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Evaluation of the potential aphrodisiac activity of sesquiterpenoids from roots of *Ferula huber-morathii* Peşmen in male rats

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ABSTRACT

Ethnopharmacological relevance: Several species of *Ferula* L. genus have been used in traditional Turkish medicine as aphrodisiac to treat male sexual dysfunction. Especially, roots and oleo gum resin of *F. elaeochytris* Korovin, *F. communis* L., *F. assa-foetida* L. and *F. gummosa* Boiss. were claimed to be used for aphrodisiac activity, menstrual regulation and treatment of gastric pain in Anatolia. *Ferula* L. is represented by 23 taxa in Turkey, 13 of which are endemic species. *F. huber-morathii* Peşmen (FHM), an endemic plant, is popularly known as "helizan, çağşır".
Aim of the study: This study aimed to isolate sesquiterpenoids from the roots of *Ferula huber-morathii* (FHM) and to confirm their aphrodisiac potential in male rats.
Material and methods: In a preliminary experiment, the effects of aqueous (H_2O) and chloroform ($CHCl_3$) extracts of FHM were tested for their potential aphrodisiac activities in male rats. Then, sesquiterpene derivatives were isolated from the active chloroform extract of FHM roots (FHM-R) and characterized (TLC, 1D, 2D NMR, HR-MS and CD). Moreover, some of the isolates with adequate quantities were evaluated for their possible aphrodisiac effects on male rats. Single doses (10 mg/kg BW) of sildenafil citrate (SC, positive control), gummosin, mogoltavidin, deacetylkellerin, ferukrin acetate with kellerin, elaeochytrin-A and ferutinin were administered orally by gavages to male Wistar albino rats. Mount latency (ML), mount frequency (MF), intromission latency (IL), intromission frequency (IF), ejaculation latency (EL) and postejaculatory interval (PEI) were studied. In addition, copulatory efficiency (CE) and intercopulatory efficiency (ICE) were calculated.
Results: The preliminary experiment revealed that the chloroform extract was the main source of the active compounds as it showed the higher aphrodisiac activity while the aqueous extract was found to be inactive. Eleven sesquiterpene derivatives, viz. gummosin, mogoltavidin, farnesiferol A, deacetylkellerin, ferukrin acetate, kellerin, teuclatriol, feruhermonin C, ferutinin, elaeochytrin A and teferidin, were isolated from the FHM-$CHCl_3$ extract. Oral administration of deacetylkellerin, elaeochytrin-A and ferutinin significantly increased MF and IF. The ML and IL were significantly reduced, and ejaculation latencies were prolonged. Administration of these sesquiterpenoids also reduced the PEI. The present results revealed that ferutinin was the most effective aphrodisiac compound compared to other sesquiterpenoids. The results of 10 mg/kg of ferutinin are comparable to SC, the positive control. The results revealed that gummosin, mogoltavidin and ferukrin acetate with kellerin did not significantly alter the aphrodisiac parameters.
Conclusions: This study has established that the $CHCl_3$ extract of FHM root contains sesquiterpene derivatives, especially coumarin ethers and benzoic esters. Findings of the present study demonstrate that the chloroform extract and some of the sesquiterpene derivatives significantly stimulates sexual behavior in male rats, thus suggesting that *F. huber-morathii* possesses an aphrodisiac activity.

1. Introduction

Sexual dysfunctions (SD) are common medical disorders in both sexes; men and women, mainly older than 40 years of age (Cohen, 1999). Particularly erectile dysfunction and premature ejaculation are highly prevalent problems in SD that affect billions of men worldwide

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(Hatzimouratidis et al., 2010). Many risk factors alone or combined together; such as psychological (depression etc.), neurological (Alzheimer, etc.), hormonal (hypothyroidism), arterial, chronic diseases (diabetes, hypertension), obesity, smoking or drug use, may cause these sexual dysfunctions (Dougherty, 2018; Lue, 2000). Penile erection is a neurovascular process including psychological, endocrine, vascular, and neurological coordination (Shamloul and Ghanem, 2013). This sexual process involves orgasm and ejaculation at the same time. On the penile erection stimulation, nerve impulses occur leading to release of neurotransmitters from corpus cavernosum for relaxation of its smooth muscle, which, in turn, increases penile blood flow (Shamloul and Ghanem, 2013). The available treatment options of SD include phosphodiesterase inhibitors like sildenafil and tadalafil, α2-adrenergic antagonists such as yohimbine and apomorphine dopamine receptor agonists (Kenmogne et al., 2016). If these oral therapies are ineffective, intracavernous and intra-urethral injections or penile prostheses are other alternatives, which are expensive and have serious side effects.

Medicinal plants have been of high significance in the traditional medicine systems for centuries (Mohammadhosseini, 2017). Because of the worrying adverse effects of many conventional drugs, the inspection of new medications from natural origin has gained attention in current years. In this matter, several species of *Ferula* genus have constantly been in the focus, particularly in the Asian and Middle East countries. *Ferula*, the third greatest genus of the family Apiaceae, is composed of 180 species (Yaqoob and Nawchoo, 2016). The genus is represented by 23 taxa in Turkey including 13 endemics (Güner, 2012). In Anatolia, *Ferula* species are known as 'Çarşır', 'Çağşır' or 'Çakşır' (Baytop, 1999; Güner, 2012). In the literature, the most common use of *Ferula* plants in traditional medicine is described as aphrodisiac (Mohammadhosseini et al., 2019), viz. *F. hermonis* Boiss. in Syria and Lebanon (Al-Ja'fari et al., 2011). Moreover, *F. narthex* is one of the plants of 'Unmadnashak Ghrita' used for its aphrodisiac properties in Ayurvedic medicine (Achliya et al., 2004). In the USA (Lilly, 1898) and Brazil (Elisabetsky et al., 1992), *F. assa-foetida* L. extracts have been used for the same purpose and to treat erectile dysfunction. Accordingly, some species of *Ferula* genus are also listed in Turkish traditional medicine as aphrodisiac such as *F. elaeochytris* Korovin and *F. communis* L. (Gülsoy Toplan et al., 2018).

The phytochemical constituents of *Ferula* species are mainly sesquiterpene esters and coumarin derivatives in addition to ole-gum resins, mono-, tri-terpenes, phenolic acids, and sulphur-containing compounds. Also, various studies regarding pharmacological activities of the *Ferula* plant extracts and purified compounds have been reported, viz. cytotoxic, anti-ulcer, antioxidant, antimicrobial, antiviral, antihypertensive, anti-inflammatory, anticonvulsant, antispasmodic, aphrodisiac, anticoagulant, anxiolytics, antihyperlipidemic, antidiabetic and hepatoprotective (Mohammadhosseini et al., 2019; Salehi et al., 2019).

F. huber-morathii Peşmen is one of the endemic and indigenous species of *Ferula* genus in the flora of Turkey (Sağıroğlu, 2005). The findings of Yusufoglu et al. showed that the methanol extract of *F. huber-morathii* had significant antioxidant and hypoglycaemic activities in diabetic rats (Yusufoglu et al., 2015). To date, a great number of active compounds possessing promising medicinal activities have been isolated from *Ferula* plants.

The present study was planned to describe the sexual properties of aqueous and organic extracts of FHM in male rats. Besides, we carried out isolation and characterization studies on the chloroform extract, and then possible aphrodisiac effects of the selected compounds were investigated in male rats.

2. Materials and methods

2.1. General experimental procedures

Optic rotations were measured using a PerkinElmer 341 polarimeter in $CHCl_3$ at 20 °C. CD and UV spectra, on a JASCO J-815 spectrophotometer were recorded in MeOH. Mass spectrometry analysis was performed on an Agilent 1200/6530 instrument (HR-MS). The 1D and 2D (COSY, HMBC, HSQC and NOESY) NMR spectra were obtained on Bruker DRX-500 NMR spectrometer with TMS as internal standard at room temperature. Proton and carbon chemical shifts are relative to the deuterium solvent signals. Column chromatography experiments were carried out on silica gel 60 (40–60 µm, Merck), Sephadex LH-20 (GE Healthcare Bio-Sciences AB) and RP-18 (25–40 µm, Merck) using analytical grade purity solvents (Merck, Sigma). TLC analyses were carried out on Silica gel 60 F254 (Merck) and RP-18 F254s (Merck) pre-coated aluminium plates. Compounds were detected by Vilber-Lourmat UV lamb (254 nm, 366 nm) and vanillin/H_2SO_4 spraying reagent followed by heating at 105 °C for 1–3 min.

2.2. Plant material

F. huber-morathii grows in Murat-Van Region of Turkey. The plant material was collected from the roadsides of Mus to Varto Village road (*ca.* 40th km, altitude 1280 m) in July 2013. The plant was identified by the authors and the voucher specimen was deposited in the herbarium of Ege University (IZEF), Faculty of Pharmacy, İzmir, Turkey (Herbarium No: IZEF 5524).

2.3. Extraction and isolation

The plant material was air-dried in the shade and then powdered (Spice Herb Grinder, IC 25B). The powdered material of *F. huber-morathii* (870 g) was extracted by percolation in methanol (MeOH) with occasional shaking for 48 h. Percolation was repeated three times and then the methanolic extracts were combined and concentrated under vacuum to give the MeOH extract (121.9 g). The dried MeOH extract was suspended in water (H_2O) and partitioned with chloroform ($CHCl_3$) to yield H_2O and $CHCl_3$ extracts (97.83 and 22.92 g, respectively). The H_2O and $CHCl_3$ extracts were tested for their potential aphrodisiac activities in male rats. The $CHCl_3$ extract was determined to be the principle source of active compounds as it exhibited high aphrodisiac activity. On the contrary, the H_2O extract was found to be inactive (data not shown). Based on these results a major part of the $CHCl_3$ extract (20 g) was fractionated on a normal phase silica gel column (400 g, 60x4 cm glass column) using gradient mixtures of hexane (Hxn):ethyl acetate (EtOAc) (10:0 to 5:5; 10% polarity increment) to yield 24 main fractions (Fr.1–24). Fr. 18 (465 mg) was crystalized with acetonitrile to yield pure FHM-N1 (297 mg). Fr. 22 (650 mg) was chromatographed with vacuum manifold system-VMC on reverse phase silica gel (RP-C18, 100 g) by eluting with MeOH:H_2O (70:30) to give five subfractions (Fr.22.A-E). For further purification, Fr.22.D (393 mg) was subjected to a silica gel column (45 g, 30x2.5 cm) and eluted with Hxn:EtOAc (30:70) to afford five subfractions (Fr.22.D.I–V). Fr.22.D.III (278 mg) was crystalized to yield FHM-N2 (35 mg). Fr.22.C (101 mg) was chromatographed on silica gel with Hxn:EtOAc (30:70) to give FHM-N3 (6.1 mg). Fr.19 (211 mg) was applied to a silica gel column and eluted with Hxn:EtOAc (50:50) affording FHM-N6 (76.4 mg). Fr. 20 (694 mg) was rechromatographed with VMC/RP-C18 and eluted with acetonitrile:H_2O mixtures (from 50:50 to 100:0 with 10% polarity decrease) to yield FHM-N4 (13.9 mg), FHM-N8 (66.9 mg), FHM-N7 (32.2 mg). The other main fraction Fr.10–12 was chromatographed on a silica gel column by eluting Hxn:EtOAc (80:20) to afford FHM-N5 (3.897 g). Fr.7 (390 mg) was applied to a silica gel column and eluted with Hxn:EtOAc (90:10) affording 4 subfractions (Fr.7.A-D). Fr.7.C (56 mg) was rechromatographed on a Sephadex LH-20 with EtOAc to give FHM-N9 (17 mg). Fr. 6 (269 mg) was subjected on a silica gel column (50 g) and eluted with Hxn:EtOAc (from 90:10 to 50:50 with 5% polarity increase) to yield FHM-N10 (16.4 mg). Some of the isolates with sufficient quantity and the original chloroform extract were tested for their aphrodisiac activities in male rats.

2.4. Animals

This study was performed on male (220–250 g) and female (150–160 g) albino rats. These rats were bred in the Lab Animal Care Unit at the Faculty of Pharmacy, Prince Sattam bin Abdulaziz University, Al-Kharj, KSA. Animals were housed singly in separate cages with free access to solid pellet diet and water ad libitum. The animal study protocol was approved by the Bioethical Research Committee (BERC), Prince Sattam Bin Abdulaziz University, Al-Kharj, KSA (approval number: BERC-001-6-19).

2.5. Chemical and drugs

The drugs used in this study were sildenafil citrate (Viagra) (Pfizer Inc, USA), hydroxyprogesterone (Bayer Pharma AG, Germany) and oestradiol benzoate (Misr Co. for Pharm. Ind., Egypt).

Sildenafil citrate and sesquiterpenoids were prepared in an aqueous solution containing 2% Tween 80 (Sigma-Aldrich, USA).

2.6. Aphrodisiac activity procedures

2.6.1. Preparation of male rats

The male animals were trained by pairing with mature female rats, three times, for 4 days prior to the starting of the experiment. Males, which did not demonstrate sexual attention during the experimental period were considered as sluggish animals.

2.6.2. Preparation of female rats

The female animals were made sexually active following injection of estradiol benzoate (10 μg/kg, sc) and hydroxyprogesterone (1.5 mg/kg, sc.), 48 and 4 h before pairing, respectively. The sexual activity of the female rats was confirmed before the experiment by pairing with males, other than the normal control, reference and experimental male rats. The most sexually active females were selected for the experiment.

2.6.3. Experimental procedure

The experiment was conducted 4 h after progesterone administration at 17:00 h in a calm laboratory under faint red light in transparent cages of 50x30x30 cm dimensions as described by (Al-Shdefat et al., 2016). Nine groups of male rats that were showing reactive sexual activity (n = 6) were selected for the experiment. Male rats were kept singly in separate cages and treated as follow:

Group I (Normal control): received 1% v/v Tween 20 as a vehicle at 5 mL/kg.

Group II (Reference): received sildenafil citrate (SC) at a dose of 10 mg/kg.

Group III: received chloroform extract at 400 mg/kg.

Groups IV-IX: received gummosin, mogoltavidin, deacetylkellerin, ferukrin acetate with kellerin, elaeochytrin-A and ferutinin, respectively at 10 mg/kg. The vehicle, SC, chloroform extract and sesquiterpene derivatives were administered orally as a single dose through an orogastric tube.

2.6.4. Sexual behavior analysis

After 30 min, female rats were introduced into the male cages with one female to one male ratio and the male sexual behavior was immediately tested and continued for first two mating series. The following parameters were determined as mentioned by Besong et al. (2018).

(i) The duration from the introducing of a female rat into the cage of the male until the first mount (mount latency; ML).
(ii) The duration from the introducing of a female rat into the cage until the first intromission by the male (intromission latency; IL).
(iii) The number of mounts before ejaculation (mount frequency; MF).
(iv) The number of intromissions before ejaculation (intromission frequency; IF).
(v) The duration from the first intromission of a series until the ejaculation (ejaculation latency; EL).
(vi) The duration from ejaculation until the first intromission of the next series (postejaculatory interval; PEI).

In the second mating series, only the EL was estimated. Depending on the previously mentioned parameters, the followings can be computed: Copulatory efficiency (CE) = (IF/MF) x 100 and intercopulatory Efficiency (ICE) = [IF/(MF + IF)] x100 (Besong et al., 2018).

2.6.5. Statistical analysis

The significance of the difference between the means was determined by a one-way analysis of variance (ANOVA) with a post-hoc't' test using SPSS 16.0 (SPSS Inc., South Wacker Drive, Chicago, USA). Significant levels were tested at $P < 0.05$.

3. Results

3.1. Elucidation of isolated compounds

The structures were elucidated by spectroscopic methods including MS, ^{1}H NMR, ^{13}C NMR, CD-analysis and optical rotation as well as comparing the obtained spectral data with those of previously established structures (Fig. 1).

***Gummosin (FHM-N1)*:** Crystalized white solid, HR-EI-MS $[M+H]^+$ $m/z = 383.2226$ (calc. for $C_{24}H_{30}O_4$, 382.21). ^{1}H NMR ($CDCl_3$, 500 MHz/ δ ppm, *J* Hz): 6.19 (*d,* 9.4 Hz, H-3), 7.59 (*d*, 9.4 Hz, H-4), 7.30 (*d,* 9.3 Hz, H-5), 6.79 (*d,* 9.0 Hz, H-6), 6.78 (*d,* 2.5 Hz, H-8), 2.04 (*m*, H-1'a), 1.02 (*dt,* 7.7 Hz, 4.9 Hz, H-1'b), 1.99 (*tdd*, 13.9 Hz, 5.5 Hz, 2.5 Hz, H-2'a), 1.61 (*dd,* 13.2 Hz, 3.0 Hz, H-2'b), 3.43 (*bs*, H-3'), 1.76 (*dd,* 12.8 Hz, 2.8 Hz, H-5'), 1.57 (*td,* 12.5 Hz, 2.5 Hz, H-6'a), 1.36 (*dd*, 13.0 Hz, 4.0 Hz, H-6'b), 2.30 (*dd,* 13.2 Hz, 6.2 Hz, H-7'a), 2.08 (*d* ,13.0 Hz, H-7'b), 2.16 (*t*, 6.0 Hz, H-9'), 4.37 (*dd,* 9.8 Hz, 5.4 Hz, H-11'a), 4.05 (*dd,* 9.8 Hz, 7.0 Hz, H-11'b), 4.77 (*s*, H-12'a), 4.67 (*s,* H-12'b), 0.97 (3H, *s*, H-13'), 0.82 (3H, *s*, H-14'), 0.96 (3H, *s*, H-15'). ^{13}C NMR ($CDCl_3$, 125 MHz): 161.4 (C2), 112.8 (C3), 143.6 (C4), 128.7 (C5), 113.3 (C6), 162.3 (C7), 101.8 (C8),112.4 (C4a), 155.9 (C8a), 29.3 (C1'), 25.6 (C2'), 76.0 (C3'), 37.6 (C4'), 40.7 (C5'), 23.0 (C6'), 32.6 (C7'), 147.0 (C8'), 57.1 (C9'), 37.7 (C10'), 68.0 (C11'), 111.1 (C12'), 28.5 (C13'), 22.4 (C14'), 22.0 (C15' (Hofer et al., 1984; Iranshahi et al., 2004; Kir'yalov and Movchan, 1966; Saidkhodzhaev and Nikonov, 1974).

***Mogoltavidin (FHM-N2)*:** Crystalized white solid, HR-EI-MS $[M+H]^+$ $m/z = 401.2352$ (calc. for $C_{24}H_{32}O_5$, 400.22). ^{1}H NMR ($CDCl_3$, 500 MHz/ δ ppm, *J* Hz): 6.22 (*d*, 9.4 Hz, H-3), 7.63 (*d*, 9.4 Hz, H-4), 7.33 (*d*, 8.5 Hz, H-5), 6.83 (*dd,* 8.6 Hz, 2.2 Hz,H-6), 6.86 (*d* , 1.9 Hz, H-8), 1.42 (*d* ,13.2 Hz, H-1'a), 1.69 (*td* , 14.0 Hz, 3.2 Hz, H-1'b), 1.93 (*m* , H-2'a), 1.59 (*m*, H-2'b), 3.42 (*bs*, H-3'), 1.53 (*dd*, 12.0 Hz,H-5'), 1.58 (1H, *m*, H-6'a), 1.34 (1H, *dd*, 12.3 Hz, 2.6 Hz, H-6'b), 1.93 (1H, *m* , H-7'a), 1.59 (*m*, 7'b), 1.88 (*t*, 4.2 Hz, H-9'), 4.39 (*dd,* 9.9 Hz, 3.8 Hz, H-11'a), 4.15 (*dd,* 9.8 Hz, 5.8 Hz, H-11'b), 1.22 (3H, *s*, H-12'), 0.97 (3H, *s*, H-13'), 0.83 (3H, *s,* H-14'), 0.92 (3H, *s,* H-15'). ^{13}C NMR ($CDCl_3$, 125 MHz): 161.48 (C2), 112.69 (C3), 143.65 (C4), 128.69 (C5), 113.11 (C6), 161.88 (C7), 101.53 (C8), 112.41 (C4a), 155.64 (C8a), 32.71 (C1'), 25.04 (C2'), 75.46 (C3'), 37.34 (C4'), 48.33 (C5'), 19.91 (C6'), 43.97 (C7'), 72.49 (C8'), 59.34 (C9'), 37.83 (C10'), 66.50 (C11'), 24.46 (C12'), 28.42 (C13'), 22.06 (C14'), 15.92 (C15') (Kasaian et al., 2015; Khasanov et al., 1974; Nabiev et al., 1982, 1979).

Teuclatriol, 1α,5β-guaiane-4β,6β,10α-triol (FHM-N3): Amorphous solid, EI-MS/MS $[M+Na]^+$ $m/z = 279.0957$ (calc. for $C_{15}H_{28}O_3$, 256.20). ^{1}H NMR ($CDCl_3$, 500 MHz/ δ ppm, *J* Hz): 1.08 (*t,* 7.4 Hz, H-1), 1.75 (*m*, H-2a), 1.55 (*m*, H-2b), 1.66 (2H, *m,* H-3), 1.75 (*d,* 8.5 Hz, H-5), 4.12 (*d*, 3.2 Hz, H-6), 1.85 (*t,* 9.5 Hz, H-7), 2.04 (*dd*, 12.8 Hz, 10.8 Hz, H-8a), 1.33 (*dd*, 14.0 Hz, 12.8 Hz, H-8b), 1.94 (*m,* H-9a), 1.36 (*m,* H-9b), 1.67 (*sept,* 6.8 Hz, H-11), 1.01 (3H, *d*, 6.8 Hz, H-12), 0.95 (3H, *d*, 6.8 Hz, H-13), 1.23 (3H, *s,* H-14), 1.25 (3H, *s,* H-15). ^{13}C

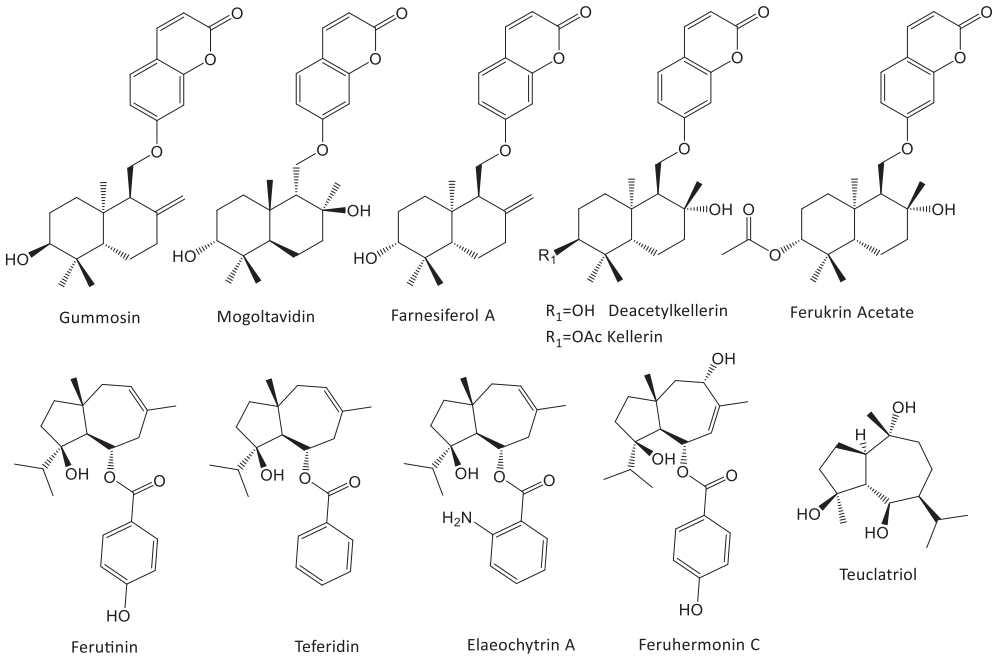

Fig. 1. Sesquiterpenoids from *Ferula huber-morathii* roots.

Table 1
Effect of sildenafil citrate (SC) and sesquiterpene derivatives at 10 mg/kg on the mount latency (ML), mount frequency (MF), intromission latency (IL) and intromission frequency (IF) of male rats.

Groups	ML (sec)	MF	IL (sec)	IF
NC	84.27 ± 4.12[a]	13.78 ± 0.65	152.24 ± 8.85[a]	4.18 ± 0.21[a]
SC	41.68 ± 2.77ǂ	28.44 ± 0.97ǂ	67.11 ± 3.47ǂ	17.50 ± 0.68ǂ
Chloroform Extract	67.6 ± 3.82ǂ[a]	16.46 ± 0.89ǂ[a]	116.7 ± 6.95ǂ[a]	6.17 ± 0.30ǂ[a]
Gummosin	80.64 ± 4.47[a]	12.48 ± 0.61[a]	161.46 ± 9.37[a]	4.44 ± 0.37[a]
Mogoltavidin	87.13 ± 5.44[a]	11.50 ± 0.58[a]	157.85 ± 7.52[a]	4.25 ± 0.25[a]
Deacetylkellerin	63.98 ± 3.60ǂ[a]	17.84 ± 0.76ǂ[a]	104.26 ± 6.53ǂ[a]	6.87 ± 0.47ǂ[a]
Ferukrin acetate + kellerin	85.20 ± 5.50[a]	13.22 ± 0.61[a]	150.38 ± 7.22[a]	4.18 ± 0.32[a]
Elaeochytrin-A	72.35 ± 3.14ǂ[a]	16.45 ± 0.55ǂ[a]	119.07 ± 6.46ǂ[a]	6.28 ± 0.53ǂ[a]
Ferutinin	47.40 ± 2.85ǂ[a]	23.81 ± 0.89ǂ[a]	83.75 ± 5.45ǂ[a]	12.72 ± 0.68ǂ[a]

Values are expressed as mean ± S.E.M., n = 6 rats/group.
ǂ indicate significance compared to normal control group at $P < 0.05$.
[a] Indicate significance compared to SC group at $P < 0.05$.

Table 2
Effect of sildenafil citrate (SC) and sesquiterpene derivatives at 10 mg/kg on the ejaculation latency in 1st series (EL-1), post ejaculatory interval (PEI) and ejaculation latency in 2nd series (EL-2) of male rats.

Groups	EL-1 (sec)	PEI (sec)	EL-2 (sec)
NC	342.35 ± 8.74[a]	528.89 ± 15.18	360.87 ± 12.73[a]
SC	450.90 ± 15.23ǂ	325.57 ± 13.73ǂ	492.60 ± 16.25ǂ
Chloroform Extract	378.60 ± 12.80ǂ[a]	414.40 ± 12.95ǂ[a]	402.47 ± 5.37ǂ[a]
Gummosin	337.71 ± 9.59[a]	541.40 ± 12.64[a]	374.52 ± 14.43[a]
Mogoltavidin	340.84 ± 8.45[a]	497.75 ± 14.55[a]	358.38 ± 16.25[a]
Deacetylkellerin	391.85 ± 13.50ǂ[a]	405.57 ± 16.64ǂ[a]	404.60 ± 15.65ǂ[a]
Ferukrin acetate + kellerin	338.69 ± 9.27[a]	506.17 ± 16.27[a]	369.20 ± 12.70[a]
Elaeochytrin-A	390.31 ± 12.63ǂ[a]	417.21 ± 17.60ǂ[a]	395.79 ± 15.37ǂ[a]
Ferutinin	432.70 ± 13.65ǂ	362.65 ± 14.16ǂ	467.72 ± 17.75ǂ

Values are expressed as mean ± S.E.M., n = 6 rats/group.
ǂ indicate significance compared to normal control group at $P < 0.05$.
[a] Indicate significance compared to SC group at $P < 0.05$.

NMR ($CDCl_3$, 125 MHz): 52.1 (C1), 23.3 (C2), 41.1 (C3), 81.3 (C4), 55.3 (C5), 71.5 (C6), 45.6 (C7), 20.6 (C8), 48.1 (C9), 75.7 (C10), 29.7 (C11), 21.6 (C12), 21.3 (C13), 22.2 (C14), 23.1 (C15) (Bruno et al., 1993; Ziaei et al., 2011).

***Farnesiferol A (FHM-N4)*:** Crystalized white solid, HR-EI-MS $[M+H]^+$ $m/z = 383.2226$ (calc. for $C_{24}H_{30}O_4$, 382.50). ^1H NMR ($CDCl_3$, 500 MHz/ δ ppm, *J* Hz): 6.19 (*d,* 9.4 Hz, H-3), 7.60 (*d*, 9.4 Hz, H-4), 7.32 (*d,* 8.6 Hz, H-5), 6.76 (*d,* 9.0 Hz, H-6), 6.77 (*m*, H-8), 1.62 (*m*, H-1'a), 1.36 (*m*, H-1'b), 1.70 (*m*, H-2'a), 1.64 (*m,* H-2'b), 3.24 (*bs*, H-3'), 1.29 (*m,* H-5'), 1.70 (*m,* H-6'a), 1.42 (*dt*, 11,5 Hz, 4.2 Hz, H-6'b), 2.29 (*d,* 13.4 Hz, H-7'a), 2.03 (*dd*, 13.0, 4.2 Hz, H-7'b), 2.16 (*t*, 5.9 Hz, H-9'), 4.29 (*dd,* 9.8 Hz, 5.6 Hz, H-11'a), 3.97 (*dd,* 10.0 Hz, 5.9 Hz, H-11'b),

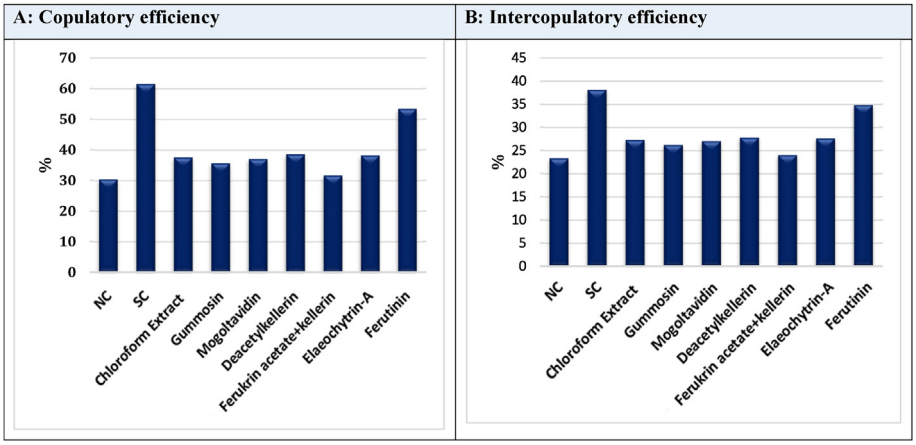

Fig. 2. Effect of sildenafil citrate (SC), chloroform extract and sesquiterpene derivatives at 10 mg/kg on the copulatory efficiency (A) and intercopulatory efficiency (B) of male rat.

4.82 (*s*, H-12'a), 4.72 (*s,* H-12'b), 1.01 (3H, *s*, H-13'), 0.77 (3H, *s*, H-14'), 0.96 (3H, *s*, H-15'). ^{13}C NMR ($CDCl_3$, 125 MHz): 161.3 (C2), 112.9 (C3), 143.5 (C4), 128.7 (C5), 113.2 (C6), 162.0 (C7), 101.6 (C8), 112.9 (C4a), 155.8 (C8a), 34.8 (C1'), 27.5 (C2'), 78.9 (C3'), 39.0 (C4'), 46.5 (C5'), 23.0 (C6'), 32.3 (C7'), 146.7 (C8'), 56.6 (C9'), 37.7 (C10'), 68.0 (C11'), 111.3 (C12'), 28.5 (C13'), 15.8 (C14'), 22.1 (C15') (Adhami et al., 2013; Hofer et al., 1984; Iranshahi et al., 2004).

***Ferutinin, 4β-hydroxy-6α-(p-hydroxy benzoyloxy)-5α(H)-dauc-8-ene (FHM-N5)*:** White-yellow resin, HR-EI-MS $[M+Na+2H]^+$ at m/z = 383.2216 (calc. for $C_{22}H_{30}O_4$, 358.21).^{1}H NMR ($CDCl_3$, 500 MHz/ δ ppm, *J* Hz): 7.92 (2H, *d*, 8.8 Hz, H-5' and H-3'), 6.88 (2H, *d*, 8.8 Hz, H-2' and H-4'), 5.55 (*t*, 5.6 Hz, H-9), 5.27 (*td*, 10.4 Hz, 2.8 Hz, H-6), 2.56 (*dd*, 12.4 Hz, 11.2 Hz, H-7a), 2.29 (*dd*, 14.0 Hz, 2.8 Hz, H-7b), 2.02 (*d*, 10.8 Hz, H-5), 2.06 (*m*, H-10a), 1.98 (*m*, H-10b), 1.92 (*m,* H-3a), 1.65 (*m,* H-3b), 1.56 (*m,* H-2a), 1.26 (*m*, H-2b), 1.86 (*sept,* 6.8 Hz, H-11), 1.81 (3H, *s*, H-15), 1.10 (3H*, s,* H-14), 0.94 (3H, *d,* 6.8 Hz, H-12), 0.85 (3H, *d,* 6.8 Hz, H-13). ^{13}C NMR ($CDCl_3$, 125 MHz): 44.0 (C1), 41.2 (C2), 31.4 (C3), 87.0 (C4), 60.1 (C5), 71.2 (C6), 41.4 (C7), 133.5 (C8), 125.2 (C9), 41.0 (C10), 37.0 (C11), 17.4 (C12), 18.5 (C13), 20.2 (C14), 26.4 (C15), 167.3 (C =O), 121.9 (C1'), 132.0 (C2', C6'), 115.4 (C3', C5'), 161.1 (C4') (Aydoğan et al., 2019; Colman-Saizarbitoria et al., 2006).

***Deacetylkellerin (FHM-N6)*:** Crystalized white solid, HR-EI-MS $[M+H]^+$ m/z = 401.2332 (calc. for $C_{24}H_{32}O_5$, 400.52) ^{1}H NMR ($CDCl_3$, 500 MHz/ δ ppm, *J* Hz): 6.17 (d, 9.4 Hz, H-3), 7.57 (d, 9.4 Hz, H-4), 7.30 (d, 8.5 Hz, H-5), 6.79 (dd, 8.6 Hz, 2.2 Hz,H-6), 6.76 (d, 1.7 Hz, H-8), 1.91 (d, 14.0 Hz, H-1'a), 0.99 (t, 12.5 Hz, H-1'b), 1.99 (t, 13.8 Hz, H-2'a), 1.49 (d, 2.6 Hz, H-2'b), 3.36 (bs, H-3'), 1.72 (dd, 17.8, 12.0 Hz, H-5'), 1.61 (m, H-6'a), 1.39 (dd, 12.3 Hz, 2.6 Hz, H-6'b), 1.70 (d, 14.8 Hz, H-7'a), 1.59 (m, 7'b), 1.52 (t, 4.2 Hz, H-9'), 4.01 (dd, 10.2 Hz, 3.8 Hz, H-11'a), 4.17 (dd, 9.8 Hz, 2.8 Hz, H-11'b), 1.25 (3H, s, H-12'), 0.82 (3H, s, H-13'), 0.94 (3H, s, H-14'), 1.30 (3H, s, H-15'). ^{13}C NMR ($CDCl_3$, 125 MHz): 161.4 (C2), 112.9 (C3), 143.6 (C4), 128.8 (C5), 113.0 (C6), 162.0 (C7), 101.5 (C8), 112.5 (C4a), 155.8 (C8a), 29.8 (C1'), 25.2 (C2'), 76.1 (C3'), 37.8 (C4'), 42.3 (C5'), 18.1 (C6'), 39.3 (C7'), 73.6 (C8'), 58.2 (C9'), 37.6 (C10'), 68.0 (C11'), 31.5 (C12'), 22.0 (C13'), 28.5 (C14'), 24.2 (C15') (Adhami et al., 2014; Andrianova et al., 1973; Nabiev et al., 1979; Perel'son et al., 1977a; Tashkhodzhaev et al., 2015).

Feruhermonin C (FHM-N7): Amorphous solid, HR-EI-MS [M +ACN + 2H]+ m/z = 417.2829 (calc. for C22H30O4, 374.21).^{1}H NMR ($CDCl_3$, 500 MHz/ δ ppm, *J* Hz): 1.62 (*dd,* 6.3, 2.8 Hz, H-2a), 1.29 (*d,* 9.9 Hz, H-2b), 1.95 (*dd*, 13.2 Hz, 9.4 Hz, H-3a), 1.60 (*dd*, 13.7 Hz, 8.5 Hz, H-3b), 2.21 (*d*, 11.0 Hz, H-5), 5.85 (*dd*, 10.9 Hz, 1.7 Hz, H-6), 5.36 (*t*, 5.6 Hz, H-7), 4.30 (*dd*, 10.5 Hz, 5.4 Hz, H-9), 2.12 (*dd,* 13.3 Hz, 5.1 Hz, H-10a), 1.64 (dd, 13.0 Hz, 2.8 Hz, H-10b), 1.75 (*sept*, 6.8 Hz, H-11), 0.89 (3H, *d*, 6.7 Hz, H-12), 0.85 (3H, *d,* 6.7 Hz, H-13), 1.89 (3H, *s*, H-14), 1.16 (3H, *s*, H-15), 7.92 (2H, *d*, 8.7 Hz, H-2' and H-6'), 6.88 (2H, *d,* 8.7 Hz, H-3' and H-5'). ^{13}C NMR ($CDCl_3$, 125 MHz): 42.5 (C1), 42.0 (C2), 31.7 (C3), 87.1 (C4), 54.9 (C5), 73.2 (C6), 126.3 (C7), 139.1 (C8), 70.0 (C9), 50.4 (C10), 37.0 (C11), 18.4 (C12), 17.6 (C13), 24.2 (C14), 19.1 (C15), 167.3 (C =O), 121.8 (C1'), 132.3 (C2', C6'), 115.7 (C3', C5'), 161.4 (C4') (Auzi et al., 2008; Fraga et al., 1985).

***Ferukrin acetate (FHM-N8, %75)*:** Amorphous white solid, HR-EI-MS $[M+Na]^+$ m/z = 465.227 (calc. for $C_{26}H_{34}O_6$, 442.55) ^{1}H NMR ($CDCl_3$, 500 MHz/ δ ppm, *J* Hz): 6.21 (*d*, 9.4 Hz, H-3), 7.62 (*d*, 9.4 Hz, H-4), 7.35 (*d*, 8.5 Hz, H-5), 6.76 (*dd*, 8.6 Hz, 2.2 Hz, H-6), 6.74 (*d*, 1.7 Hz, H-8), 1.75 (*d*, 14.0 Hz, H-1'a), 1.63 (*t*, 12.5 Hz, H-1'b), 1.58 (*t* ,13.8 Hz, H-2'a), 1.36 (*d* ,2.6 Hz, H-2'b), 4.39 (*bs*, H-3'), 1.47 (*dd,* 17.8, 12.0 Hz, H-5'), 1.71 (*m*, H-6'a), 1.53 (*dd*, 12.3 Hz, 2.6 Hz, H-6'b), 1.72 (2H, *d*, 14.8 Hz, H_2-7'), 1.52 (*t*, 4.2 Hz, H-9'), 4.04 (*dd* , 10.2, 3.8 Hz, H-11'a), 4.10 (*dd* , 9.8 Hz, 2.8 Hz, H-11'b), 1.26 (3H, *s*, H-12'), 0.88 (3H, *s*, H-13'), 0.83 (3H, *s*, H-14'), 1.33 (3H, *s,* H-15'), ^{13}C NMR ($CDCl_3$, 125 MHz): 161.7 (C2), 113.1 (C3), 143.5 (C4), 128.9 (C5), 112.9 (C6), 161.2 (C7), 101.3 (C8), 112.8 (C4a), 155.9 (C8a), 23.6 (C1'), 35.3 (C2'), 80.9 (C3'), 37.7 (C4'), 48.5 (C5'), 18.1 (C6'), 39.4 (C7'), 73.2 (C8'), 57.6 (C9'), 38.0 (C10'), 67.5 (C11'), 31.5 (C12'), 28.6 (C13'), 16.7 (C14'), 24.3 (C15'),171.0 (C=O), 21.3 (Ac-CH_3) (Khasanov et al., 1974; Nabiev et al., 1979; Perel'son et al., 1977b).

***Kellerin (FHM-N8, %25)*:** Amorphous white solid, HR-EI-MS $[M+Na]^+$ m/z = 465.227 (calc. for $C_{26}H_{34}O_6$, 442.55) ^{1}H NMR ($CDCl_3$, 500 MHz/ δ ppm, *J* Hz): 6.21 (*d*, 9.4 Hz, H-3), 7.61 (*d*, 9.4 Hz, H-4), 7.34 (*d*, 8.5 Hz, H-5), 6.83 (*dd*, 8.6 Hz, 2.4 Hz, H-6), 6.87 (*d*, 2.4 Hz, H-8), 1.49-1.51 (2H, *m*, H_2-1'), 1.85 (*t* ,5.2 Hz, H-2'a), 1.59 (*dd* ,12.4, 4.3 Hz, H-2'b), 4.63 (*t*, 2.8 Hz, H-3'), 1.47 (*d,* 11.4 Hz, H-5'), 1.91 (*m*, H-7'a), 1.57 (*dd*, 12.8 Hz, 3.3 Hz, H-7'b), 1.48 (2H, *m*, H-7'a), 1.85 (*t*, 5.7, Hz, H-9'), 4.15 (*dd* , 9.9, 5.5 Hz, H-11'a), 4.33 (*dd* ,12.6 Hz, 5.15 Hz, H-11'b), 1.22 (3H, *s*, H-12'), 0.85 (3H, *s*, H-13'), 0.93 (3H, *s*, H-14'), 0.87 (3H, *s,* H-15'), ^{13}C NMR ($CDCl_3$, 125 MHz): 161.8 (C2), 112.87 (C3), 143.5 (C4), 128.79 (C5), 113.12 (C6), 161.2 (C7), 101.6 (C8), 112.7 (C4a), 155.87 (C8a), 33.5 (C1'), 22.6 (C2'), 77,67 (C3'), 36.6 (C4'), 49.6 (C5'), 19.8 (C6'), 43.95 (C7'), 72.57 (C8'), 59.3 (C9'), 37.7 (C10'), 66.66 (C11), 24.8 (C12'), 28.0 (C13'), 15.9 (C14'), 21.7 (C15'), 170.7 (C=O), 21.2 (Ac-CH_3) (Adhami et al., 2014; Andrianova et al., 1973; Perel'son et al., 1977a; Tashkhodzhaev et al., 2015).

Elaeochytrin-A, 4β-hydroxy-6α-(o-amino benzoyloxy)-5α(H)-dauc-8-ene (FHM-N9): Amorphous solid, HR-EI-MS $[M+H]^+$ m/z = 358.2371 (calc. for $C_{22}H_{31}NO_3$, 357.23). ^{1}H NMR ($CDCl_3$, 500 MHz/ δ ppm, *J* Hz): 7.78 (*dd*, 8.0 Hz,1.6 Hz, H-6'), 7.27 (*ddd,* 7.2 Hz, 6.8 Hz, 1.6 Hz, H-4'), 6.67 (*dd,* 8.0 Hz, 0.8 Hz, H-3'), 6.64 (*td,* 8.0 Hz,1.2 Hz, H-5'), 5.55 (*bs*, H-9), 5.27 (*ddd,* 10.8 Hz, 10.4 Hz, 2.8 Hz, H-6), 2.54 (*dd*, 12.4 Hz, 11.6 Hz, H-7a), 2.27 (*dd*, 14.0 Hz, 2.4 Hz, H-7b), 2.00 (*d,* 10.8 Hz, H-5), 2.06 (*m,* H-10a), 1.91 (*m*, H-10b), 1.91 (*m*, H-3a), 1.60 (*m,* H-3b), 1.54 (*m*, H-2a), 1.30 (*m*, H-2b), 2.04 (*m*, H-11), 1.82 (3H, *s*, H-15),

1.11 (3H, *s*, H-14), 0.95 (3H, *d*, 6.8 Hz, H-12), 0.85 (3H, *d*, 6.8 Hz, H-13). ^{13}C NMR ($CDCl_3$, 125 MHz): 44.2 (C1), 41.5 (C2), 31.8 (C3), 86.5 (C4), 60.1 (C5), 70.7 (C6), 41.6 (C7), 134.4 (C8), 125.4 (C9), 41.2 (C10), 37.4 (C11), 17.7 (C12), 18.7 (C13), 20.3 (C14), 26.6 (C15), 168.3 (C =O), 111.0 (C1'), 151.1 (C2'), 117.0 (C3'), 133.7 (C4'), 116.4 (C5'), 131.0 (C6') (Alkhatib et al., 2008).

Teferidin, 4β-hydroxy-6α-benzoyloxy-5α(H)-dauc-8-ene (FHM-N10): Yellow resin, HR-EI-MS $[M+Na]^+$ *m/z* =365.2138 (calc. for $C_{22}H_{30}O_3$, 342.2). 1H NMR (CDCl3, 500 MHz/ δ ppm, J Hz):7.89 (2H, *d,* 7.2 Hz, H-2' and H-6'), 7.61 (*t,* 7.2 Hz), 7.50 (2H, *dd*, 8.0 Hz, 7.2 Hz, H-3' and H-5'), 5.50 (*bs*, H-9), 5.09 (*td*, 10.2 Hz, 2.4 Hz, H-6), 2.39 (*dd*, 12.8 Hz, 10.8 Hz, H-7a), 2.16 (*dd,* 14.0 Hz, 12.8 Hz, H-7b), 1.96 (*d*, 9.6 Hz, H-5), 1.96 (*m*, H-10a), 1.85 (*m*, H-10b), 1.92 (*m*, H-3a), 1.50 (*m*, H-3b), 1.43 (*m*, H-2a), 1.20 (*m*, H-2b) 2.10 (*sept,* 6.8 Hz, H-11), 1.75 (3H, *s*, H-15), 1.01 (3H, *s*, H-14), 0.94 (3H, *d*, 6.8 Hz, H-13), 0.75 (3H, *d*, 6.8 Hz, H-12). ^{13}C NMR ($CDCl_3$, 125 MHz): 43.9 (C1), 41.0 (C2), 32.4 (C3), 85.1 (C4), 59.4 (C5), 70.9 (C6), 41.5 (C7), 133.7 (C8), 125.3 (C9), 40.9 (C10), 36.5 (C11), 18.1 (C12), 18.8 (C13), 20.6 (C14), 26.6 (C15), 165.2 (C =O), 131.3 (C1'), 129.3 (C2'), 129.0 (C3'), 133.3 (C4'), 129.0 (C5'), 129.3 (C6') (Geroushi et al., 2011).

3.2. Sexual behavior results

3.2.1. Male sexual behavior study

From the sixty sexually trained rats, only fifty-four males that showed sexual activity were selected. In the present study, the extracts and sesquiterpene derivatives were tested for their potential in enhancing the sexual behavior of male rats, and sildenafil citrate was applied as the reference drug. The results presented in Tables 1 and 2 showed that SC and ferutinin significantly ($P < 0.05$) reduced the mounting latency (41.68 ± 2.77 and 47.40 ± 2.58 s, respectively) and intromission latency (67.11 ± 3.47 and 83.75 ± 5.45 s, respectively) as compared to the normal control group (84.27 ± 4.12 and 152.24 ± 8.85 s, respectively). Both significantly ($P < 0.05$) increased the mount frequency (28.44 ± 0.97 and 23.81 ± 0.89, respectively), intromission frequency (17.50 ± 0.68 and 12.72 ± 0.68, respectively) and prolonged ejaculation latency in 1st series (450.90 ± 15.23 and 432.70 ± 13.65 s, respectively) of male animals as compared to the normal rats (13.78 ± 0.65, 4.18 ± 0.21 and 342.35 ± 8.74 s, respectively). Also, they prolonged post-ejaculatory interval (325.57 ± 13.73 and 362.65 ± 14.16 s, respectively) and reduced the ejaculation latency in 2nd series (492.60 ± 16.25 and 467.72 ± 17.75 s, respectively) as compared to the normal control group (528.89 ± 15.18 and 360.87 ± 12.73 s, respectively). The percentages of copulatory and the intercopulatory efficiencies were the highest in the group exposed to SC compared with the normal control group (Fig. 2). This was, however, not significantly different ($P < 0.05$) compared to male animals that were administered ferutinin. A moderate improvement in the sexual behavior of male rats was observed in deacetylkellerin, the chloroform extract and elaeochytrin-A groups compared to the normal control rats and this improvement was statistically significant ($P < 0.05$). On the contrary, administrations of gummosin, mogoltavidin and ferukrin acetate with kellerin did not alter the sexual behavior parameters ($P < 0.05$) in rats when compared to the normal rats.

4. Discussion

As several species of *Ferula* genus have been used in folk medicine as aphrodisiac, this study firstly examined the effect of the FHM extracts on the sexual efficiency of male rats including ML, IL, MF, and IF. Generally, MF and ML reflect sexual interest or libido, whereas the IF and IL are useful indices of the sexual excitement and the efficiency of erection (Ågmo, 1997; Che Musa et al., 2018). Sildenafil citrate was used as positive reference drug. The results demonstrated that especially the less-polar organic phase of FHM ($CHCl_3$) was effective in sexual activity, and no significant effect was observed in the water phase. Thus, a phytochemical study was performed on the $CHCl_3$ extract resulting in isolation of sesquiterpene derivatives, which were also screened for their effects on sexual behavior parameters in male rats. In parallel to our results, Zanoli et al. reported that *F. hermonis* extract (30 and 60 mg/kg) was able to improve sexual activity acutely in rats with an increase in testosterone levels, and the acetone extract also improved male sexual appetitive behavior in potent rats by ML and IL significantly (Zanoli et al., 2003; Zanoli et al., 2005).

In this study, the reduced durations of ML and IL as well as the increased values of MF and IF recorded in deacetylkellerin, elaeochytrin-A and ferutinin-treated rats suggest enhanced sexual interest, libido and erection (Tajuddin et al., 2004). This suggestion is supported by Yakubu et al. who reported that plants with sexual enhancing potential should induce considerable improvements in the IFand MF and significant reductions in the IL and ML (Yakubu et al., 2005). The marked increase in the duration of ejaculation latency in the 1st and 2nd series (EL-1 and EL-2, respectively) as well as the decrease in the duration of the refractory period between the 1st and 2nd series of mating (PEI), confirm that deacetylkellerin, elaeochytrin-A and ferutinin improved sexual activity of male rats. The significant reduction in copulatory and intercopulatory efficiencies in deacetylkellerin, elaeochytrin-A and ferutinin-treated rats are indications of increased sexual activity (Gauthaman et al., 2002). The highest sexual improving activity was observed in the ferutinin-treated rats.

A number of sesquiterpenes were isolated from the roots of *Ferula* plants, one of which was ferutinin as major constituent (Ikeda et al., 2002). In accordance with our studies, Zanoli et al. showed that when ferutinin, teferin and teferidin (2.5 mg/kg) were given orally to ovariectomized female rats, ferutinin caused a significant decrease lordosis quotient and lordosis rating values (P. Zanoli et al., 2005). Moreover, ferutinin is a powerful phytoestrogen possessing agonistic actions over the α and β subunits of estrogenic receptors (Appendino et al., 2002). It activates phospholipase C that hydrolyse phosphatidylinositol (4,5) biphosphate to generate inositol (1,4,5)-trisphosphate (IP3) and diacylglycerol leading to the liberation of intracellular Ca^{2+}. The release of calcium ions from its stores increases nitric oxide synthase (NOS) activity and consequently catalysing the production of nitric oxide (NO) (Colman-Saizarbitoria et al., 2006). Thus, phytoestrogen-induced NO production may play a substantial function in the control of the hypothalamic-pituitary-gonadal axis and could be responsible for the aphrodisiac effect of ferutinin (Brann et al., 1997). Furthermore, some natural coumarin derivatives have demonstrated positive effects on erectile dysfunction. For example, umbelliferone exhibited erectile responses mediated via NO/cGMP-dependent pathway, whereas ostholeshowed a dose-related corpus cavernosal relaxant-vasodilation, which played a critical role in erection mediated by NO. Another coumarin, namely icariin, potently inhibited PDE5A1 with an IC_{50} value very close to that of sildenafil (Dell'Agli et al., 2008; Karakaya et al., 2019; Ongaro et al., 2019; Tharakan and Manyam, 2005).

When our results taken into consideration with those of previously reported data, it can be stated that daucane framework with a benzoyl group including electron donating groups (OH or NH_2) is important in sexual activity (ferutinin and elaeochytrin A). In the case of sesquiterpene coumarin conjugates, deacetylkellerin was more active than its counterparts implying a complex relationship between structure and activity. As coumarin unit of these compounds is a well-known aphrodisiac (umbelliferone), one can speculate that the sesquiterpene-coumarin structure stays intact in rats.

5. Conclusion

Taken together, our results demonstrated that some of the sesquiterpene derivatives of *F. huber-morathii* significantly stimulates sexual behavior in male rats, thus suggesting that the plant possesses an aphrodisiac activity. Based on our results, we conclude that especially

ferutinin have potential to be used as an effective therapeutic alternative to current modalities for the management of sexual dysfunction in males. Thus, future studies are warranted to reveal the mechanism(s) responsible for the sexual behavior enhancement effect and the probable side effects of pure sesquiterpenoids and their combination therapies among males with sexual dysfunction.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jep.2020.112868.

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