Journal of King Saud University – Science 35 (2023) 102616

HOSTED BY

Contents lists available at ScienceDirect

Journal of King Saud University – Science

journal homepage: www.sciencedirect.com

Review

Effect of *Ferula hermonis* Boiss. on fertility potential in vitro and in vivo human and animal studies- an update review

Mohsen Ghaleb Al-Mutary

Department of Biology, College of Science, Imam Abdulrahman Bin Faisal University, P.O. Box 383, Dammam 31441, Saudi Arabia
Basic and Applied Scientific Research Center (BASRC), Imam Abdulrahman Bin Faisal University, P.O. Box 1982, Dammam 31441, Saudi Arabia

ARTICLE INFO

Article history:
Received 16 October 2022
Revised 15 January 2023
Accepted 18 February 2023
Available online 23 February 2023

Keywords:
Ferula hermonis
Infertility
Reproductive disorder
Herbal extract

ABSTRACT

The inability to have a child is couple's tragedy due to personal frustration and social stress. Botanical extracts have been used empirically as crude extracts and semi-purified compounds to treat infertility problems. These herbal extracts are used to treat sperm disorders, sexual asthenia, libido and erection. In vitro and in vivo research have revealed that plant extracts contain a wide range of pharmacological potentials. Secondary metabolites from plants provide a treatment option for infertility due to their accessibility, affordability, and availability. However, botanical products are still traditionally used world-wide to solve reproductive disorders. For instance, extracts of *Ferula hermonis* have shown positive effects on different fertility problems, such as libido, erection, and sperm parameters. Therefore in this review, we have presented most of the data dealing with the reported activities of *F. hermonis* in different extracts on reproductive functions.

Contents

E-mail address: Mgalmutary@iau.edu.sa
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jksus.2023.102616
1018-3647/

1. Introduction

Infertility is the 3rd most common health issue after cancer and heart diseases (Cong et al., 2016). Around 48.5 million couples experience pregnancy problems, and many babies are conceived with fertility medications (Mascarenhas et al., 2013). The consequences of infertility are psychosocial and physical disorders. Psychosocial conditions caused by this disease include decreased self-esteem, social isolation, interpersonal relationship problems, depression, mental health, guilt, anxiety, and despair (Abrao et al., 2013). The physical symptoms include excessive hair growth, weight gain, changes in sex drive and menstrual disorders such as no periods, abnormal and painful periods (See Fig. 1).

Infertility is influenced by several nutritional factors, environmental, genetic, social, physiological, and infection (Santiago et al., 2001, Mascarenhas et al., 2013). Assisted reproductive technology (ART) is an essential method of increasing fertility chances (Sunderam et al., 2017). ART involves many prescriptions and techniques to improve the likelihood of fertility (Al-Shawaf et al., 2005).

Medications used to treat infertility can cause many adverse effects. The commonly encountered adverse effects with infertility agents to treat female infertility are hot flushes, visual disturbances, multiple gestations, cervical mucus abnormalities, luteal phase deficiency, nausea, postural hypotension, ovarian hyperstimulation syndrome, multiple gestations (Derman and Adashi 1994), osteoporosis and ovarian hyper-stimulation syndrome (Klemetti et al., 2005) (Shelley et al., 1999). In males, infertility agents can inhibit spermatogenesis, decrease semen volume and seminal emission, impair sexual function, and cause retrograde ejaculation (Samplaski and Nangia 2015).

There is a growing interest in looking for safe alternatives to treat reproductive disorders to overcome hormonal therapy risks. Plants are a rich source of phytochemicals that improves male and female reproductive function (Mbemya et al., 2017) such as biochanin A, daidzein, genistein, and formononetin (Akbaribazm et al., 2021).

There are around 180–185 species in the genus Ferula (Apiaceae) (Pimenov and Leonov 2004). It is a shrub abundantly found in Lebanon and Syria, and it is commonly known as 'Hashishat-al-kattira or 'Shilsh-el-zallouh (Lev and Amar 2002). Herders observed the sexual influence of F. hermonis on sheep during the mating season (Sattar and Iranshahi 2017). Herbalists have used the plant for healing purposes (Gonzalez and Barrera 1995). One of the herbal treatments for infertility most commonly used by Palestinian herbalists is *F. hermonis* roots (Frequency of Citation 96.08%) (Jaradat and Zaid 2019). Many herbalists believe the plant has a potent anti-impotence and aphrodisiac potential (Hadidi et al., 2003).

In the Middle East, the plant is traditionally consumed to treat menopausal disturbances and erectile dysfunction (El-Thaher et al., 2001). The plant is sold under the name Lebanese viagra or sex root. In Jordan, the seeds, roots and resin are consumed to increase sexual strength and treat infertility and sexual weakness (Lev and Amar 2002). Therefore in this review, we have presented most of the data dealing with the reported activity of *F. hermonis* in different extracts on reproductive functions.

2. Biological activities

2.1. Effect on testis

Normal testis functions are vital to health. Testicular dysfunction may lead to infertility, poor muscle strength, hypogonadism, low libido and erectile dysfunction, which affect the quality of males' life (Karagiannis and Harsoulis 2005). Osman and his group investigated the protective effect of *F. hermonis*, bee honey or their

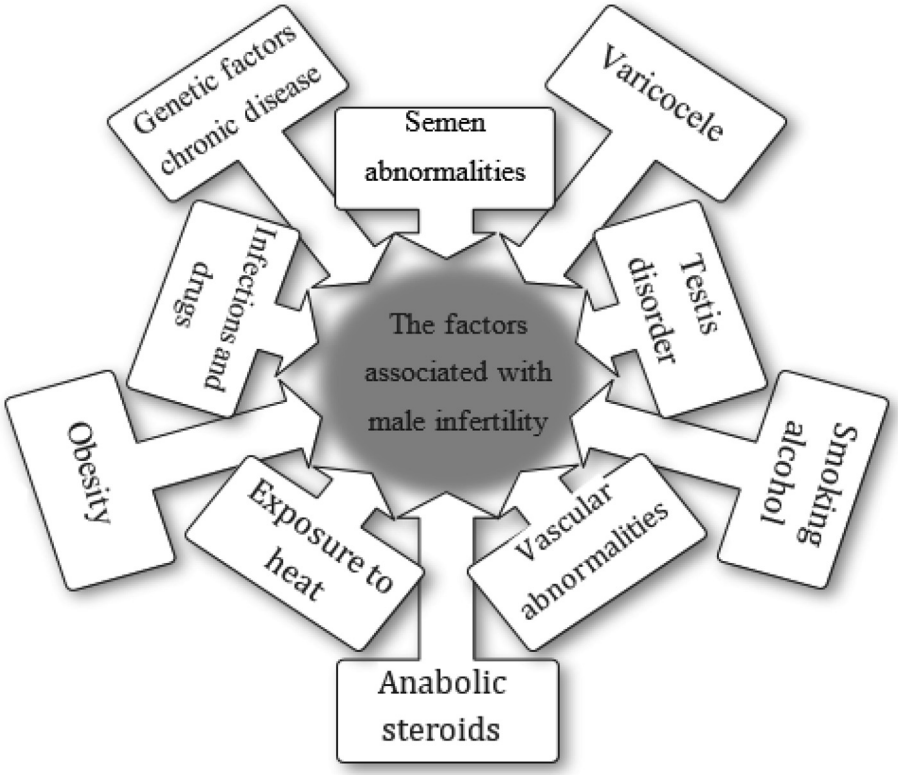


Fig. 1. Some of the factors affecting male infertility.

mixture on induced testicular toxicity in rats using gamma irradiation. Ionizing radiation is one of the environmental factors that may contribute to reproductive dysfunction by oxidative stress. The orally pretreated rats with *F. hermonis* (3 mg/kg), bee honey (1.5 ml/ Kg) and their combination for ten consecutive days prior to and twenty days after exposure to gamma irradiation revealed that all the extracts and their combination possess a significant protective potential against irradiation-induced testicular damage. They normalized the weight reduction in testis, restored the antioxidant testicular activities, antagonized the significant changes in alkaline phosphatase, lactate dehydrogenase, acid phosphatase and restored the serum level of testosterone, follicle-stimulating and luteinizing hormones (Osman 2011).

In most mammalian species, the temperature is tightly regulated to maintain optimal reproductive activity. In a study conducted by Hanafi and his group to assess the role of *F. hermonis* herb in relieving heat stress drawbacks on reproductive performance. Albino rats were exposed to different treatments, and after 8 weeks of treatment, The heat-stressed animals' control group showed oligozoospermia, teratozoospermia and chromosomal aberrations. Analysis of serum chemistry showed elevation in glutamyl transferase, cholesterol, low-density lipoprotein, total lipids, malondialdehyde, uric acid, creatinine, and blood glucose. However, the total antioxidant, protein, testosterone, cholinesterase, DNA, and RNA were markedly decreased in the testis, liver, kidney and brain tissue. The administration of the plant extract has no side effects and showed a protective effect from heat stress (Hanafi et al., 2010).

Following oral administration of 200 and 100 mg for 42 days, local drakes displayed increased weight, volume, width, and length as well as luteinizing hormone (LH), testosterone, and follicle-stimulating hormone (FSH) levels. They also have larger seminal tube diameter and thicker seminiferous epithelium (Al-Salhie and Al-Hummod 2019).

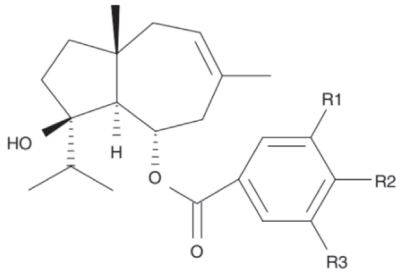
According to research, plant extract enhances animal testicular development and raises FSH, testosterone, and LH levels. The plant also has a protective effect against gamma irradiation-induced testicular dysfunction and health hazards resulting from heat stress in tropical and subtropical regions.

2.2. Effect on libido

Substances that increase performance sexual desire and enjoyment are called aphrodisiacs. They exert their sexual enhancing potentials by promoting erection, causing relaxation of corpus cavernosal smooth muscle and increasing blood flow (Thakur et al., 2009). Botanical extracts have continued to gain consideration as a substitute for improving sexual life due to their affordability, approachability no side effects belief.

The oral administration of ethyl acetate and petroleum ether extracts *F. hermonis* root extract (600 mg/kg) exhibited a decrease in the intromission rate and prolongation of intromission latency compared with control and sildenafil groups. However, the methanolic extract caused a significant rise in mount rate and an insignificant effect on intromission rate or intromission latency compared with the control (Hadidi et al., 2003).

In another report, the influence of oral administration of ferutinin, teferin and teferdin for Fig. 2 10 days at the dose of 2.5 (acute) and 0.25 mg/kg/day (subchronical) using sexually impotent and potent male rats was studied. Ferutinin administered (2.5 mg/kg) in potent rats reduced intromission latency and mount rate. However, it shortened the ejaculation latency in impotent rats and increased testosterone levels, as teferdin did. However, ferutinin administered (0.25 mg/kg/day) to potent rats negatively affected appetitive and consummatory behaviour), as well as testosterone serum levels. In summary, ferutinin stimulated sexual behaviour



Name	R1	R2	R3
Ferutinin	H	OH	H
Teferdin	H	H	H
Teferin	H	OH	OCH_3

Fig. 2. Major bioactive compounds reported from *F. hermonis* and play an important role in fertility.

after acute ingestion but negatively impacted the potent animals' sexual capacity. The only compound that improves the efficacy of copulation in impotent male rats is ferdin (Zanoli et al., 2005).

The chronic administration of different doses (0.5 and 0.2 mg/kg daily for 28 days) of ferutinin using ovariectomized non-estrogen primed rats increased the receptive behaviour in rats. In ferutinin-treated animals, the proceptive behaviours increased the preference for a sexually active male over a sexually receptive female compared with the control. In addition, the suppressed normal mating behaviour due to ovariectomy was restored by ferutinin treatment. These results revealed that the administration of ferutinin caused an estrogenic effect in ovariectomized, non-estrogen-primed rats (Zavatti et al., 2009).

2.3. Effect on erection/ejaculation function

Erectile dysfunction is a male health issue affecting the relationship between husbands and wives. In addition to various commercially available medications, many researchers are working to provide herbal remedies (Baum et al., 2000). The sexual potential of oil extracted from the seeds of *F. harmonis* enhanced erectile function dose-dependently. But, it turns out to be toxic if used for an extended period (El-Thaher et al., 2001). Similarly, Ayoub et al. recommended using *F. hermonis* root extract for erection and fertility problems. However, he recommended that it be consumed for a short time and with caution (Ayuob et al., 2014).

Sexual behaviour and penile erection are androgen-dependent. The testosterone treatment of castrated rats restored penile erection and sexual desire (Heaton and Varrin 1994). The mechanism of action of androgens improves penile erection by controlling corporal nitric- oxide synthase activity (Zvara et al., 1995). It has been reported (Bucci et al., 2009) that testosterone can elicit vasodilatation by modulating hydrogen peroxide levels through the conversion of L-cysteine to hydrogen peroxide. Likewise, Some natural products possess phosphodiesterase type 5 (PDE5) inhibitory activity. PDE5 is highly concentrated in the corpus cavernosum smooth muscle and breaks down cyclic guanosine monophosphate (cGMP).As a result, this leads to the corpus cavernosum smooth muscle relaxation that allows penile erection (Ko et al., 2004). The erectile effect of *F. hermonis* is not yet known. However, Colman et al. reported the signalling pathway of ferutinin through the rise of nitric oxide (NO) synthase activity in the brain. This signify that ferutinin is linked to the activation of NO production, which is known to be crucial for maintaining homeostasis (Colman-Saizarbitoria et al., 2006).

This plant contains potent antioxidant compounds (daucane sesquiterpenoid and fucose-rich sulfated polysaccharide). Knowing that oxidative stress was associated with erectile dysfunction pathophysiology (Azadzoi et al., 2005), *F. hermonis* could be an encouraging solution for solving this dysfunction (Abbas 2017).

2.4. Effect on sperm parameters

The botanical extracts positively affect sperm parameters through venotonic, anti-oedematous, anti-inflammatory, and antioxidant activity. Medicinal plants may contain compounds that increase the level of serum testosterone and the generation of sperms (Tahvilzadeh et al., 2016). The ethanolic extracts (seed and root) of *F. harmonis* increased erection in rats and exhibited a high safety level. Additionally, consuming one tablet of *F. harmonis* daily for 90 days increased sperm motility and sperm count in men (Kassis et al., 2009). In addition, it was found that *F. harmonis* improves testosterone serum level and sperm count due to its antioxidant potential against toxicity induced in rat testis (Rajeh and Al-Shehri 2019). Similarly, results revealed a decrease in the number of morphologically abnormal sperms post-treatment with the extract on male albino mice at doses 25, 50, 100, and 500 when compared with controls (Adel Mahdi, 2019). Likewise, the administration of *F. hermonis* was found to ameliorate the detrimental effect of heat stress on semen picture, and the values returned to normal compared to the control (Hanafi et al., 2010). In another report, supplementing methanol extract of *F. hermonis* with Cycram (Cycram + *F. hermonis* 0.025 ml/100 g body weight/day) protects induced alterations in sperm abnormalities of male rats against Cycram toxicities. The protective actions of *F. harmonis* is attributed to the increasing antioxidant enzyme activities and plasma lipid peroxidation suppressing (Girgis et al., 2021).

2.5. Effect on testosterone level

It is well known that spermatogenesis is stimulated by the rise in testosterone levels. Before concluding the ability of botanical extracts to enhance libido and increase the testosterone level, the treatment period must be specified. There are contradicting results reported in acute and subchronic toxicity studies. Zanoli et al. (Zanoli et al., 2003) reported that the acute and subchronic treatments of *F. hermonis* on males enhanced testosterone levels, improved copulatory performance and stimulated sexual desire in potent and impotent rats, respectively. However, after receiving the extract for 10 days, there was a notable decline in the proportion of rats who were able to ejaculate, as well as a significant drop in testosterone and deterioration of the copulatory pattern.

In another study, testosterone levels markedly increased 30 min after *F. hermonis* root extract administration and remained elevated for the following 24 h, whether vitamin C was administered alone or in combination. This significant increase in testosterone stopped after 3 days.

However, the 3 weeks of administration caused a significant decline in testosterone in all groups. Contrarily, after 42 days of treatment, testosterone levels rose more in the group receiving F. hermonis and vitamin C than in the group receiving F. hermonis alone. However, the chronic administration of the extract impaired fertility and significantly reduced the testosterone level (Ayuob et al., 2014).

The impact of *F. hermonis* was not explored on prolactin (linked to sexual dysfunction), 5- alpha-reductase (necessary for the testosterone conversion to dihydrotestosterone) and on aromatase enzyme (essential for the synthesis of oestrogen from testosterone) that are important for sexual function (Smith 2007) (Creasy 2001) (De Ronde and de Jong 2011). In a recent study, Sesquiterpenes such as Ten-uferidin, Ferutidin, and Ferutinin were reported to increase permeability of lipid bilayer and mitochondria, Suggesting that these compounds may increase hormonal levels (Naguib 2003).

2.6. Effect on fertility

The pregnancy rate of females mated with male mice who received *F. hermonis* extract (42 days) was markedly reduced. However, A significant reduction in offspring /mother was also seen. Moreover, the weight of litters born to those mothers was lower than the control and the number of pregnant mice after being matted to males (administered with F. hermonis/ vit C) was statistically insignificant (Ayuob et al., 2014).

2.7. Effect on epididymis

Chronic administration of *F. hermonis* (42 days) caused a reduction in ERβ expression in the epididymis and marked degenerative histopathological changes in epididymis (Ayuob et al., 2014). Interference of phytoestrogens in steroid regulation might drop the quality of sperm, thereby fecundity. However, several parameters can be evaluated on epididymis, such as epididymal sperm counts, reproductive organs' weight, sperm density, sperm parameters, epididymal cell protein secretion and many more. However, non of the above parameters were reported to the best of our knowledge using *F. hermonis* (Glover and Assinder 2006).

2.8. Effect on implantation

The estrogen and progesterone hormones enable the implantation process and the maintenance of embryo implantation (Al-Dissi et al., 2001). The abortifacient and anti- implantation activities of plant secondary metabolites may be accredited to their effects on blood estrogenic and progesterone levels, interfering with the fertility process. The anti-implantation of *F. hormonis* extract (3 mg/kg/day) for 42 days has been investigated in female mice and resulted in a few viable fetuses and implantations. These alternations were also associated with degeneration of ova, increased connective tissue and ovarian atrophy, while most ovarian follicles suffered follicular atresia (Homady et al., 2002). However, the exact mechanism of this effect of the extract remains unclear.

2.9. Effect on menstrual regulation

Female reproductive problems are a global health issue. The alcoholic extract of *F. hermonis* root extract (6 mg/kg) showed a moderate estrogenic effect, potent FSH -like, and LH-like activities. The ferutinin content in *F. hermonis* methanol extract was 92 ± 1. 33 mg/g. Molecular docking of target proteins, FSHR and ERα with ferutinin, showed strong interaction. Based on these data, it can be inferred that this plant is a promising female fertility-improving agent (Elmotayam et al., 2022).

2.10. Effect on aged laying hens

Consuming ferula has been associated with higher animal productivity, quality, and yield of animal products such milk, meat, and eggs. In older laying hens, ferula, a dietary supplement, increased the expression of the reproductive genes ERα and FSHR and promoted the production of reproductive hormones. These effects improved production efficiency throughout the post-peak egg-laying period and were advantageous for ovarian function by encouraging follicle development and ovulation. These findings demonstrate that the Ferula supplement can enhance the hor-

monal profile, reproductive gene expression, egg quality, and productive performance of aged laying hens (Hao et al., 2021).

2.11. Secondary metabolites of plant

Plant secondary metabolites contain diverse compounds synthesized from different biosynthetic pathways (Piasecka et al., 2015). They are generally classified into phenolics, flavonoids, terpenes, alkaloids, and steroids (Kessler and Kalske 2018). Phytochemical studies of *F. hermonis* showed the presence of different sesquiterpenes, terpenoid and saponins (Al-Ja'fari et al., 2011). However, the hormonal actions of the *F. hermonis* are mostly accredited to the primary sesquiterpene ester, ferutinin. Several reports have highlighted the ferutinin estrogenic potential (Sattar and Iranshahi 2017) (Elmotayam et al., 2022). Several reports revealed that ferutinin is an effective substitute hormonal therapy to treat and prevent postmenopausal symptoms since ferutinin can imitate the endocrine function of the ovaries (Tiosano et al., 2014) (Ferretti et al., 2012). Ferutinin is also classified as a phytoestrogen with an affinity for the G protein-coupled estrogen receptor and estrogen receptor subtypes ERβ and ERα (Oseni et al., 2008). Molecular docking of ferutinin with ERα and FSH receptors pinpointed the ferutinin contribution in regulating female reproductive function (Elmotayam et al., 2022). The antioxidants of plant secondary metabolites are promising agents that treat oxidative stress (Sm and Mahaboob Basha 2017), repair damage (Smits

Table 1
Biological activities of different plant parts of *Ferula hermonis*.

	Part used	Solvent used	Animal model	Dose	Biological activity	Mechanism of action	references
1	Root	Ethyl acetate	Male Swiss-Webster-mice (alloxan-induced diabetic)	1.6 mg/Kg	In vivo antioxidant and antihyperglicemic activity	Prevents oxidative stress in diabetic animals	(Raafat and El-Lakany 2015)
2	Root	Methanol	Female rat	6 mg/kg	Moderate estrogenic and strong gonadotropic effects	In silico study of ferutinin with ERα and FSHR	(Elmotayam et al., 2022)
3	Root	Aqueous	Albino mice	3 mg/kg 42 days	The number of pregnant mice, epididymal sperm, sperm motility was reduced. An increase in abnormalities of sperm	–	(KHLEIFAT et al., 2001)
4	Root	Ethanolic	mice	3 mg/kg 42 days	A decrease in female fertility, male mating ability, number of implantations and viable fetuses.		(Homady et al., 2002)
5	Root	Ecetonic	Sprague–Dawley rat	60 mg/kg 20 days	An increase in nuclear number, fibre size and muscle weight, Serum testosterone concentration was also increased		(Allouh 2011)
6	Root	Aqueous extract		6 mg/kg 42 days	Impaired fertility. Reduction in testosterone level. Reduction in estrogen receptor (ER) β expression in the testes, epididymis, and seminal vesicle. Improved erectile and fertility problems		(Ayuob et al., 2014)
7	Ferutinin, teferdin and teferin	Pure compounds	Sprague–Dawley rat	2.5 mg/kg and 0.25 mg/kg 10 days	Ferutinin, but not teferdin and teferin, decreased mount and intromission latencies (0.25 mg/kg) ferutinin or teferdin increased serum testosterone levels (0.25 mg/kg), however at 2.5 mg/kg the hormone was reduced		(Zanoli et al., 2005)
8	Ferutinin	Pure compound	Ovariectomized progesterone primed Sprague–Dawley rat	2, 3 and 28 days	Ferutinin given alone increased the intensity of the lordotic but failed to affect proceptivity.	Ferutinin increased ERα expression when administered alone Suggesting that Ferutinin displays estrogenic or antiestrogenic activity through ERα in the hypothalamus	(Zanoli et al., 2009)
9	Ferutinin	Pure compound	Ovariectomized Sprague–Dawley rat	2 mg/Kg 60 days	Prevent the excessive gain of weight and the osteoporos caused by estrogen deficiency		

et al., 2018) and imitate endogenous estrogen actions, modulate and inhbit hormone productions and actions (Mvondo et al., 2017). Numerous in vivo and in vitro techniques have been used to demonstrate the antioxidant capacity of phytochemicals. There are several report on the antioxidant activities of *F. hermonis* crude extracts (Dehghan et al., 2007, Kose and Sarikuuml 2010) and isolated compound such as daucane sesquiterpenoid esters (Ibraheim et al., 2012) and fucose-rich sulfated polysaccharide (El Rashed et al., 2021).

2.12. Other biological activity

Different biological activities were reported, including antioxidant (El Rashed et al., 2021), antimicrobial (Kuete et al., 2012) (Boghrati and Iranshahi 2019), antidiabetics (Ghareeb et al., 2014), anti-inflammatory (Geroushi et al., 2010), anticancer (Abutaha et al., 2019) (Kuete et al., 2012), antiviral, Alzheimer's, (Ghareeb et al., 2014), immunomodulatory effects and to treat and ameliorate diabetes neuropathy (Zanoli et al., 2005), antispasmodic, and analgesic. The plant also treats dysentery, stomach disorders, fever and skin infections (Elmotayam et al., 2022). Other traditional uses for *F. hermonis* are increasing cows' milk production, cauterizing wounds, and curing animal infections (Canogullarİ et al., 2009) (See Table 1).

3. Toxicity

Although different parts of *F. hermonis* are used to cure infertility problems, precautions should be practised while using this plant. The chronic oral administration (6 mg/kg) of *F. hermonis* root extract for 42 days significantly reduced the testosterone level and impaired fertility. In addition, histopathological changes were also observed in seminal vesicle, epididymis and testes (Ayuob et al., 2014). Similar to this, following 42 days of intragastric injection of the alcoholic extract of F. hormonis (3 mg/kg each day), ovarian atrophy and connective tissue atrophy increased. The ova showed deterioration in addition to follicular atresia in the ovarian follicles (Homady et al., 2002). The in vivo effects of column chromatography isolated ferutinin from *F. hermonis* seeds, and a standard ferutinin was reported. Strychnine's toxic effects were reserved after standard ferutinin (0.1 mg/kg) was preinjected into mice (Homady et al., 2002) (See Table 1).

However, better effects were noticed with isolated ferutinin (0.1 mg/kg) as the toxicity of strychnine was reversed as they did not show tonic extensor convulsions nor lethal effects. Even so, the mice were protected against the toxicity of strychnine by the the highest dose of standard ferutinin (1 mg/kg ip). While 1 mg/kg of isolated ferutinin aggravated strychnine toxicity (Raafat 2013). Ferutinin was also reported to induce apoptosis through the activation of the mitochondria (Macho et al., 2004). However, ferutinin can dose-dependently trigger eryptosis/erythroptosis and hemolysis in human RBCs. Therefore, using ferutinin to treat cancer may cause anaemia through the induction of eryptosis/erythroptosis. More research is needed to understand the eryptotic activity of ferutinin before employing it as a phytoestrogen due to its harmful effect on RBCs (Gao et al., 2013). In an oral acute toxicity study, the LD_{50} value of *F. harmonis* seed oil was 10.602 g\kg. In the subacute toxicity study at the doses of 0.5 and 0.05 g\kg (treated group), all the rats survived the 28 days without deaths, whereas in the group treated with 2 g\kg, five deaths were reported. No statistically significant difference was observed in hematocrit, eosinophils, monocytes, lymphocytes, neutrophils, and platelets between the control, and treated groups. However, compared with the control, the values of haemoglobin and red blood cells were markedly less in treated groups. However, when doses were given daily for 28 days, it decreased body weight, testicular atrophy, hepatomegaly, and a decrease in red blood cell count, cholesterol level and haemoglobin. Results indicate that crude oil is toxic if used for a long time (El-Thaher et al., 2001). Natural products derived from *F. hermonis*, either in the form of pure compounds or solvent extracts, have shown different important biological activity and health benefits. However, adverse effects were also reported; therefore, additional clinical investigations are needed to assess the efficiency and safety of the *F. hermonis extract.*

4. Clinical study

F. hermonis is safe to use and contains aphrodisiac properties that can improve erection hardness and sexual function in humans, according to clinical study. Within a few days, *F. hermonis* worked immediately for some and delayed for others. These reports revealed that men (60 to 88 %) experienced improved erections and increased desire after consuming *F. hermonis* root. However, less than 4% suffered from flushing and headaches (Naguib 2003). The plant was also patented for weight reduction of 4 to 6 lb and for lowering blood sugar after ingesting 3.5 g (twice a day) of *F. hermonis* with meals for one month (Naguib 2004).

5. Limitations and future recommendations

Most of the reported studies based their conclusion on short duration and small sample sizes. Therefore, it is early to conclude their various effects. More well-controlled experiments and clinical trials are required to confirm their safety, adverse effects and efficacies before they are recommended for treatment. Moreover, standardization of methods for assessing their safety, efficacy, bioavailability, composition, manufacturing processes, quality, regulatory and approval practices must be carried out on *F. harmonis* to fulfil the international parameters. Combining the advantages of both modern and traditional medicine has been recommended as a promising approach to bring new herb-derived substances from *F. harmonis* to market. Additional or synergistic effects of fertility drugs and botanical secondary metabolites with less side effects have been recommended. Thus, in recent years, the fertility properties of plant extracts are attracting researchers due to their reported traditional results in fertility increase.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abbas, M., 2017. Is the use of plants in Jordanian folk medicine for the treatment of male sexual dysfunction scientifically based? Review of in vitro and in vivo human and animal studies. Andrologia 49 (3), e12619.
Abrao, M.S., Muzii, L., Marana, R., 2013. Anatomical causes of female infertility and their management. Int. J. Gynecol. Obstet. 123, S18–S24.
Abutaha, N., Nasr, F.A., Al-Zharani, M., et al., 2019. Effects of hexane root extract of ferula hermonis boiss. On human breast and colon cancer cells: an in vitro and in vivo study. BioMed Res. Int..
Adel Mahdi, E., Study the Effect of Ferula Hermonis Extract on Fertility in Male Mice. vol. 1, KS Omniscriptum Publishing, 30012019. p. 50.
Akbaribazm, M., Goodarzi, N., Rahimi, M., 2021. Female infertility and herbal medicine: an overview of the new findings. Food Sci. Nutr. 9 (10), 5869–5882.
Al-Dissi, N.M., Salhab, A.S., Al-Hajj, H.A., 2001. Effects of Inula viscosa leaf extracts on abortion and implantation in rats. J. Ethnopharmacol. 77 (1), 117–121.
Al-Jafari, A.-H., Vila, R., Freixa, B., 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.

Allouh, M.Z., 2011. Effect of Ferula hermonis root extract on rat skeletal muscle adaptation to exercise. Exp. Biol. Med. 236 (12), 1373–1378.
Al-Salhie, K., Al-Hummod, S., 2019. Ferula hermonis roots extract on testicular biometry and reproductive hormones in local ducks. Indian Vet. J. 96 (12), 14–17.
Al-Shawaf, T., Zosmer, A., Dirnfeld, M., et al., 2005. Safety of drugs used in assisted reproduction techniques. Drug Saf. 28 (6), 513–528.
Ayuob, N.N., Al-Harbi, M.S., Abdulhadi, S.S., 2014. Is the chronic use of Ferula harmonis to enhance mice erectile function effective and safe? A histopathological study. Syst. Biol. Reprod. Med. 60 (5), 282–292.
Baum, N., Randrup, E., Junot, D., et al., 2000. Prostaglandin E1 versus sex therapy in the management of psychogenic erectile dysfunction. Int. J. Impot Res. 12 (3), 191–194.
Boghrati, Z., Iranshahi, M., 2019. Ferula species: a rich source of antimicrobial compounds. J. Herbal Med. 16, 100244.
Bucci, M., Mirone, V., Di Lorenzo, A., et al., 2009. Hydrogen sulphide is involved in testosterone vascular effect. Eur. Urol. 56 (2), 378–384.
Canogullarİ, S., Baylan, M., Copur, G., et al., 2009. Effects of dietary Ferula elaeochytris root powder on the growth and reproductive performance of Japanese quail (Coturnix coturnix japonica): it is not recommended in a breeder diet. Archiv für Geflügelkunde. 73 (1), 56–60.
Colman-Saizarbitoria, T., Boutros, P., Amesty, A., et al., 2006. Ferutinin stimulates nitric oxide synthase activity in median eminence of the rat. J. Ethnopharmacol. 106 (3), 327–332.
Cong, J., Li, P., Zheng, L., et al., 2016. Prevalence and risk factors of infertility at a rural site of Northern China. PLoS One 11 (5), e0155563.
Creasy, D.M., 2001. Pathogenesis of male reproductive toxicity. Toxicol. Pathol. 29 (1), 64–76.
De Ronde, W., de Jong, F.H., 2011. Aromatase inhibitors in men: effects and therapeutic options. Reprod. Biol. Endocrinol. 9 (1), 1–7.
Dehghan, G., Shafiee, A., Ghahremani, M.H., et al., 2007. Antioxidant potential of various extracts from Ferula szovitsiana. in relation to their phenolic content. Pharm. Biol. 45 (9), 691–699.
Derman, S.G., Adashi, E.Y., 1994. Adverse effects of fertility drugs. Drug Saf. 11 (6), 408–421.
El Rashed, Z., Lupidi, G., Kanaan, H., et al., 2021. Antioxidant and Antisteatotic activities of a new Fucoidan extracted from Ferula hermonis roots harvested on Lebanese mountains. Molecules 26 (4), 1161.
Elmotayam, A.K., Elnattat, W.M., Ali, G.A., et al., 2022. Assessment of Ferula hermonis Boiss fertility effects in immature female rats supported by quantification of ferutinin via HPLC and molecular docking. J. Ethnopharmacol. 289, 115062.
El-Thaher, T., Matalka, K., Taha, H., et al., 2001. Ferula harmonis 'zallouh'and enhancing erectile function in rats: efficacy and toxicity study. Int J Impot Res 13 (4), 247–251.
Ferretti, M., Bertoni, L., Cavani, F., et al., 2012. Structural and histomorphometric evaluations of ferutinin effects on the uterus of ovariectomized rats during osteoporosis treatment. Life Sci. 90 (3–4), 161–168.
Gao, M., Wong, S.Y., Lau, P.M., et al., 2013. Ferutinin induces in vitro eryptosis/erythroptosis in human erythrocytes through membrane permeabilization and calcium influx. Chem. Res. Toxicol. 26 (8), 1218–1228.
Geroushi, A., Auzi, A.A., Elhwuegi, A.S., et al., 2010. Antinociceptive and anti-inflammatory activity of Ferula hermonis root oil in experimental animals. Lat. Am. J. Pharm. 29.
Ghareeb, D.A., ElAhwany, A.M., El-Mallawany, S.M., et al., 2014. In vitro screening for anti-acetylcholiesterase, anti-oxidant, anti-glucosidase, anti-inflammatory and anti-bacterial effect of three traditional medicinal plants. Biotechnol. Biotechnol. Equip. 28 (6), 1155–1164.
Girgis, S.M., ElRaouf, A.A., Abdou, H.S., 2021. Protective effect of Ferula hermonis root extract against cycraminduced DNA, biochemical and testicular damage in rats. Jordan J. Biol. Sci. 14 (1).
Glover, A., Assinder, S., 2006. Acute exposure of adult male rats to dietary phytoestrogens reduces fecundity and alters epididymal steroid hormone receptor expression. J. Endocrinol. 189 (3), 565–573.
Gonzalez, A., Barrera, J.B., 1995. Chemistry and sources of mono-and bicyclic sesquiterpenes from Ferula species. Fortschritte der Chemie organischer Naturstoffe/Progress in the Chemistry of Organic Natural Products. Springer, 1–92.
Hadidi, K., Aburjai, T., Battah, A., 2003. A comparative study of Ferula hermonis root extracts and sildenafil on copulatory behaviour of male rats. Fitoterapia 74 (3), 242–246.
Hanafi, E.M., Raouf, A., Kassem, S.S., et al., 2010. A novel herbal remedy to alleviate drawbacks of heat stress in rats with special references to some reproductive and molecular alterations. Global J. Biotechnol. Biochem. 5 (3), 145–152.
Hao, E., Chang, L., Wang, D., et al., 2021. Dietary supplementation with ferula improves productive performance, serum levels of reproductive hormones, and reproductive gene expression in aged laying hens. Brazilian. J. Poultry Sci. 23.
Heaton, J.P., Varrin, S.J., 1994. Effects of castration and exogenous testosterone supplementation in an animal model of penile erection. J. Urol. 151 (3), 797–800.
Homady, M.H., Khleifat, K.M., Tarawneh, K.A., et al., 2002. Reproductive toxicity and infertility effect of Ferula hormonis extracts in mice. Theriogenology 57 (9), 2247–2256.
Ibraheim, Z.Z., Abdel-Mageed, W.M., Dai, H., et al., 2012. Antimicrobial antioxidant daucane sesquiterpenes from Ferula hermonis Boiss. Phytother. Res. 26 (4), 579–586.
Jaradat, N., Zaid, A.N., 2019. Herbal remedies used for the treatment of infertility in males and females by traditional healers in the rural areas of the West Bank/Palestine. BMC Complement. Altern. Med. 19 (1), 1–12.
Karagiannis, A., Harsoulis, F., 2005. Gonadal dysfunction in systemic diseases. Eur. J. Endocrinol. 152 (4), 501–513.
Kassis, E., Fulder, S., Khalil, K., et al., 2009. Efficacy and safety assessments of Ferula assa-foetida L., traditionally used in Greco-Arab herbal medicine for enhancing male fertility, libido and erectile function. Open Complementary Med. J. 1 (1).
Kessler, A., Kalske, A., 2018. Plant secondary metabolite diversity and species interactions. Annu. Rev. Ecol. Evol. Syst. 49, 115–138.
Khleifat, K., Homady, M.H., Tarawneh, K.A., et al., 2001. Effect of Ferula hormonis extract on social aggression, fertility and some physiological parameters in prepubertal male mice. Endocr. J. 48 (4), 473–482.
Klemetti, R., Sevón, T., Gissler, M., et al., 2005. Complications of IVF and ovulation induction. Hum. Reprod. 20 (12), 3293–3300.
Ko, W.-C., Shih, C.-M., Lai, Y.-H., et al., 2004. Inhibitory effects of flavonoids on phosphodiesterase isozymes from guinea pig and their structure–activity relationships. Biochem. Pharmacol. 68 (10), 2087–2094.
Kose, E.O., Sarikuuml, C., 2010. Chemical composition, antimicrobial and antioxidant activity of essential oil of endemic Ferula lycia Boiss. J. Medicinal Plants Res. 4 (17), 1698–1703.
Kuete, V., Wiench, B., Hegazy, M.-E.-F., et al., 2012. Antibacterial activity and cytotoxicity of selected Egyptian medicinal plants. Planta Med. 78 (02), 193–199.
Lev, E., Amar, Z., 2002. Ethnopharmacological survey of traditional drugs sold in the Kingdom of Jordan. J. Ethnopharmacol. 82 (2–3), 131–145.
Macho, A., Blanco-Molina, M., Spagliardi, P., et al., 2004. Calcium ionophoretic and apoptotic effects of ferutinin in the human Jurkat T-cell line. Biochem. Pharmacol. 68 (5), 875–883.
Mascarenhas, M.N., Flaxman, S.R., Boerma, T., et al., 2013. Trends in primary and secondary infertility prevalence since 1990: a systematic analysis of demographic and reproductive health surveys. Lancet 381, S90.
Mbemya, G.T., Vieira, L.A., Canafistula, F.G., et al., 2017. Reports on in vivo and in vitro contribution of medicinal plants to improve the female reproductive function. Reprodução & Climatério. 32 (2), 109–119.
Mvondo, M.A., Sakock, A.J.T., Ateba, S.B., et al., 2017. Emmenagogue properties of Milicia excelsa (welw.) cC Berg (moraceae) based, at least in part, on its ability to correlate the activity of the hypothalamic-pituitary axis to that of the ovaries. J. Ethnopharmacol. 206, 283–289.
Naguib, Y.M., 2003. Pharmaceutically active composition extracted from Ferula hermonis and process of its extraction, Google Patents.
Naguib, Y. M., 2004. Herbal compositions and methods for diabetes and weight loss management, Google Patents.
Oseni, T., Patel, R., Pyle, J., et al., 2008. Selective estrogen receptor modulators and phytoestrogens. Planta Med. 74 (13), 1656–1665.
Osman, N., 2011. Antioxidant Effects of Ferula Hermonis and Bee Honey on {gamma}-Radiation-Induced Oxidative Testicular Damage in Rats. J. Radiat. Res. Appl. Sci. 4.
Piasecka, A., Jedrzejczak-Rey, N., Bednarek, P., 2015. Secondary metabolites in plant innate immunity: conserved function of divergent chemicals. New Phytol. 206 (3), 948–964.
Pimenov, M., Leonov, M., 2004. The Asian Umbelliferae biodiversity database (ASIUM) with particular reference to South-West Asian taxa. Turk. J. Bot. 28 (1–2), 139–145.
Raafat, K., 2013. Exploration of the protective effects of some natural compounds against neurodegeneration exploiting glycine receptors in vivo model. Nat. Products Chem. Res..
Raafat, K., El-Lakany, A., 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 (1), 1–14.
Rajeh, N. A. and A. M. Al-Shehri, 2019. Antioxidant effect of Ferula hermonis Boiss on acrylamide induced testicular toxicity in male rats.
Samplaski, M.K., Nangia, A.K., 2015. Adverse effects of common medications on male fertility. Nat. Rev. Urol. 12 (7), 401–413.
Santiago, B., Claudio, C., Susana, K., 2001. Definition and causes of infertility. Reprod. Biomed. Online 2 (1), 173–185.
Sattar, Z., Iranshahi, M., 2017. Phytochemistry and pharmacology of Ferula hermonis Boiss.–a review. Drug research. 67 (08), 437–446.
Shelley, J., Venn, A., Lumley, J., 1999. Long-term effects on women of assisted reproduction. Int. J. Technol. Assess. Health Care 15 (1), 36–51.
Sm, S., Mahaboob Basha, P., 2017. Fluoride exposure aggravates the testicular damage and sperm quality in diabetic mice: protective role of ginseng and banaba. Biol. Trace Elem. Res. 177 (2), 331–344.
Smith, S., 2007. Drugs that cause sexual dysfunction. Psychiatry 6 (3), 111–114.
Smits, R.M., Mackenzie-Proctor, R., Fleischer, K., et al., 2018. Antioxidants in fertility: impact on male and female reproductive outcomes. Fertil. Steril. 110 (4), 578–580.
Sunderam, S., Kissin, D.M., Crawford, S.B., et al., 2017. Assisted reproductive technology surveillance—United States, 2014. MMWR Surveill. Summ. 66 (6), 1.
Tahvilzadeh, M., Hajimahmoodi, M., Toliyat, T., et al., 2016. An evidence-based approach to medicinal plants for the treatment of sperm abnormalities in traditional P ersian medicine. Andrologia 48 (8), 860–879.
Thakur, M., Chauhan, N.S., Bhargava, S., et al., 2009. A comparative study on aphrodisiac activity of some ayurvedic herbs in male albino rats. Arch. Sex. Behav. 38 (6), 1009–1015.

Tiosano, D., Paris, F., Grimaldi, M., et al., 2014. Evidence of ERalpha and ERbeta selectivity and partial estrogen agonism in traditional Chinese medicine. Reprod. Biol. Endocrinol. 12 (1), 1–14.
Zanoli, P., Benelli, A., Rivasi, M., et al., 2003. Opposite effect of acute and subchronic treatments with Ferula hermonis on copulatory behavior of male rats. Int. J. Impot Res. 15 (6), 450–455.
Zanoli, P., Rivasi, M., Zavatti, M., et al., 2005. Activity of single components of Ferula hermonis on male rat sexual behavior. Int. J. Impot Res. 17 (6), 513–518.
Zanoli, P., Zavatti, M., Geminiani, E., et al., 2009. The phytoestrogen ferutinin affects female sexual behavior modulating ERα expression in the hypothalamus. Behav. Brain Res. 199 (2), 283–287.
Zavatti, M., Benelli, A., Montanari, C., et al., 2009. The phytoestrogen ferutinin improves sexual behavior in ovariectomized rats. Phytomedicine 16 (6–7), 547–554.
Zvara, P., Sioufi, R., Schipper, H.M., et al., 1995. Nitric oxide mediated erectile activity is a testosterone dependent event: a rat erection model. Int. J. Impot Res. 7 (4), 209–219.