isolated. Their structures were elucidated by spectroscopic methods. Later farnesiferone A **(135)** and farnesiferone B **(136)** found from another specie *F. sinkiangensis* K.M. Shen [13, 15].

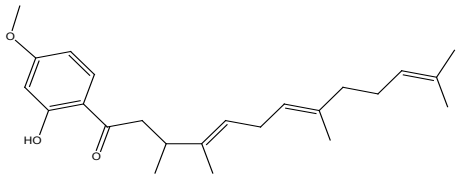
Fig. 4 (b). Furanocoumarins isolated from *Ferula* L.



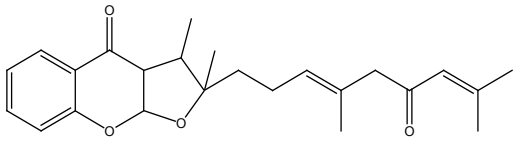
Constituents	R_1	R_2	R_3
Fukanefuromarin M **(72)**		–	–
Fukanefuromarin H **(73)**		–	OH
Fukanefuromarin I **(74)**		–	OH
Fukanefuromarin A **(75)**		–	OH
Fukanefuromarin B **(76)**		–	OH
Fukanefuromarin C **(77)**		–	OH
Fukanefuromarin D **(78)**		–	OH
Fukanefuromarin E **(79)**	–		MeO
Fukanefuromarin F **(80)**	–		MeO
Fukanefuromarin G **(81)**		–	MeO
Baigene C **(82)**		–	OH
O-methyl baigene C **(83)**		–	MeO

The resins of *F. assa-foetida* L. and *F. sinkiangensis* K.M. Shen were extracted with chloroform. Successive chromatographic separation led to the isolation of two new sesquiterpene coumarins, designated assafoetidnol A **(137)** and assafoetidnol B **(138)**. In addition to six other compounds, gummosin **(92)**, polyanthin **(139)**, badrakemin **(140)**, neveskone **(141)**, samarcandin **(89)**, galbanic acid **(125)** and saradaferin **(142)** determinate in roots *F. assa-foetida* L. [15, 22, 39].

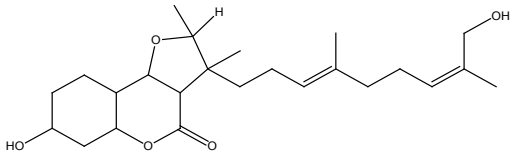
Fig. 4 (c). Sesquieterpene coumarin isolated from *Ferula* L.



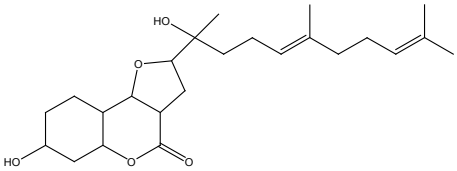
Latisectin **(84)**



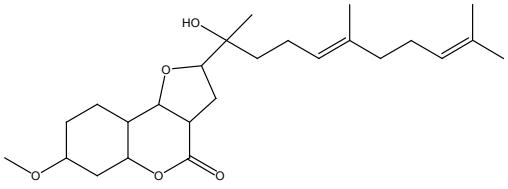
Kopetdaghin C **(85)**



Ferulin A **(86)**

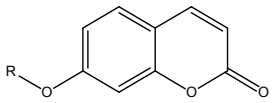


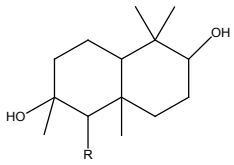
Ferulin B **(87)**



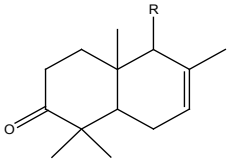
Ferulin C **(88)**

Fig. 5 (a). Coumarins isolated from *Ferula* L.

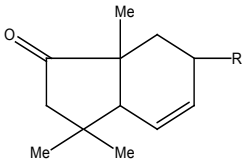




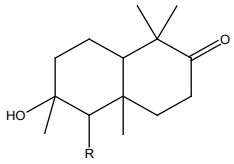
Samarcandin **(89)**



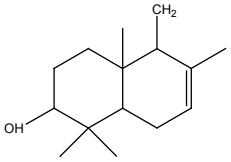
Conferone **(94)**



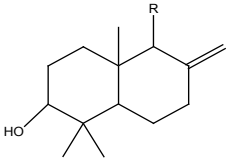
Tavicone **(98)**



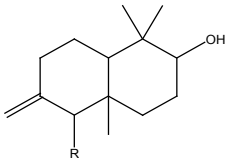
Samarcandone **(91)**



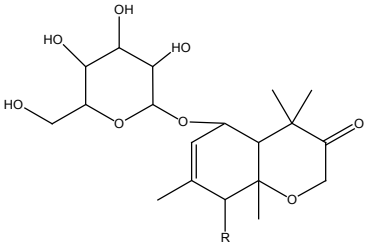
Conferol **(95)**



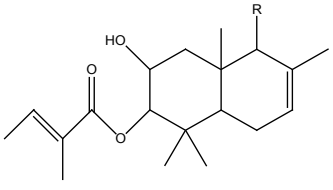
Mogoltadin **(108)**



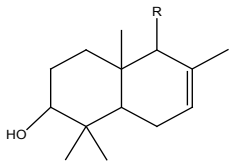
Gummosin **(92)**



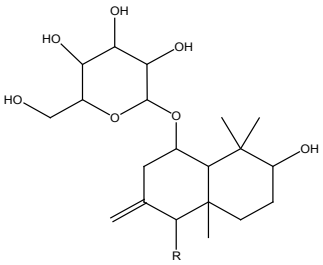
Conferoside **(96)**



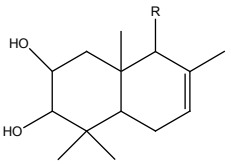
Mogoltavinin **(109)**



Feselol **(93)**

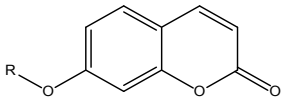


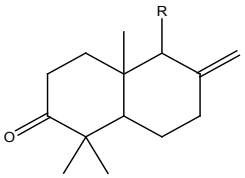
Cauferoside **(97)**



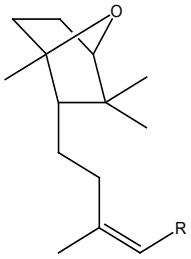
Mogoltin **(111)**

Fig. 5 (b). Coumarins isolated from *Ferula* L.

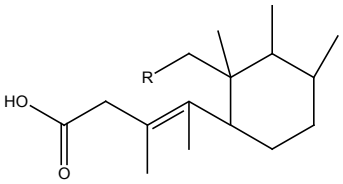




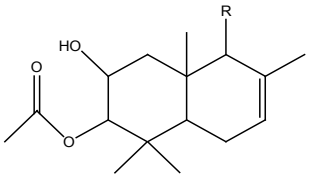
Mogoltadone (**114**)



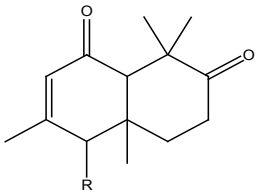
(-)-Farnesiferol C **(120)**



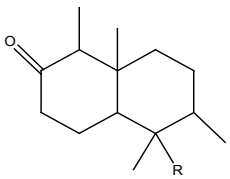
Galbanic acid **(125)**



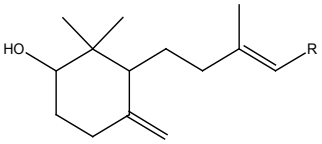
Mogoltavin **(115)**



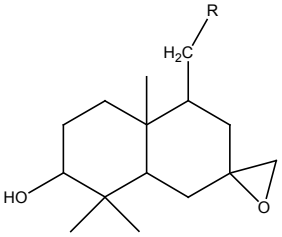
Epi-conferdione **(122)**



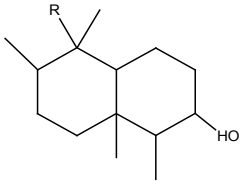
Kamolone **(126)**



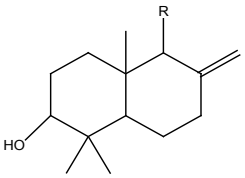
Farnesiferol B **(117)**



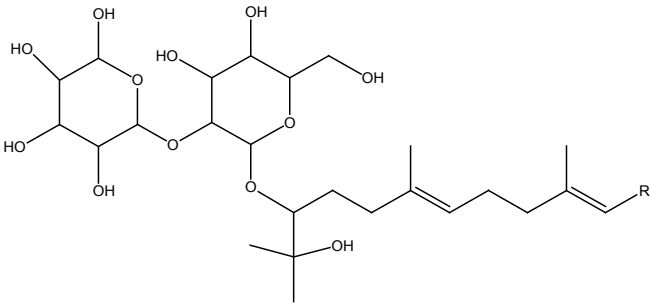
Sumferin **(124)**



Kamolol **(127)**



Farnesiferol A **(119)** colladonin **(123)**



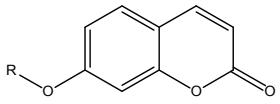
Reoselin **(128)**

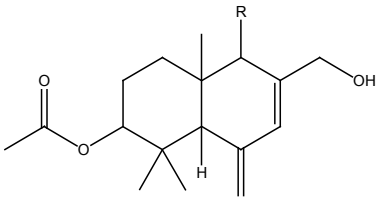
Isofeterin **(143)**, shinkianone **(144)** and lehmannolol **(145)**, lehmannolone **(146)** were identified from the 95% ethanol extract of the roots of *F. teterrima* Kar. & Kir. and *F. sinkiangensis* K.M. Shen [14, 33].

Bashir and colleagues have isolated two sesquiterpene coumarins, fnarthexone **(147)**, fnarthexol **(148)**, as three known derivatives from the methanol extract of *F. narthex Boiss*. obtained by using a maceration method. It is interesting to note that from the stereochemical point of view, fnartexol **(148)** is the epimer at C-5′ of conferol, a natural compound also identified in *F. nartex Boiss*. during the reported study [40].

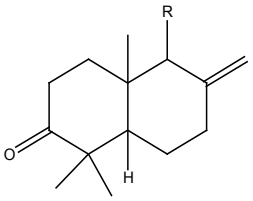
The chloroform extract of *F. sinkiangensis* K. M. Shen significantly inhibited the NO production in LPS-induced BV-2 microglial cells. Sixteen bioactive sesquiterpene coumarins (3′S, 8′R, 9′S, 10′R)-sinkianol A, B **(149, 150)**, ferukrin **(151)**, (5′S, 8′R, 9′S, 10′R)-ferukrinone **(152)**, (3′S,5′S, 8′R, 9′S, 10′R)-kellerin **(153)**, (3′S,5′S, 8′R, 9′S, 10′R)-deacetylkellerin **(154)**, polyanthinin **(139)**, methyl galbanate **(155)** were reported [22].

Fig. 6 (a). Coumarins isolated from *Ferula* L.

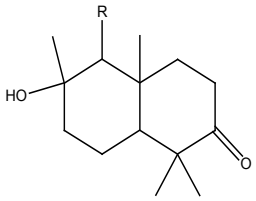




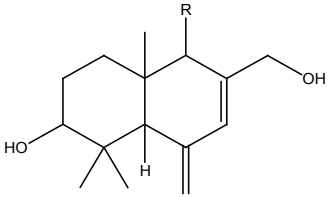
Sinkiangenol A **(129)**



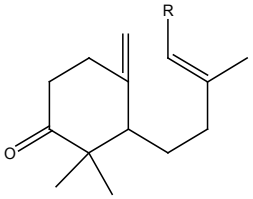
Farnesiferone A **(135)**



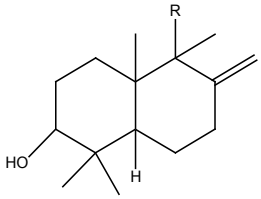
Neveskone **(141)**



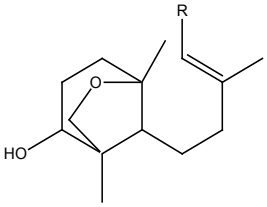
Sinkiangenol B **(130)**



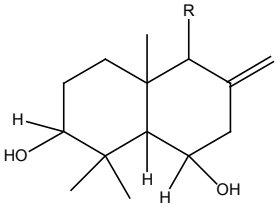
Farnesiferone B **(136)**



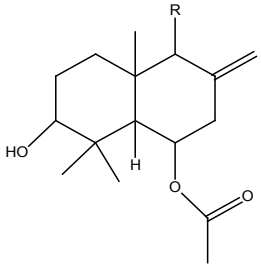
Saradaferin **(142)**



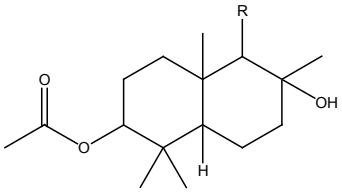
Sinkiangenol C **(131)**



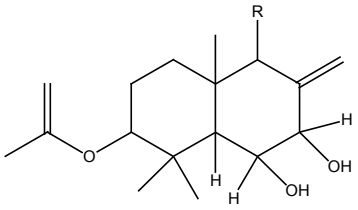
Assafoetidnol A **(137)**



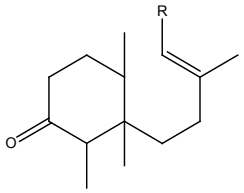
Isofeterin **(143)**



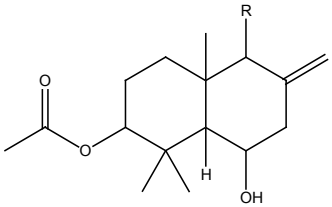
Sinkiangenol D **(132)**



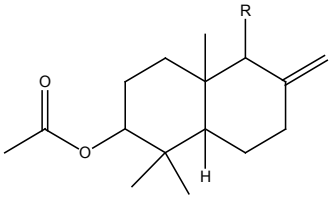
Assafoetidnol B **(138)**



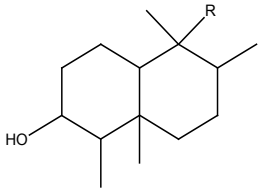
Shinkianone **(144)**



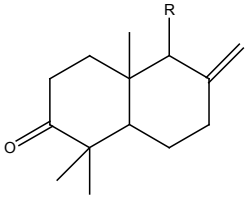
Sinkiangenol E **(133)**



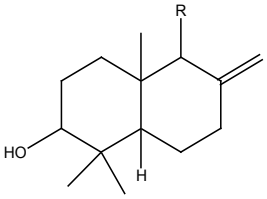
Polyanthinin **(139)**



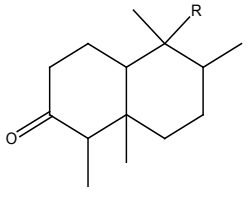
Lehmannolol **(145)**



Badrakemone **(134)**

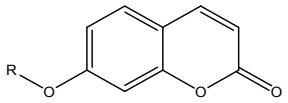


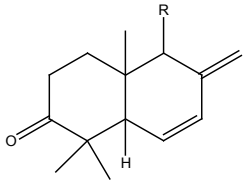
Badrakemin **(140)**



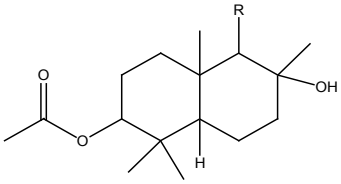
Lehmannolone **(146)**

Fig. 6 (b). Coumarins isolated from *Ferula* L.

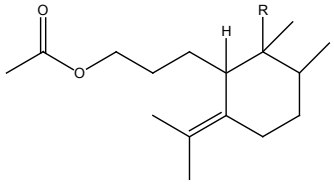




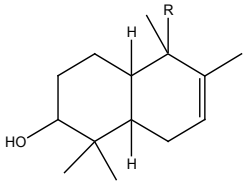
Fnarthexone **(147)**



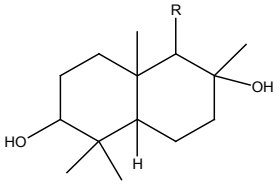
(3’S,5’S,8’R,9’S,10’R)-kellerin **(153)**



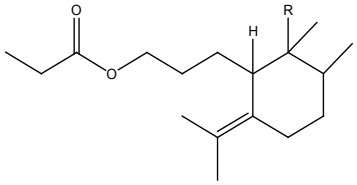
Fekrynol acetate **(159)**



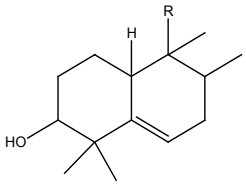
Fnarthexol **(148)**



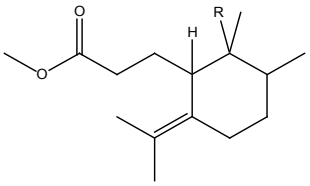
(3′S,5′S, 8′R,9′S,10′R)-deacetylkellerin **(154)**



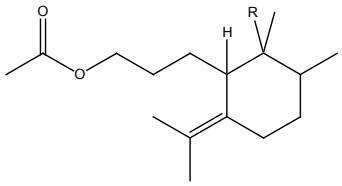
(8’S,9’S,10’S)-Propionyl fekrynol **(160)**



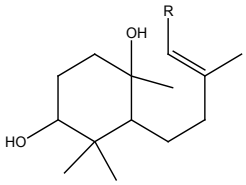
(3’S,8’R,9’S,10’R)-sinkianol A **(149)**



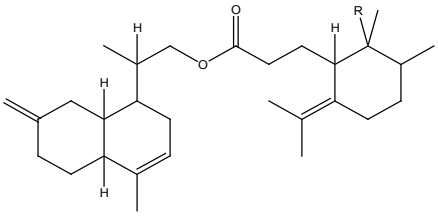
Methyl galbanate **(155)**



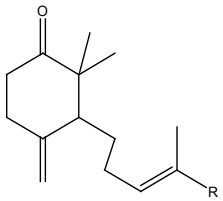
Ethyl galbanate **(161)**



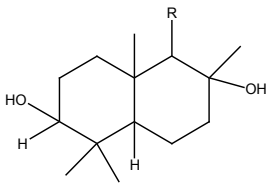
(3′R,5′R,10′R)-sinkianol B **(150)**



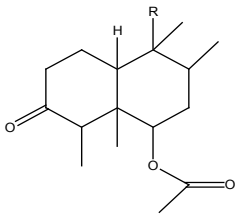
Sanandajin **(156)**



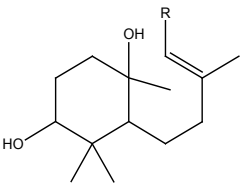
Fekolone **(162)**



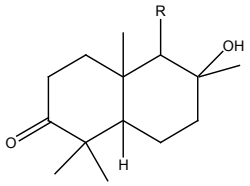
Ferukrin **(151)**



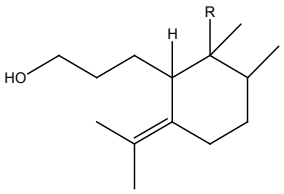
Kamolonol acetate (**157**)



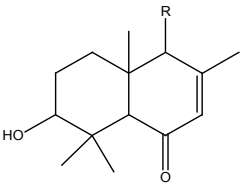
Fekrol **(163)**



(3’S,5’S,8’R,9’S,10’R)-ferukrinone (**152**)



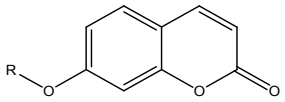
Fekrynol **(158)**

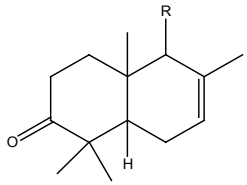


Ferocaulidin **(164)**

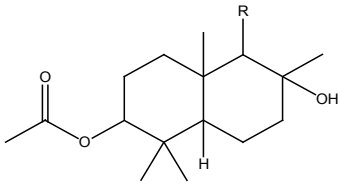
The rare first disesquiterpene coumarin, sanandajin **(156)**, and sesquiterpene coumarins kamolonol acetate **(157)**, fekrynol **(158),** fekrynol acetate **(159)**, (8’S ,9’S,10’S)- propionyl fekrynol **(160)**, ethyl galbanate **(161)**, methyl galbanate **(155)**, farnesiferol B **(117)** isolated from a n-hexane extract of *F. pseudalliacea* roots and *F. sinkiangensis* K.M. Shen [15, 36]. The structures of coumarins are shown in Fig. 6 (a).

Fig. 6 (c). Coumarins isolated from *Ferula* L

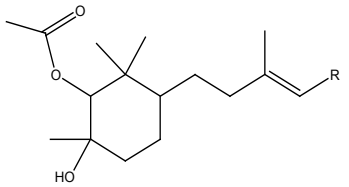




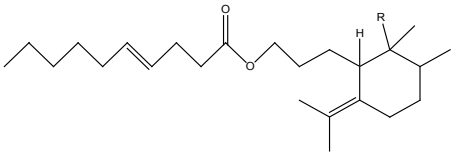
Isosamarcandin **(165)**



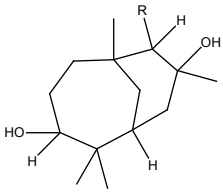
Colladocin **(170)**



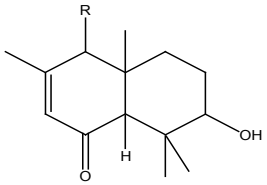
8-O-acetyl sinkiangenorin F **(175)**



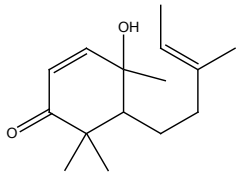
Ferusingensine F **(166)**



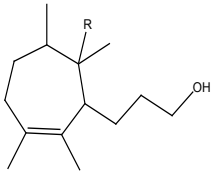
Sinkiangenorin E **(171)**



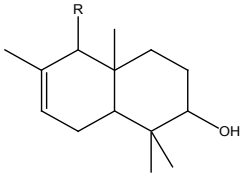
Ligupersin A **(176)**



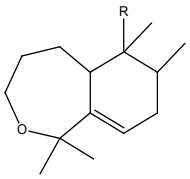
Ferusingensine G **(167)**



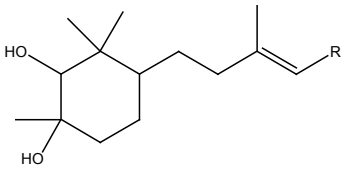
Sinkiangenorin D **(172)**



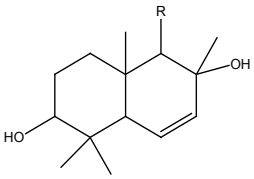
Mogoltacin **(177)**



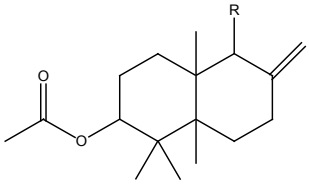
Ferusingensine H **(168)**



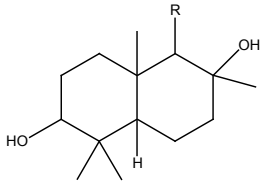
Sinkiangenorin F **(173)**



Gumosin **(178)**



Coladin **(169)**



Episamarcandin **(174)**

Ten sesquiterpene coumarins from *F. sinkiangensis* K.M. Shen fekolone **(162)**, fekrol **(163)**, ferocaulidin **(164)**, isosamarcandin **(165)**, ferusingensine F **(166)**, ferusingensine G **(167)**, ferusingensine H **(168)**, coladin **(169)**, colladocin **(170)**, sinkiangenorin E **(171)** were reported [15]. In additionally, Li et al. characterized series sinkiangenorin D **(172)** and F **(173)**, together with known compounds, lehmannolol **(145)**, lehmannolone **(146)**, episamarcandin **(174)**, colladonin **(123)**, sinkianone **(175)**, fekrynol **(158)**, fekolone **(162)**, feselol **(93)**, umbelliprenin (5), and farnesiferol C **(120)**. Two new sinkiangenorin F **(173)** and 8-O-acetyl sinkiangenorin F **(175)** were isolated from the seeds. The structures of the new compounds, including the relative stereochemistry and the absolute configuration were elucidated through extensive spectroscopic methods. The two metabolites were tested against the K562, HeLa, and AGS human cancer cell lines and showed cytotoxic activities [15, 41]. The structures of coumarins are shown in Fig. 6 (b) and Fig. 6 (c).

The resins of *F. assa-foetida* L. and *F. sinkiangensis* K.M. Shen were extracted with chloroform. Successive chromatographic separation led to the isolation of two new sesquiterpene coumarins, designated assafoetidnol A **(137)** and assafoetidnol B **(138)**. In addition to six other compounds, gum-

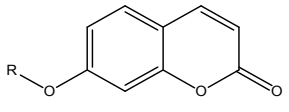
mosin **(92)**, polyanthin **(139)**, badrakemin **(140)**, neveskone **(141)**, samarcandin **(89)**, galbanic acid **(125)** and saradaferin **(142)** determinate in roots *F. assa-foetida* L. [15, 22, 39].

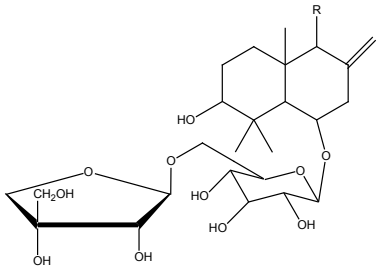
Two compounds ligupersin A **(176)** and mogoltacin **(177)** have considerable activity against influenza A virus isolated from an extract of *F. assa-foetida* L. and *F. persica* [12].

Three sesquiterpene derivatives obtained from the methanol extract from the roots of *F. gummosa Boiss*. Among those three compounds, gumosin **(178)** is a coumarin derivative, and gumosides A **(179)** and B **(180)** are glycosides. Iranshahi et al. have reported new sesquiterpene coumarin glycosides including persicaosides A-D **(181-184)** from the roots of *F. persica* [15, 42].

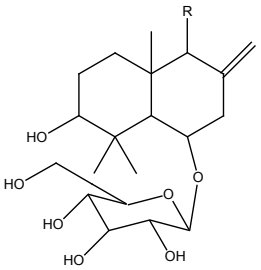
The structures of coumarins are shown in Fig. 7.

Fig. 7. Glycosides isolated from *Ferula* L.

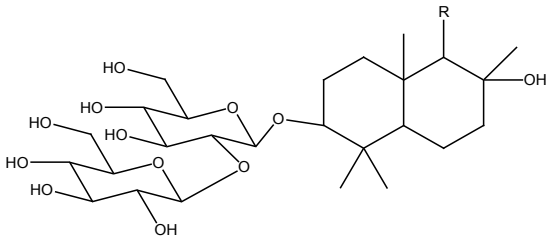




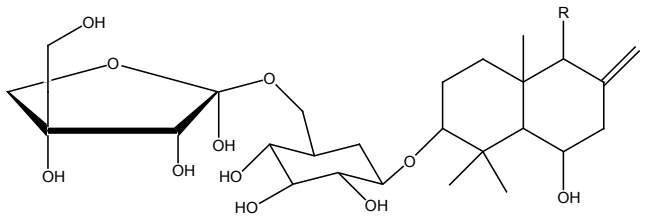
Gumosides A **(179)**



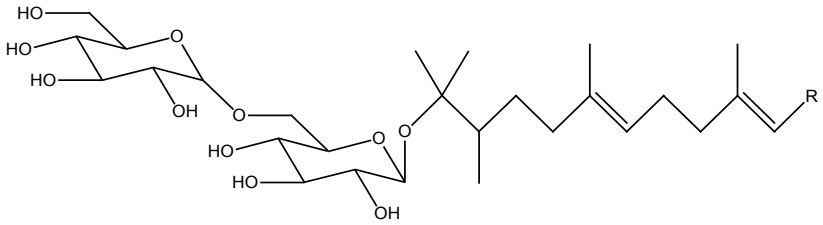
Gumosides B **(180)**



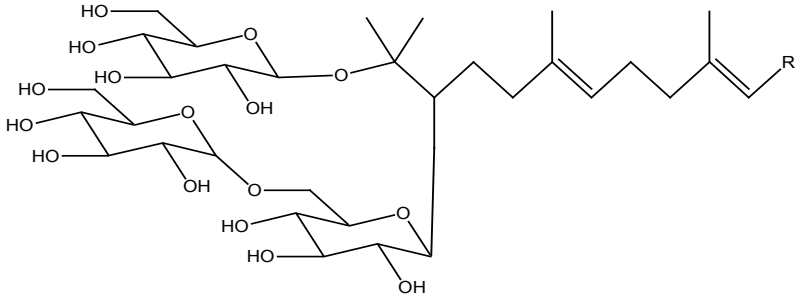
Persicaosides A **(181)**



Persicaosides B **(182)**



Persicaosides C **(183)**



Persicaosides D **(184)**

This review was shown the perceptivity for the study of original species of local flora containing various polyphenolic compounds with a wide range of biological activities [43]. Nowadays, research has been intensively carried out on the modification of polyfenolic compounds. The number of works dedicated to the modification of natural metabolites, including coumarins, furanocoumarins, using transition metal catalyzed reaction are given in the review [44].

3. Conclusions

Nearly 185 coumarins from 35 species of the genus *Ferula* L. growing in different countries were reported. Coumarins are represented mainly by umbelliferone (7-O-hydroxycoumarin) derivatives substituted in the C-7 position of aglycone, furanocoumarins and metabolites have a terpene fragment (hemiterpene, monoterpen, sesquiterpene), esters, and glycosides. Additionally, umbelliferon found as a taxon for the genus *Ferula* L. Furocoumarins are of the psoralen type, containing a furan ring in the C-6 and C-7 positions of the primary skeleton. Some «unusual» metabolites have a furan fragment attached to the pyrone ring of the coumarin. The biological activities of some extracts and some individual metabolites such as antiinflammatory, cytotoxicity, antibacterial, antileishmanial, antiviral, antigenotoxic, antitumor, anticoagulant, antioxidant, antimycobacterial, inhibition a-glucosidase, antileishmanial were found.

References

[1]. M.S. Sagyndykova, A. Imanbayeva, Y. Suleimen, M. Ishmuratova, *Bulletin of the Karaganda University* (chemistry series) 96 (2019) 25–34.

[2]. N.V. Pavlov, Flora Kazahstana [Flora of Kazakhstan], Izdatel'stvo akademii nauk Kazahskoj SSR: Alma-Ata, 1963. Vol. 6. p. 466 (in Russian).

[3]. L.M. Grudzinskaya, N.G. Gemedzhieva, N.V. Nelina, Zh.Zh. Karzhaubekova, Annotirovannyj spisok lekarstvennyh rastenij Kazahstana [Annotated list of medicinal plants of Kazakhstan] Almaty, 2014. p. 200. (in Russian)

[4]. K. Kamoldinov, M. Sobirov, A. Nishonov, et al., *Universum: Chemistry and biology* 7 (2021) 22–26. https://7universum.com/ru/nature/archive/item/12051

[5]. Z.-Q. Wang, C. Huang, J. Huang, H.-Y. Han, et al., *RSC Adv.* 4 (2014) 14373–14377. DOI: 10.1039/c4ra00547c

[6]. J. Huang, H.-Y. Han, G.-Y. Li, H.-Y. Wang, et al., *J. Asian Nat. Prod. Res.* 15 (2013) 1100–1106. DOI: 10.1080/10286020.2013.818660

[7]. H. Hashemzadeh, M. Iranshahy, M. Iranshahi, H. Raissi, C*omput. Biol. Med*. 146 (2022) 105566. DOI: 10.1016/j.compbiomed.2022.105566

[8]. C. Kahraman, G. Topcu, E. Bedir, I.I. Tatli, et al., *Saudi Pharm. J.* 27 (2019) 525–531. DOI: 10.1016/j.jsps.2019.01.016

[9]. R. Niazmand, B. Razavizadeh, *J. Food Sci. Technol.* 58 (2021) 2148–2159. DOI: 10.1007/s13197-020-04724-8

[10]. M. Iranshahy, K.H. Mohammad, *J. Essent. Oil-Bear. Plants* 11 (2013) 350–355. DOI: 10.1080/0972060x.2008.10643640

[11]. R. Han, Y. Sun, R. Ma, D. Wang, et al., *Evid.-Based Complement. Altern. Med.* 29 (2022) 5092742. DOI: 10.1155/2022/5092742

[12]. Z.E. Nazari, M. Iranshahi, *Phytother. Res.* 25 (2011) 315–323. DOI: 10.1002/ptr.3311

[13]. Z. Sattar, M. Iranshahi, *Iran J. Basic Med. Sci.* 20 (2017) 1–8. DOI: 10.22038/ijbms.2017.8085

[14]. M. Mohammadhosseini, A. Venditti, S.D. Sarker, L. Nahar, et al., *Ind. Crops Prod.* 1 (2018) 350–394. DOI: 10.1016/j.indcrop.2018.12.012

[15]. M.T. Khayat, M. Alharbi, K.F. Ghazawi, G.A. Mohamed, et al., *Plants* 12 (2023) 902. DOI: 10.3390/plants12040902

[16]. P. Taghinia, M.H. Haddad Khodaparast, M. Ahmadi, *J. Food Meas. Charact.* 13 (2019) 2980–2987. DOI: 10.1007/s11694-019-00218-0

[17]. A.R. Kurbonov, M.G. Pimenov, *Botanical Journal* 101 (2016) 1220–1239. DOI: 10.1134/S0006813616100070

[18]. E.Kh. Batirov, M.P. Yuldashev, G.A. Nezhinskaya, V.M. Malikov, *Chem. Nat. Compd*. 5 (1979) 727–728. DOI: 10.1007/BF00565951

[19]. Z.A. Kuliev, T.Kh. Khasanov, V.M. Malikov, Coumarins of Ferula conocaula, *Chem. Nat. Compd*. 1 (1982) 120–121.

[20]. A.A. Nabiev, V.M. Malikov, T.Kh. Khasanov, *Chem. Nat. Compd.* 19 (1983). DOI: 10.1007/BF00575721

[21]. N.E. Ermatov, A.I. Ban'kovskii, M.E. Perel'son, *Chem. Nat. Compd*. 2 (1967) 125–127. DOI: 10.1007/BF01134229

[22]. Y. Xing, N. Li, D. Zhou, G. Chen, et al., *Planta Med*. 83 (2017) 135–142. DOI: 10.1055/s-0042-109271

[23]. P. Zhou, Y. Takaishi, H. Duan, B. Chen, et al., *Phytochemistry* 53 (2000) 689–697. DOI: 10.1016/s0031-9422(99)00554-3

[24]. H. Zarei, R. Rezaee, E. Behravan, F. Soltani, F. Mosaffa, et al., *Nat. Prod. Res.* 27 (2013) 1016–1019. DOI: 10.1080/14786419.2012.688053

[25]. M.H. Abd El-Razek, Y.-C. Wu, F.-R. Chang,

J. Chin. Chem. Soc. 54 (2007) 235–238. DOI: 10.1002/jccs.200700035
[26]. I.A. Kiryanova, Yu.E. Sklyar, M.G. Pimenov, *Chem. Nat. Compd.* 18 (1982). DOI: 10.1007/BF00579653
[27]. K. Kojima, K. Isaka, P. Ondognii, O. Zevgeegiin, et al., *Chem Pharm Bull*. 48 (2000) 353–356. DOI: 10.1248/cpb.48.353
[28]. T. Motai, A. Daikonya, S. Kitanaka, *Chem. Pharm. Bull.* 61 (2013) 618–623. DOI: 10.1248/cpb.c12-01028
[29]. M.I. Choudhary, I. Baig, M. Nur-e-Alam, S. Shahzad-ul-Hussan, P. Öndognii, et al., *Helv. Chim. Acta* 84 (2001). DOI: 0.1002/1522-2675(20010815)84:8<2409::AID-HLCA2409>3.0.CO;2-D
[30]. M. Iranshahi, F. Amanolahi, B. Schneider, *Avicenna J. Phytomed.* 2 (2012) 133–138. DOI: 10.22038/ajp.2012.99
[31]. K.A. Eshbakova, A.I. Saidkhodzhaev, *Chem. Nat. Compd.* 39 (2003) 221–222. DOI: 10.1023/A:1024886502827
[32]. É.K. Khalilova, A.I. Saidkhodzhaev, *Chem. Nat. Compd.* 34 (1998) 506–507. DOI: 10.1007/bf02329608
[33]. G. Li, X. Li, L. Cao, L. Zhang, et al., *Fitoterapia* 103 (2015) 222–226. DOI: 10.1016/j.fitote.2015.03.022
[34]. M.S. Abdel-Kader, M.H. Alqarni, S. Baykan, B. Oztürk, et al., *Separations* 8 (2022) 206. DOI: 10.3390/separations9080206
[35]. V.Y. Bagirov, N.P. Kir'yalov, V.I. Sheichenko, *Chem. Nat. Compd*. 5 (1969) 504–505. DOI: 10.1007/bf0056860
[36]. D. Dastan, P. Salehi, A. Reza Gohari, S. Zimmermann, et al., *Phytochemistry* 78 (2012) 170–178. DOI: 10.1016/j.phytochem.2012.02.016
[37]. A.U. Babekov Terpenoidnye kumariny i slozhnye efiry dvuh vidov roda Ferula L. [Terpenoid coumarins and esters of two species of the genus Ferula L.] Innovacionnye usloviya razvitiya nauki i obrazovaniya v mezhkul'turnom vzaimodejstvii: kompleksnyj podhod, Cuhum, 09–12 dekabrya 2015 goda. Cuhum: Ural'skij gosudarstvennyj pedagogicheskij universitet. 2015. P. 25-28. (in Russian).
[38]. G.A. Zhukov, A.P. Prokopenko, *Chem. Nat. Compd.* 3 (1967) 177–176. DOI: 10.1007/BF00567997
[39]. M.H. Abd El-Razek, S. Ohta, A.A. Ahmed, T. Hirata, *Phytochemistry* 58 (2001) 1289–1295. DOI: 10.1016/s0031-9422(01)00324-7
[40]. S. Bashir, M. Alam, A. Adhikari, R.L. Shrestha, et al., *Phytochem. Lett.* 9 (2014). DOI: 10.1016/j.phytol.2014.04.009
[41]. G. Li, J. Wang, X. Li, L. Cao, et al., *Phytochem. Lett.* 13 (2015) 123–126. DOI: 10.1016/j.phytol.2015.06.002
[42]. M. Iranshahi, M. Mojarab, H. Sadeghian, M.Y. Hanafi-Bojd, et al., *Phytochemistry* 69 (2008) 473–478. DOI: 10.1016/j.phytochem.2007.08.001
[43]. N.A. Sultanova, Zh.A. Abilov, A.K. Umbetova, M.I. Choudhary, *Eurasian Chem.-Technol. J.* 15 (2013) 219–226. DOI: 10.18321/ectj225
[44]. E. Shults, *Eurasian Chem.-Technol. J.* 15 (2013) 175–187. DOI: 10.18321/ectj221