BAU Journal - Health and Wellbeing

Volume 6 | Issue 1
ISSN: 2789-8288

Article 4

April 2024

REVIEW ON CHEMICAL CONSTITUENTS AND BIOLOGICAL ACTIVITIES OF GENUS FERULA

Rima Mohammad Kheir Boukhary
Assistant Professor, Pharmaceutical Sciences Department, School of Pharmacy, Lebanese International University, Beirut, Lebanon, boukharyrima@yahoo.com

Zeina Omeiche
PharmD, Pharmaceutical Sciences Department, Faculty of Pharmacy, Beirut Arab University, Beirut, Lebanon, zeinaomeiche@gmail.com

Mohamad Ali Hijazi
Associate Professor of Pharmacognosy and Medicinal Plants, Pharmaceutical Sciences Department, Faculty of Pharmacy, Beirut Arab University, Beirut, Lebanon, m.hijazi@bau.edu.lb

Ali Wassef Assi
Pharmacy student, Faculty of Pharmacy, Beirut Arab University, Beirut, Lebanon, aliwassefassi@gmail.com

Tamar Houri
Pharmacy student, Faculty of Pharmacy, Beirut Arab University, Beirut, Lebanon, houritamar@gmail.com

See next page for additional authors

Recommended Citation

Boukhary, Rima Mohammad Kheir; Omeiche, Zeina; Hijazi, Mohamad Ali; Assi, Ali Wassef; Houri, Tamar; Al Jawiche, Lynn; Dirani, Maria; Abdel Nabi, Rasha; Tabbara, Mohamad; El-Lakany, Abdalla; and Aboul Ela, Maha Prof. (2024) "REVIEW ON CHEMICAL CONSTITUENTS AND BIOLOGICAL ACTIVITIES OF GENUS FERULA," *BAU Journal - Health and Wellbeing*: Vol. 6: Iss. 1, Article 4.
DOI: https://doi.org/10.54729/2789-8288.1200

REVIEW ON CHEMICAL CONSTITUENTS AND BIOLOGICAL ACTIVITIES OF GENUS FERULA

Abstract

Genus Ferula comprises about 220 species of flowering plants belonging to family Apiaceae, distributed in the Mediterranean region and Asia and used in the treatment of different diseases as anti-oxidant, aphrodisiac, carminative, antinociceptive, anti-depressant, antibacterial, anti-fungal, anti-leishmanial, and anti-inflammatory. Moreover, species of this plant are used for dizziness, asthma, bronchitis, and gastrointestinal discomfort. It was reported that all the pharmacological effects of these plants are due to the presence of different phenolic constituents including flavonoids, sesquiterpenes, coumarins and polysulfides. Sesquiterpene coumarins were responsible for the anti-inflammatory and anti-cancer activities by blocking the 5-lipoxygenase enzyme that catalyzes the biosynthesis of leukotrienes (LTs) being a group of lipid mediators of inflammation . This review covers most of the identified chemical constituents of plants from the genus Ferula reported in literature between 2001 and 2023. In addition, the biological activities of the different species of genus Ferula are presented.

Keywords

Ferula, Active constituents, Anti-oxidant activity, Phenolic constituents

Authors

Rima Mohammad Kheir Boukhary, Zeina Omeiche, Mohamad Ali Hijazi, Ali Wassef Assi, Tamar Houri, Lynn Al Jawiche, Maria Dirani, Rasha Abdel Nabi, Mohamad Tabbara, Abdalla El-Lakany, and Maha Aboul Ela Prof.

1. INTRODUCTION

Genus *Ferula* comprises about 220 species and belongs to family Apicaceae native to the Mediterranean region and widely distributed in Afghanistan, Iraq, Turkey, East of Iran, Europe and North Africa (Sahebkar, 2010). They are herbaceous perennial plants growing up to 4 m height characterized by their yellow flower clusters, juicy stems and roots rich in resins (Amalraj, 2017). This genus has been used as sedative and for the treatment of several disorders such as headache, arthritis, diabetes and rheumatism. In addition the essential oils of *Ferula* have demonstrated antibacterial, antiviral, antifungal and anticancer properties (Seyyed, 2017). Asafoetida has a sulfurous odor and is a popular in the Indian kitchen processing because of its odor like garlic and onion (Takeoka, 2001). *Ferula* is also used as a digestive aid by affecting the odor and color of some foods and thus increasing the appetite (Amiri, 2013). It was reported that the resin collected from this species is used in the treatment of whooping cough, cholesterol, cancer and hypertension (Mahendra, 2012). It has a cardio protective effect in low doses, is toxic in higher doses and used in organic farming in order to kill insects (Kavoosi, 2013). Researchers reported that *Ferula orientalis* was used as stimulant and aphrodisiac (Aysu, 2013). Reports of the chemical components of many of genus of *Ferul*a determined the presence of coumarins, sesquiterpenes, hyperoside, chlorogenic acid and caffeic acid responsible for diverse pharmacological effects and antioxidant activity (Hatice, 2021). Twenty two constituents mainly monoterpenes were identified in *Ferula microcole* from the oil (Amiri, 2013). In addition, a study performed on F. hermonis growing in Lebanon has revealed its neuroprotective potentials (Raafat, 2016; & El-Lakany, 2015). Reports of the chemical constituents of many of them suggested their use in cosmetic preparations and pharmaceuticals thus replacing the synthesized toxic antioxidants (Sahebkar, 2010). This article aims to provide an overview of chemical constituents, medical uses, pharmacological activities and safety of *Ferula* species indicating their impact in phytotherapy and the possibility of including some of them in the field of drug industry.

Table 1: Figures of the most common *Ferula* species

***Ferula* species**	**Illustration**	**Ref.**
F. assafoetida		**(Amalraj et al., 2017)**
F. communis		**(Akaberi, et al., 2015)**
***F. elaeochytris* Korovin**		**(Aydogan., et al., 2020).**

F. gummosa		**(Amir, et al., 2022)**
F. hermonis. Boiss		**(Karim, et al., 2019)**
F. jaeschkeana		**(Ubaid et al., 2017)**
F . microcolea		**(Usama et al., 2013)**
***F. orientalis* L**		**(Aysu et al., 2013)**

Table 2. Sesquiterpene coumarins isolated from the genus *Ferula*

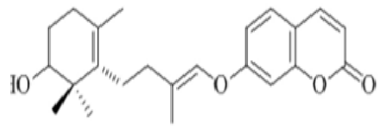
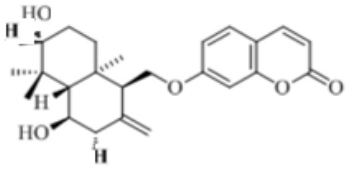
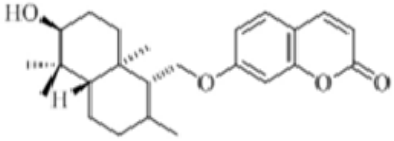
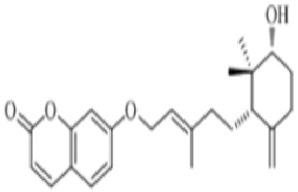
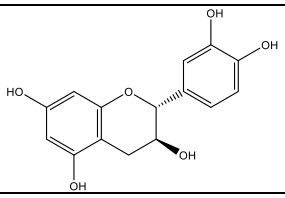
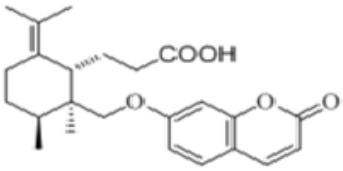
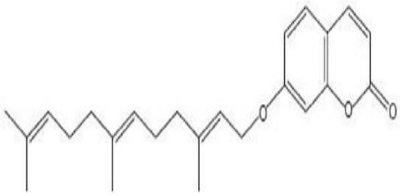
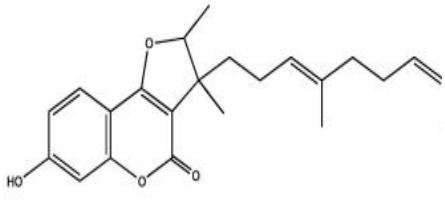
Name	*Ferula* species (Part used)	Structure	Reference
Assafoetidin	*F. assafoetida* (Flowers)		(Augustine *et al*., 2017)
Assafoetidinol A	*F. assafoetida* (Leaf & gum extracts)		(Augustine *et al*., 2017)
Conferol	*F. assafoetida*		(Akaberi *et al*., 2015)
Franesiferol B	*F. assafoetida* (Leaf & gum extracts)		(Augustine *et al*., 2017)
Franesiferol C	*F. assafoetida* (Leaf & gum extracts)		(Akaberi *et al*., 2015)
Galanic acid	*F. assafoetida* (Leaf & gum extracts)		(Niazmand et al., 2021)
Umbelliprenin	*Ferula szowitsiana* (Leaf & gum extracts) *Ferula* sinkiang ensis (Leaf & gum extracts)		(Omid et al., 2012) (Lijing et al., 2015)
2,3-dihydro-7-hydroxy-2,3-dimethyl-3-[40,80-dimethyl-30,70-nonadienyl]-furo[3,2,c]coumarin	*Ferula caspica* M. Bieb (aerial parts)		(Cigdem et al., 2015)

Table 3. Sulfur compounds isolated from the genus *Ferula*

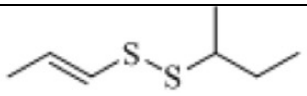
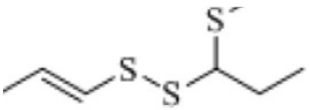
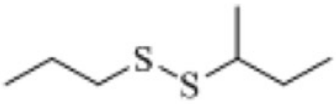
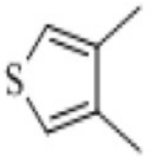
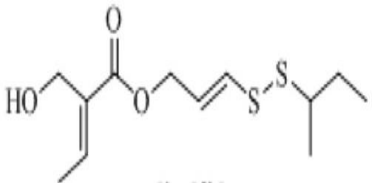
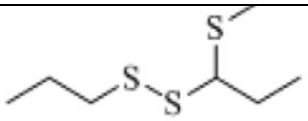
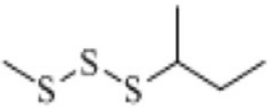
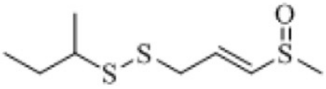
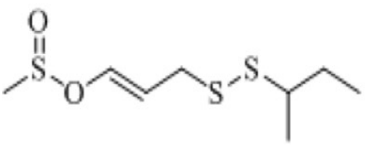
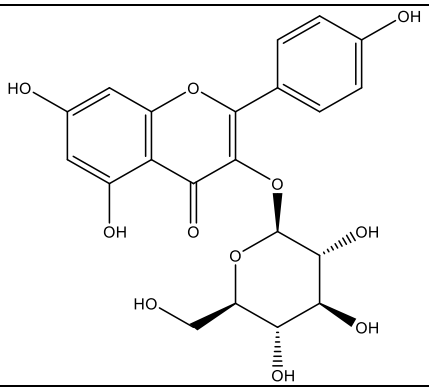
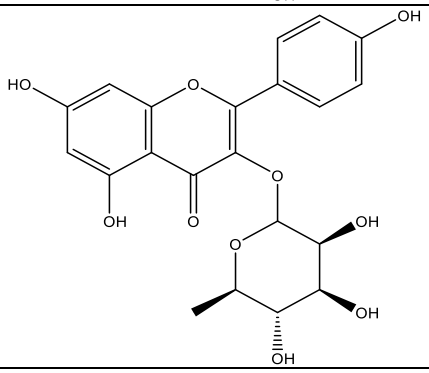
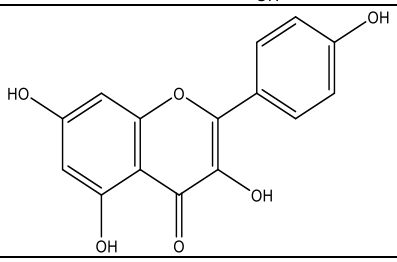
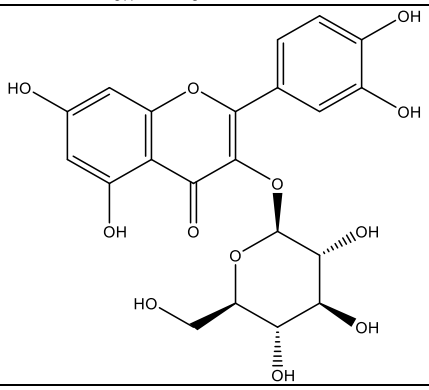
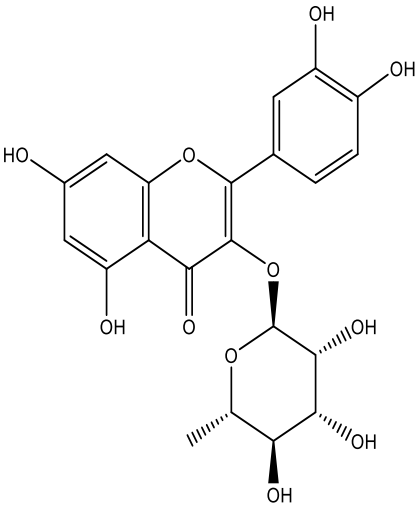
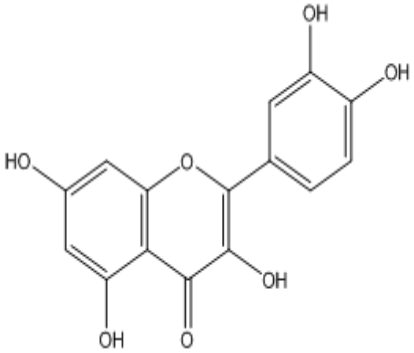
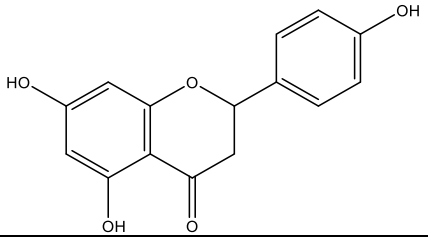
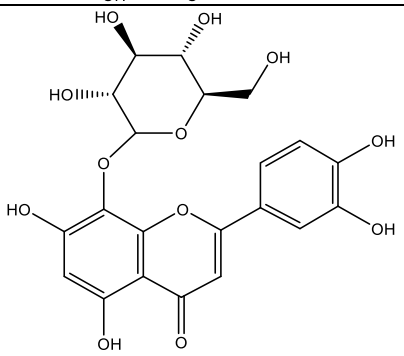
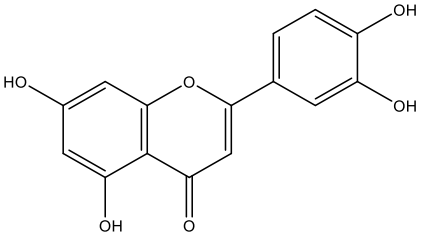
Name	*Ferula* species (Part used)	Structure	Reference
2-butyl-1-propenyl disulfide	*F. assafoetida* (Leaf & gum extracts)		(Augustine *et al*., 2017) (Takeoka.,2001)
1-(methylthio) propyl1-propenyl disulfide	*F. assafoetida* (Leaf & gum extracts)		(Augustine *et al*., 2017)
2 –buthyl- propyl disulfide	*F. assafoetida* (Leaf & gum extracts)		(Takeoka. *et al*., 2001)
3,4 dimethylthiophene	*F. assafoetida* (Leaf & gum extracts)		(Augustine *et al*., 2017)
Asadisulfide	*F. persica* (Leaf & gum extracts)		(Iranshahi et al., 2006)
1-(methylthio)propyl propyl disulfide	*F. assafoetida* (Leaf & gum extracts)		(Iranshahi et al., 2006)
2- butyl methyl trisulfide	*F. assafoetida* (Leaf & gum extracts)		(Iranshahi et al., 2006)
Foetisulfide A	*F. assafoetida* (Leaf & gum extracts)		(Augustine *et al*., 2017)
Foetisulfide C	*F. assafoetida* (Leaf & gum extracts)		(Augustine *et al*., 2017)

Table 4. Flavonoids isolated from the genus *Ferula*

Name	*Ferula* species (Part used)	Structure	Reference
Kaempferol-3-O-*b*--rhamnopyranoside	*Ferula caspica* M. Bieb (aerial parts)		(Cigdem et al., 2015)
kaempferol-3-O-*a*-rhamnopyranoside	*Ferula caspica* M. Bieb (aerial parts)		(Correia et al., 2008)
kaempferol	*F. hermonis. Boiss* (roots)		(Karim et al., 2019)
Quercetine-3-O-*b*-glucopyranoside	*Ferula caspica* M. Bieb (aerial parts)		(Han et al., 2004)

Quercitrin	*Ferula orientalis* L. (aerial & root extracts)		(Hatice et al., 2021)
Quercetin	*Ferula orientalis* L. (aerial & root extracts)		(Hatice et al., 2021)
Naringenin	*Ferula orientalis* L. (aerial & root extracts)		(Hatice et al., 2021)
Orientin	*Ferula orientalis* L. (aerial & root extracts)		(Hatice et al., 2021)
3',4',5,7-tetrahydroxyflavone.	*Ferula schair* and *F. samarkandica*		(Savinoz et al., 2019)

2. PHARMACOLOGICAL ACTIVITIES

2.1. Antioxidant and Anti-Inflammatory Activities

The potential antioxidant activity was documented in several reports proving the antioxidant potential for methanol extracts of the aerial parts of *F. assafoetida* at different concentrations using DPPH radical scavenging activity, nitric oxide-scavenging activity and fe^{2+}chelating activity by which antioxidant effect, total phenolics and flavonoids were calculated. They obtained a good Fe(2+) chelating ability (IC(50) was 0.57 +/- 0.02 mg ml(-1)) and nitric oxide-scavenging activity (IC(50), was 270 +/- 3) in correlation to the isolated major products Phenol and 2-methyl-5-(1-methylethyl). (Dehpour et al., 2009).

In addition several studies carried out on *F. microcolea* indicated that antioxidant activity of the methanol extracts of aerial parts was higher than that of the essential oil. For this reason, the methanol extracts of *Ferula microcolea* may be used as an alternative additive in foods, pharmaceuticals, and cosmetic preparations instead of toxic artificial antioxidants. Further studies are needed for better clarifying the cytotoxicity and other biological properties of this plant (Amiri et al., 2013).

Further studies were carried out to evaluate the antioxidant effect of *F. szowitsiana.* The compound Aurapten exhibited antigenotoxic properties on DNA damage in human T cells through superoxide anion inhibition. It significantly decreased the genotoxicity induced by H_20_2 at different concentrations. Remarkably, its effectiveness was superior to that of ascorbic acid. (Ghasemi et al., 2021).

2.2 Antidiabetic activity

Species belonging to the Apiaceae family are widely reported for their traditional remedy of diabetes (Sahebkar, 2010). For that, the antidiabetic activity of *Ferula tunetana* containing various phenolic constituents such as anthocyanins, phenolic acids, dihydrochalcones and flavonones was reported by (Baccari et al., 2023). *In silico* and in *vitro* studies were carried out on ethyl acetate and *butanol* extracts of the seeds in order to assess the *α*-amylase inhibitory properties *which is* involved in the management of carbohydrate digestion. As reported, ethyl acetate seed extract exhibited the highest total phenolic content, antioxidant potential and *α*-amylase inhibition activity with IC_{50} values of 17.39 ± 0.92 μg/ml and thus control diabetes in correlation with the main identified constituents including caffeic, vanillic, and neochlorogenic acids. Ethyl acetate extract was found to have the best inhibitory activity leading us to develop newly safe treatment for diabetes in the future (Rahimi *et al., 2016).*

In addition a study carried out by Karim et al., on Ferula hermonis. Boiss. ethyl acetate *root extracts* exerted notable hypoglycemic activities by ameliorating DM and long standing diabetes complications in comparison to tramadol and glibenclamide GB, as positive controls in correlation to ferutinin (1.4 folds more effective than GB). *Other studies reported that F. varia* and *F. pseudoreoselinum* showed the most potent potential of alpha-amylase inhibition as they are rich in 4-Terpineol and alpha-pinene (Youssef., 2020).

Moreover, Sonigra et al., investigated the hypoglycemic effect of the essential oils of *F. gummosa* on streptozotocin-induced diabetic rats for 30 days then lipid profiles and serum glucose that shows significant reduction in triglycerides level in diabetic rats (Karimlar et al., 2019).

2.3 Aphrodisiac activity

A study carried out by Aydogan et al. determined the aphrodisiac property of genus *Ferula* in the treatment of male sexual dysfunction by carrying out the study on the oleo gum and roots of *F. elaeochytris* Korovin, *F. assa-foetida* L., *F. communis* L., and *F. gummosa* Boiss. (Aydogan et al., 2020). The research revealed that the isolated sesquiterpene from the chloroformic extract known as ferutinin administered orally as 10 mg/kg in male rats was the most efficient aphrodisiac compared to a subcutaneous control and to other sesquterpenoids and thus ejaculation latencies were prolonged.

Another study performed proved the aphrodisiac effect of *Ferula drudeana* Korovin root extracts administered orally to male rats. (Alqarni et al., 2020). These results supported the folkloric use of different *Ferula* species for male sexual impotency as the sexual behavior of male rats was enhanced.

2.4 Antidepressant Properties

Ferula species revealed prominent antidepressant activity by acting directly on serotonergic pathways in parallel with their antioxidant activity as patients suffering from Depressive Disorder have important levels of free radicals provoking this illness. As known, monoterpenes are one of the main important compounds exerting antidepressant effect by acting via the monoaminergic pathway (Guzmán et al., 2015).

A study performed on mice showed that essential oil of *F. gummosa* containing α-pinene, β-Pinene, bulnesol, β-myrcene α-Bisabolol as major components exerted an important antidepressant effect similar to *Fluoxetine* and higher than Impiramine which is promising for the development of drugs treating this illness in the future (Abbasi et al., 2015). In addition, in another study, α-pinene was found at higher levels in the rats' brains suggesting its penetration through the blood brain barrier and as well proving its direct action on GABA receptors (Kasuya et al., 2015). For this reason Genus *Ferula* demonstrates a direct effect and is an excellent candidate for the management of depression in future upcoming studies.

2.5 Antimicrobial activity

Most antimicrobial bioactive compounds in plants are anthraquinones, sesquiterpene coumarins and flavonoids which are effective against several human pathogenic bacteria (Mostafa et al., 2011).

Augustine et al. reported that crude extracts of *F*. asafoetida were evaluated for their antimicrobial activity against diverse bacterial and fungal and strains (Augustine et al., 2017). It was shown that the aqueous, ethyl acetate, ethanol and methanol extracts showed considerable effect against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Aspergillus niger* and *Escherichia coli* by adopting the agar disc diffusion method. This exerted effect is due to the presence of sesquiterpenes and sulfur compounds. Agar disc diffusion assay yielded an inhibitory zone of 4-16 mm diameter. Asafoetida can be recommended for therapeutic and medicinal purposes. Moreover, hexane extracts of white and red asafoetida have shown the maximum antibacterial activity against *Shigella flexneri* (Bhatnager et al., 2015).

Another study was conducted in order to determine the significant antimicrobial activities of sesquiterpenes isolated from *F. kuhistanica* against methicillin-sensitive and methicillin-resistant *S. aureus* (Tamemoto et al. 2001). Furthermore, a research reported that the essential oil extracted from *F. tunetana seeds* inhibited fungi and Gram (+)/Gram (-) bacteria (Znati et al., 2017).

Other species such as *Ferula hermonis* Boiss. showed inhibitory effects against many strains of fungus such *Trichophyton mentagrophytes* and showed more activity than nystatin and amphotericin B. This activity is correlated to the occurrence of α-pinene and α-bisabolol identified by NMR in roots and rhizomes. (Al-Ja'fari et al., 2011).

2.6 Anticancer activity

In different studies, several *Ferula* species showed valuable effects as cancer chemopreventive agents (Valiahdi, et al., 2013). The anticancer activity and antimetastasis effects of *F. assafoetida* oleo gum resin in a mouse mammary tumor model was reported the first two weeks using the metastasis-specific mouse mammary carcinoma 4T1 cells model as they look like metastatic breast cancer in human patients and are considered as suitable model for evaluation of the efficacy of anti-cancer drugs (Taheri et al., 2012).

Further study was carried out by Panwar et. al, and determined the chemopreventive potential of diverse doses of *F. asafoetida* oleo-gum-resin on 1,2- dimethylhydrazine induced rat colon carcinogenesis by evaluating tumor size in rats. The minimum dose of asafoetida (10 mg/100 g) exhibited more prominent effect as it continuously influenced all the tested biochemical parameters which can be used as a promising chemopreventive agent against colon carcinogenesis (Augustine et al.,2017).

2.7 Memory enhancing activity

As known, the memory loss is one of the main symptom occurring in greater number t of humans suffering from Alzheimer's disease everywhere. Vijayalakshmi et al investigated the effect of the *F. asafetida* extract on learning and memory and learning in rats (Vijayalakshmi et al., 2012). Memory enhancing potential of *F. asafetida* is caused by the inhibition of acetylcholinesterase inhibiting and due to its valuable antioxidant properties. For this reason, it can be used in the treatment of dementia (Bagheri et al., 2015). In addition, *F. asafoetida* accelerate the healing in peripheral nerves and is also proved by the histological and behavioral studies by stimulating axonal regeneration (Moghadam et al., 2014) .

3. DISCUSSION

Plants are a rich source of phytochemicals exerting various biological activities. Their functional properties are related to a great number of secondary metabolites (Murugan et al., 2014). It is well known that free radicals are the chief cause of a range of chronic and degenerative diseases like heart disease, inflammation, diabetes, pneumonia and cancer (Mondal et al., 2019). As well known, the role of plant in treating diseases is correlated to the presence of phytochemicals like phenolic compounds including tannins, sulfur compounds, flavonoids and sesquiterpenes….. Flavonoids act as potent antioxidants depending on their molecular structures and the position of the hydroxyl group on the structure (Ghassan et al., 2023). Several of these phytochemicals are limited to this genus so they may be considered as chemotaxonomic markers. This literature review of the phytochemistry and pharmacology of genus *Ferula* revealed that the anti-inflammatory and anti-oxidant activity of different species mainly *F. assafoetida, F. hermonis*. Boiss, *F. tunetana, F. szowitsiana and F. microcolea* are due to their high phenolic compounds including flavonoids like quercetin, naringin and orientin, playing an important role as free radical scavengers and thus treating heart, cerebral diseases and tumors too. Moreover, the resulted antioxidant activity of *F. microcolea* cultivated in Iran is correlated also to the presence of monoterpenes *α-pinene and β-pinene* obtained by gas *chromatography* that ascertain it. (Amiri et al., 2013). Moreover, this review showed the antidiabetic activity of genus *Ferula* as reported by Baccari et al. and demonstrated by an in vitro studies carried out on ethyl acetate and *butanol* extracts of the seeds of *F. tunetana*

by assessing the *α*-amylase inhibitory properties involved in the management of carbohydrate digestion as a result of its rich contents in flavonoids, stilbenes and phenolic acids. In addition, an in vivo study carried out by Karim at al proved that *F hermonis*. Boiss growing in Lebanon was the best one exerting a highest hypoglycemic effect as it is rich in flavonoidal aglycone kaempferol and phytoestrogen ferutinin identified by HPLC and obtained from ethyl acetate root extracts. In addition, the aphrodisiac property of genus *Ferula such as F. elaeochytris* Korovin, *F. assa-foetida* L., *F. communis* L., and *F. gummosa* Boiss in the treatment of male sexual dysfunction was revealed too and provoked by sesquiterpenes mainly ferutinin. (Aydogan., et al 2020). Furthermore, it showed the broad antimicrobial potential of both alcoholic and aqueous extracts of *Ferula asafetida* against diverse bacterial and fungal strains by adopting the agar disc diffusion method showing considerable effect against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Aspergillus niger* and *Escherichia coli* due to their sesquiterpenes and sulfur compounds. Accordingly, its essential oil provokes an important antibacterial and anti fungal effects due to high contents of bicyclic monoterpenes [α-pinene and β-pinene]. (Augustine et al., 2017).

4. CONCLUSION

This review of genus *Ferula* highlights a variety of bioactive compounds present mainly flavonoids, sulphur compounds, and sesquiterpene coumarins which have the potential to be targeted in drug manufacturing and expansion for the treatment of several diseases that provide scientific evidence for some folkloric and popular uses in several fields. Based on the results we conclude that *Ferula* species have potent antimetastasis and antitumor effects on breast cancer and is a potential source of natural antitumor agents. Hopefully, based on the promising results collected in this manuscript, we recommend further research to be carried out on the extracts of plants of this genus for the extraction and identification of further molecules which will be responsible for new biological activities. We recommend also to carry out further studies to better understand the cytotoxicity and other biological properties of plants in this genus which will be useful for use in industrial pharmacy. We urge that more research be done on the extracts of plants of this genus in order to identify and extract more compounds that will be responsible for new biological activities, based on the encouraging data gathered in this work.

REFERENCES

- Abbasi, M., Yousefi, H., Sharafkhani, R., & Azarsa, M. (2023). Antidepressant Potential of Ferula gummosa Essential Oil in Mouse Models. *Research Journal of Pharmacognosy*. 10 (3), 1-4.
- Amalraj. A., & Gopi S. (2017). Biological activities and medicinal properties of Asafoetida: A review. *Afr J Tradit Complement Altern Med*. 7 (3):347-59.
-Amiri , H. (2014). Chemical Composition and Antioxidant Activity of Essential Oil and Methanolic Extracts of *Ferula microcolea* (Boiss.) Boiss (Apiaceae). *International Journal of Food Properties*, 17:4, 722-730, DOI: 10.1080/10942912.2012.665403.
-Amir, R. A, Seyed, H. M., & al. (2022). *Ferula gummosa* gum exerts cytotoxic effects against human malignant glioblastoma multiforme. *Res Pharm Sci*, 17 (5):585–593
-Augustine, A., Sreeraj, G. (2017). Biological activities and medicinal properties of Asafoetida: A review. *Journal of Traditional and Complementary Medicine.* 7 :347-359.
-Appendino, G., Maxia. L., Bascope, M., &t al.(2006). A meroterpenoid NF-kB inhibitor and drimane sesquiterpenoids from asafetida. *J Nat Prod*. 69:1101-1104.
-Alqarni, M.H., & Soliman, G.A. The potential aphrodisiac effect of *Ferula drudeana* korovin extracts and isolated sesquiterpene coumarins in male rats. (2020). *PHARMACOG MAG*, 16 (70).
-Akaberi, M., Iranshahy, M., & Iransha. (2015). M. Review of the traditional uses, phytochemistry, pharmacology and toxicology of giant fennel (*Ferula communis* L. subsp. *communis*). 8 (11): 1050-1062.
-Al-Ja'fari, A. H., Vila, R., Freixa, B., Tomi, F., Casanova, J., Costa, J., et al. (2011). Composition and antifungal activity of the essential oil from the rhizome and roots of *Ferula hermonis*. *Phytochemistry*. 72 (11–12), 1406–1413.
- Aydogan. F., Baykan. S., Soliman, G.A., Yusufoglu H., & Bedir. E. (2020). Evaluation of the potential aphrodisiac activity of sesquiterpenoids from roots of *Ferula huber-morathii* Peşmen in male rats. J Ethnopharmacology, 257.
-Aysu, T., & Kucuk, M. M. (2013). Liquefaction of giant fennel (*Ferula orientalis* L.) in supercriticalorganic solvents: Effects of liquefaction parameters on product yields and character. *J. Supercrit. Fluids.* 83: 104-123.
-Baccari, W., Saidi, I., Znati, M., Mustafa, A.M., Caprioli, G., Harrath, A. H., & Jannet, H. B. (2023). HPLC-MS/MS analysis, antioxidant and ***α***-amylase inhibitory activities of the endemic plant *Ferula tunetana* using *in vitro* and *in silico* methods. *Process Biochemistry.*129:230-240.
- Bagheri, S. M., Hedesh, S. T., Mirjalili, A., & Dashti-R, M. H. (2015). Evaluation of Anti-inflammatory and Some Possible Mechanisms of Antinociceptive Effect of *Ferula assafoetida* Oleo Gum Resin. *Journal of Evidence-Based Complementary & Alternative Medicine*, *21* (4), 271–276. https://doi.org/10.1177/2156587215605903
-Bhatnager. R., Ran. R., & Dang, A.S. (2015). Antibacterial activity of *Ferula asafoetida*: a comparison of red and white type. *J Appl Biol Biotechnol*. 3:18-21.
-Cigdem, K., Gulacti, T., Erdal, B., Irem, T.,, Melike, E., & Zeliha, S. A. (2015). Phytochemical screening and evaluation of the antimicrobial and antioxidant activities of Ferula caspica M. Bieb. Extracts. *Saudi Pharmaceutical Journa.l*. 27 : 525-531.
-Correia, S.J., David, J.M., Silva, E.P., David, J.P., Lopes, L.M.X., & Guedes, M.L.S. (2008).

Flavonóides, norisoprenóides e outros terpenos das folhas de Tapirira guianensis. Flavonoids, norisoprenoids and other terpenes from leaves of Tapiriraguianensis. *Quím. Nova*. 31, 2056–2059. https://doi.org/10.1590/s0100-40422008000800027 (Portuguese).

- Dehpour, A. A., Ebrahimzadeh, M. A., Fazel, N. S., & Mohammad, N. S. (2009). Antioxidant activity of the methanol extract of Ferula assafoetida and its essential oil composition. *Grasas y Aceites*, *60*(4), 405–412. https://doi.org/10.3989/gya.010109

-Ghassan, M. S., Assi, M., Nada, M. S., Rima, B., & Mohamad, R. (2022). Antioxidant activity, metal content, and essential oil composition of two desert truffles species: *Terfezia boudieri* and *Terfezia claveryi. Journal of Pharmacognosy and Phytochemistry*, 11(4): 10-19.

-Ghasemi, Z., Rezaee, R., Aslani, M. R., & Boskabady, M. H. (2021). Anti-inflammatory, anti-oxidant, and immunomodulatory activities of the genus Ferula and their constituents: A review. *Iranian Journal of Basic Medical Sciences*, *24* (12), 1613-1623.

-Han, J.T., Bang, M. H., Chun, O.K., Kim, D.O., Lee, C.Y., & Baek, N. I. (2004). Flavonol
glycosides from the aerial parts of Aceriphyllum rossii and their antioxidant activities. *Arch. Pharm. Res*. 27 (4),: 390–395. https://doi.org/10.1007/ bf02980079.

-Hatice, K., Ahmet, C., Zeynebe, B., Saleh, H., & İlhami, G. (2021). Anticholinergic, Antidiabetic and Antioxidant Activities of *Ferula orientalis* L. Determination of Its Polyphenol Contents by LC-HRMS . *Rec. Nat. Prod*. 15(6), 513-528.

-Guzmán, Gutiérrez., Silvia Laura., & al. (2015) . "Linalool and β-pinene exert their antidepressant-like activity through the monoaminergic pathway." *Life sciences* vol. 128 : 24-9.

- Iranshahi, M., Amin, G., Salehi, S. M., Shafiee, A., & Hadjiakhoondi, A. (2006). Sulphur-containing compounds in the essential oil of the root of Ferula persica willd. var. persica. *Flavour Frag* J. 21:260-261.

- Karimlar, S & Naderi, A. (2019). Hypoglycemic and Hypolipidemic Effects of *Myrtus communis*, *Trachyspermum copticum* and *Ferula gummosa* Essential Oils on Streptozotocin Induced Diabetic Rat. *Nutrition and Food Sciences Research* . 6 (1):1-6.

- Kasuya , H., Iida, S., Ono, K., Satou, T., & Koike, K. (2015). Intracerebral distribution of α-pinene and the anxiolytic-like effect in mice following inhaled administration of essential oil from *Chamaecyparis obtusa*. *Nat Product Commun*.10:19.

-Kavoosi G., & Rowshan V. (2013). Chemical composition, antioxidant and antimicrobial activities of essential oil obtained from *Ferula asafoetida* oleo-gum-resin: effect of collection time. *Food Chem*. 138:2180 2187.

-Lijing, Z., Jianyong, Si., & Guangzhi, Li. (2015). Umbelliprenin and lariciresinol isolated from a long-term-used herb medicine *Ferula sinkiangensis* induce apoptosis and G0/G1 arresting in gastric cancer cells. *RSC Advances*, 110.

- Mahendra, P., & Bisht S. (2012). *Ferula asafoetida* : Traditional uses and pharmacological activity. *Pharmacognosy Reviews*. 6:141.

-Moghadam, FH., Dehghan , M, Zarepur, et al. (2014). Oleo gum resin of *Ferula asafetida* L. ameliorates peripheral neuropathy in mice. *J Ethnopharmacol*. 154: 183-189.

-Mohammed. H. Alqarni., Gamal, A., & al. (2020). Effect of *Ferula drudeana* Korovin Extracts and Isolated Sesquiterpene Coumarins in Male Rats. *Pharmacognosy Magazine*, Volume 16, Issue 70.

--Mondal, M, Hossain, MS., Das, N., Khalipha, ABR., Sarkar, AP, Islam, MT., et al. (2019). Phytochemical screening and evaluation of pharmacological activity of leaf Methanolic extract of Colocasia affinis Schott [Internet]. *Clinical Phytoscience*, 5.

-Niazmand, R., Marzieh, B. (2021). *Ferula asafoetida*: chemical composition, thermal behavior, antioxidant and antimicrobial activities of leaf and gum hydroalcoholic extracts. J Food Sci Technol . 58 (6):2148-2159.

- Omid, J., & Mahmood, J. T. (2012). Iranian Umbelliprenin from *Ferula szowitsiana* Activates both Intrinsic and Extrinsic Pathways of Apoptosis in Jurkat T-CLL cell line. *Journal of Pharmaceutical Research, IJPR*: 12(3): 371-376.

-Panwar, R., Rana, S., Dhawan , D. K.,& Prasad, K. K. (2015). Chemopreventive efficacy of different doses of *Ferula asafoetida* oleo-gum-resin against 1,2-dimethylhydrazine (DMH) induced rat colon carcinogenesis. *J Phytopharm*. 4: 282-286.

-Rahimi. M., *et al.* (2016) The research and development on the antioxidants in prevention of diabetic complications. *Asian Pac. J. Trop. Med*. 9 (9): 825-831.

-Raafat, K. (2019)."PHYTOCHEMICAL AND NEUROPROTECTIVE INVESTIGATION ON FERULA HERMONIS". *BAU Journal - Health and Wellbeing*: Vol. 1: Iss. 2.

- Raafat, K , & El-Lakany. (2015). Acute and subchronic in-vivo effects of *Ferula hermonis* L. and *Sambucus nigra* L. and their potential active isolates in a diabetic mouse model of neuropathic pain. BMC *Complement Altern Med*. 15: 257.

- Sahebkar, A., & Iranshahi, M. (2010). Biological activities of essential oils from genus *Ferula* (Apiaceae). *Asian Biomedicine*. 4 (6), 835–847.

-Sarvinoz, I. , Nargiza, A. T. et al. (2019). Effect of plant flavonoids on the volume regulation of rat thymocytes under hypoosmotic stress. *Pharmacological Reports*. 71: 1079–1087 .

- Seyyed, M. B., Amir. A., Mahin ,T. M , Yadegari,M., Aghdas, M. , Fatemeh, Z. M., & Haniyeh. M. (2017). Antitumor effect of *Ferula assa foetida* oleo gum resin against breast cancer induced by 4T1 cells in BALB/c mice. Journal of Ayurveda and Integrative Medicine, 8 : 152-158.

- Sonigra, P., & Meena, M. (2021). Metabolic Profile, Bioactivities, and Variations in the Chemical Constituents of Essential Oils of the Ferula Genus (Apiaceae). *Frontiers in Pharmacology*, 11. https://doi.org/10.3389/fphar.2020.608649.

-Taheri, A., Dinarvand, R, Ahadi, F, Khorramizadeh, MR.,& Atyabi, F.(2012). The in vivo antitumor activity of LHRH targeted methotrexat-human serum albumin nanoparticles in 4T1 tumor-bearing Balb/c mice. *Int J Pharm*431.(1):183-9.