

Efficacy and Safety Assessments of *Ferula assa-foetida* L., Traditionally used in Greco-Arab Herbal Medicine for Enhancing Male Fertility, Libido and Erectile Function

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Abstract: Based on knowledge from traditional Arabic and Islamic herbal medicine, this study aims to examine the effects of extracts from *Ferula assa-foetida* L on male fertility and sexual functioning in rats and in man. Therefore, ethanol extract from seeds and 50% water-ethanol extracts from roots were prepared into so-called "Masculine" tablets and assessed for their safety and efficacy in enhancing male libido. Results obtained show that Masculine exhibit high levels of safety in both cultured human fibroblasts and in experimental studies on rats with a LD₅₀ of 5 g/kg. Antioxidant properties were substantial both in rat liver cells and in human sperm cells at a concentration of 50µg/ml. Experiments with rat arterial rings with and without their endothelial tissue revealed, that Masculine is a potent vasodilator due to an endothelia-mediated effect rather than a direct effect on smooth muscle cells. Episodes of penile erection were studied in two groups of rats and were significantly augmented in the Masculine treated group. Furthermore, two groups of healthy young men were studied and followed for 3 months while consuming one Masculine tablet daily. Masculine was well tolerated by all men and no side effects were reported. Both groups were recruited from fertility clinics, the first group (n = 60) was recruited due to incomplete azospermia that was medically untreatable, and the second group (n = 25) was recruited due to erectile dysfunction and impotence of no treatable cause. Quantitative and qualitative improvements of sperm counts were reported after two months of treatment in 17% and 60%, in the first and second group, respectively. In addition, 60% of the second group reported remarkable improvements in both their libido and erectile function. Taken collectively, our results indicate that Masculine is a safe sexual tonic enhancing male sexual functioning in animals and in man.

Keywords: *Ferula asafoetida*, male impotence, erectile function, fertility, masculine, Arab herbal medicine.

INTRODUCTION

Many people in Mediterranean region who consult with spiritual healers, homeopaths and herbalists are utilizing traditional therapies. These are the first choice for problems such as liver diseases, inflammation, skin diseases, infertility, impotence, diabetes, obesity, epilepsy, psychosomatic troubles, and many other diseases [1]. The modern use of Arab botanical medicines has historical roots in Ancient Arabic medicine. Arab herbalists, pharmacologists, chemists, and physicians adapted in the Middle Ages the ancient medicinal practices of Mesopotamia, Greece, Rome, Persia, and India [2]. Medical innovations introduced by Arab physicians included: The discovering of the immune system, the introduction of microbiological science, and the separation of medicine from pharmacological science [1-7]. The most common plants used in Arabic medicine for aphrodisiac action are: *Trigonella foenum*, *Eurica sativa*, *Clematis cirrhosa*, *Pistacia palasestina*, *Zingiber officinale*, *Smilax as-*

pera, *Salvia dominica*, *Nasturtium officinale*, *Raphanus raphanistrum*, *Poenix dactylifera* and *Allium cepa* [1, 8-9]. Zallouh is the common name in the Middle East for the roots of the species *Ferula hermonis* growing on the slopes of Mount Hermon in the Syrian Golan Heights which has been used for centuries as a folk remedy to treat frigidity in women, and erectile and sexual dysfunction in men. This plant is botanically quite close to *Ferula communis*, the Giant Fenel. *Ferula* is the Latin name for "walking stick", a word mentioned in the Old Testament as the Hebrew name "kelech", in the context that its stem was used as a walking stick. There are several species of *Ferula* that grow throughout the world including the species *Ferula asa-foetida* L. This plant is native to central Asia (Iran and Afghanistan), however it was well integrated in the Greek-Arab medicinal system and still employed in all Arab countries. According to the Greek herbalists, Dioscorides and Galen, this plant is used for the treatment of tiredness and impotence [10]. The rich traditional knowledge of Arabic/Hippocratic medicine gives support to its use as a sexual tonic to encourage potency. Al-Razi (Rhazes 841-926 A.D) reported that Indians use *Ferula asa-foetida* L as the main botanical aphrodisiac, several centuries before his time [11]. Ibn Sina (Avisine) and

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Al-Antaki have also emphasized the aphrodisiac effect of *Ferula assa-foetida* L. [12]. There is considerable confusion in the identification of aphrodisiac species of plants especially due to their extensive use as aphrodisiac agents, plant part used and relatively similar smell. They are called names such as "Helitit", "Andujan", "Kallch", "Aqir Qarha" or "Oud alkerach algabali" [13,14]. All the well known traditional herbalists agree that these species are used to manage tiredness and impotence and they describe a unique method of preparation that includes boiling of the roots to dryness sometimes with oil addition.

The roots of *Ferula assa-foetida* L., "Devil's Dunk", produce the well-known spice asafoetida used to flavour foods until today all over the world [15,16]. The plant is approved for food use in both the EU and USA [17] and ingestion of 15 grams of it did not produce any adverse effect [18]. The herbal use of *Ferula assa-foetida* L. seems thus to be without safety concerns and this was confirmed in two clinical studies in India [19] and in Germany [20]. The plant disclosed hypolipidemic properties in patients [19] and was a useful treatment of irritable bowel syndrome [20], with no side effects whatsoever [19-20]. Supportive action of asafoetida on the digestive process was also evidenced in animal studies suggesting the spice as a carminative that is able to stimulate pancreatic digestive enzymes [21].

Possible aphrodisiac effects have been investigated in animal models mainly using *Ferula hermonis*. The present study used extracts from seeds and roots of *Ferula assa-foetida* L. and aimed at investigating their safety and possible cytotoxic or cytoprotective properties as well as their aphrodisiac effects in animal models and in human volunteers. The study was undertaken in accord with legal and ethical requirements as well as current scientific standards as indicated by European Clinical Practice Guidelines and the Declaration of Helsinki.

MATERIAL AND METHODS

Preparation of Masculine: The seeds and the roots of *Ferula assa-foetida* L. were obtained from the folk medicinal plant market of Jerusalem. Concentrated absolute ethanol extracts from seeds and 50% ethanolic root extract were prepared at Antaki-laboratories, Kfar Cana, Israel. Masculine tablets (310 mg/tablet) were prepared at Karmat Micro Encapsulation laboratories, Kibbutz Ramot Menashe, Israel. Each tablet contained 98 mg seed dried extract, 63 root dried extract, 4.1 mg Vitamin E, and 144.9 mg Tricalcium phosphate (TCP). Vitamin E and TCP were added to the powder during the formulation. For the animal and in vitro experiments, only plant dry extracts were used.

Assessment of LD₅₀: Thirty-four rats were given a progressive overdose of the extract to determine the lethal dose sufficient to kill half of them (LD₅₀). Experiments were carried out at the Pharmacology laboratories, Technion University, Haifa, Israel.

LDH assay: Toxicity of the extract was estimated in cultured cells by the LDH-release-assay. Release of the intracellular enzyme LDH is the consequence of necrotic or toxic cell-membrane-rupture. Integrity of the cell membrane was determined by measuring the LDH-activity released into the

culture medium. LDH-activity was monitored following the oxidation of NADH as the decrease in absorbance at 490 nm. The reaction was carried out in a potassium phosphate buffer (40 mM K₂HPO₄, 10 mM KH₂PO₄, pH 7.5), containing 0.24 mM NADH and 0.62 mM pyruvate. The percentage of LDH released was defined as the ratio of LDH activity in the supernatant compared to the sum of LDH amount released plus LDH activity measured in the cell lysate. Human fibroblasts were incubated with different amounts of the product extracts and LDH activity was measured in the medium at 24, 48 and 72 hours of incubation.

Lipid peroxidation: Oxidative stress leads to generation of reactive oxygen species (ROS) that play an important pathogenetic role in different disease-states. Lipid peroxidation has damaging effects on cell membranes. The extent of lipid peroxidation was measured using a technique based on a thiobarbituric acid reactive substance (TBARS) assay that detects malondialdehyde (MDA), an end product of peroxidative decomposition of polyenoic fatty acids in *in-vitro* systems [22-23]. To accurately quantify TBARS in the analytical procedure, the protein was precipitated before the addition of thiobarbituric acid to the reaction, while the antioxidant butylated hydroxytoluene was added before heating of samples. Antioxidant properties of the product were investigated both in rat liver cells and in human sperm cells using the Bylund protocol [24] for isolating the sperm membranes. Rat liver homogenates or human sperm cells were incubated with 100 μM FeSO₄ as ROS generating system and with various concentrations of the extract.

Vasodilatation properties: Arterial rings were harvested from Sprague-Dawley rats. Anaesthesia was induced by subcutaneous injection of 10% chloral hydrate, thoracic aorta were dissected and rapidly immersed in Krebs-Henseleit solution and all conjunctive and adipose tissues were removed [25-27]. Two arterial rings each of 0.4 cm in diameter were obtained and the endothelium was mechanically removed from one of them. Each ring was suspended by a fine steel wire and connected to isometric tension transducer (Myograph F60). The transducer was connected to a Narco Trace 40 polygraph (Narco-Bio-Systems Inc., Texas, USA). The rings were maintained in 15 ml Krebs-Henseleit solution at 37°C. A tension of 500 mg was maintained during an equilibrium period of 60 minutes during which the bathing medium was changed every 20 minutes. The rings were then incubated with potassium chloride (10 mM), a concentration that induces 60 - 70 % of maximal contraction, and the developed tension was measured. The same incubate was exposed to five different product concentrations and the developed tension was measured.

Penile erection: Two groups of 10 male rats each were used. Single daily dose of 200 mg/kg was orally given to one group for one week. On day 7, three female rats in heat were placed in a cage near the two male groups in order to stimulate sexual responses in them. The study started 30 minutes after forced feeding with normal food to the control group and food enriched with an overdose of the plant extract (500 mg/kg) to the treated group (to avoid any direct effects on stomach). The study consisted of counting episodes of penile erection in each of the 10 rats in each group every hour for 3 hours [28].

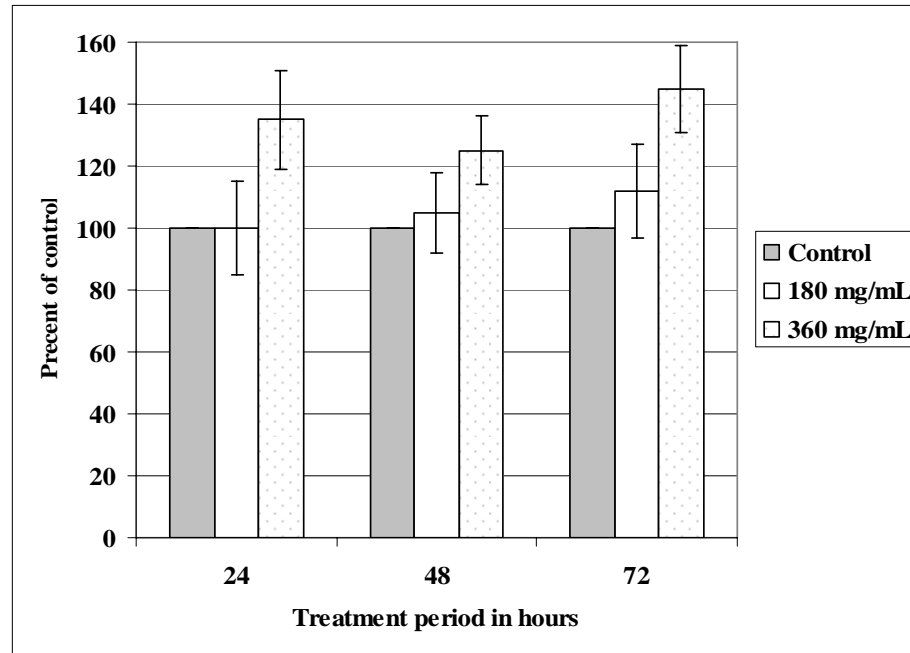


Fig. (1). LDH-release in arbitrary units from cultured human fibroblasts at baseline (0) and during incubating the fibroblasts with two concentrations (180 & 360 mg/ml) of “Masculine” extract at 24, 48 and 72 hours of incubation time. Values given represent the mean \pm standard deviations ($*P < 0.05$ significant as compared to controls) of three independent experiments carried out in triplicates.

Clinical Investigations: Two groups of healthy young men visiting fertility clinics due to fertility reasons or erectile dysfunction and impotence were selected for the study. They were recruited from two clinics in Haifa (New Medical Center run by Dr. F. Nahhas and Lyn Medical Center run by Dr. B Laver). The one group ($n = 60$) was selected on the basis of infertility (azospermia) including volunteers who have developed azospermia after a period of normal fertility, that was medically untreatable and the other ($n = 25$) was selected on the basis of erectile dysfunction and/or impotence that did not originate in a medically treatable cause. After a thorough review of the herbal component of “Masculine” informed consent was obtained from each subject who was asked to continue his daily activities and habits unchanged but to take one tablet of “Masculine” daily for 3 months. A review of wellbeing and possible adverse effects was undertaken in all men at baseline and at 3 months together with quantitative and qualitative evaluation of their sperm counts. Reports of sexual functioning were obtained at baseline and at 3 months in the group of 25 men with sexual problems.

STATISTICS

The Wilcoxon signed-rank test was used. Comparison between groups was performed by the Wilcoxon rank-sum test. A 0.05 level of significance was set. Data obtained were expressed as mean \pm standard error of mean (SEM).

RESULTS

Toxicity measurements: A very high dose of 5 g/kg was necessary to obtain the LD50 in rats. LDH-release from cultured human fibroblasts is expressed in arbitrary units in Fig.

(1), at baseline (0, left column), after incubating the fibroblasts with 2 concentrations of Masculine extract of 180 mg/ml (middle column) and 360 mg/ml (right column). Figs. (2A, 2B and 2C) express the results at 24, 48 and 72 hours of incubation time respectively. Compared to baseline no substantial difference in LDH-release is noted whether as a function of increasing the extract concentration or prolonging the incubation period.

Antioxidant properties: Results of lipid peroxidation are shown in Figs. (2 and 3) as the extent of MDA production at baseline (0) and during the addition of several product concentrations. The addition of very low dose of Masculine extract (0.01 mg/ml) to the incubate of rat liver cells-ferrosulphate (Fig. 2), significantly reduces MDA-release from 0.27 ± 0.02 to 0.17 ± 0.02 ng/mg protein ($p < 0.01$). Higher concentrations (0.05 mg/ml) further reduce MDA-release to 0.13 ± 0.01 ng/mg protein ($p < 0.001$), whereas, those of 0.1 mg/ml or 1 mg/ml both do not substantially add to further reductions in MDA-release. The results of the addition of Masculine extracts to the incubate of human sperm cells-ferrosulphate are expressed in Fig. (3). The addition of a low concentration of 0.01 mg/ml reduces MDA-release from 0.52 ± 0.03 to 0.31 ± 0.02 ng/mg proteins ($p < 0.001$). A higher concentration (0.05 mg/ml) further reduces the released MDA to 0.16 ± 0.02 ng/mg protein ($p < 0.0005$), but no further antioxidant effect is obtained at the concentration of 0.1 mg/ml of the studied extract.

Vasodilatation properties: Fig. (4) summarizes the results of incubating the contracted arterial rings with different product concentrations. At baseline, the induced contraction (tension) measured in arterial rings is about 800 ± 30 mg and

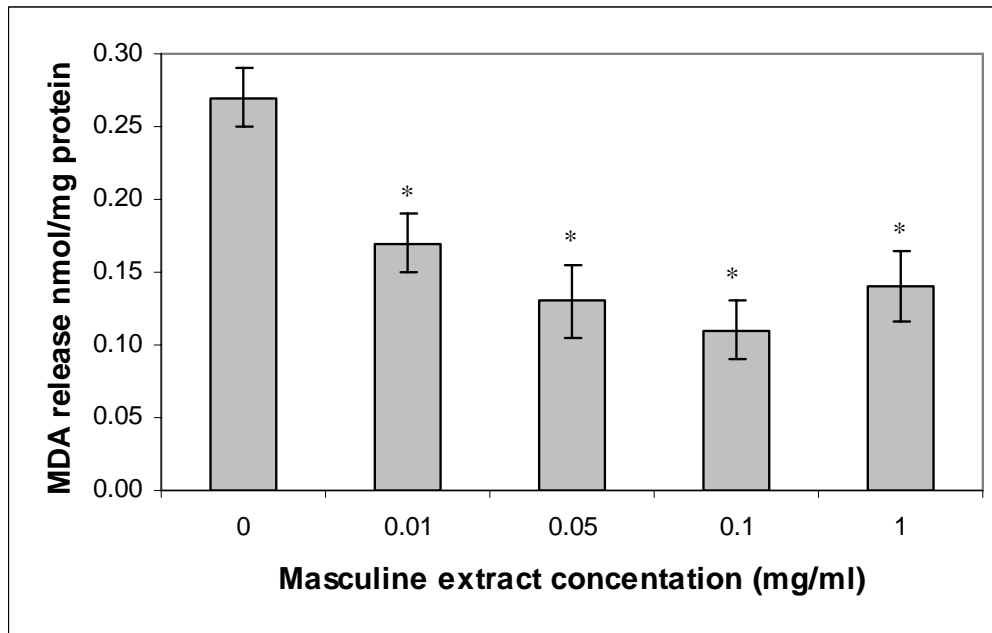


Fig. (2). Effects of “Masculine” extract at different concentrations upon malondialdehyde (MDA) released and produced by lipid peroxidation in rat liver cells incubated with 100 μ M ferrous sulphate. Values given represent the mean \pm standard deviations (* P < 0.05 significant as compared to controls) of three independent experiments carried out in triplicates.

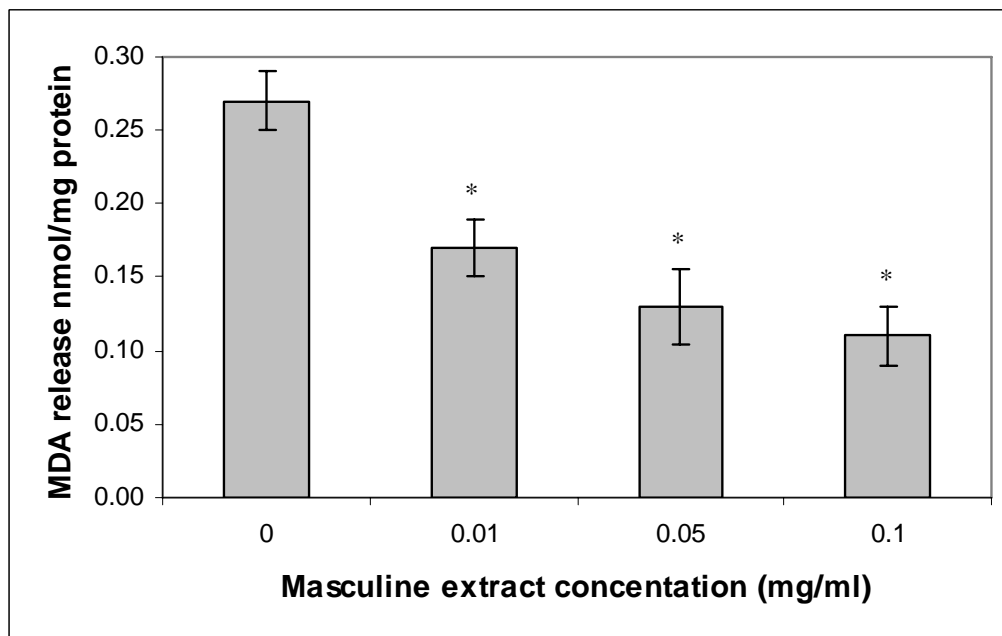


Fig. (3). Effects of “Masculine” extract at different concentrations upon MDA released and produced by lipid peroxidation in human sperm cells incubated with 100 μ M Ferro sulphate. Values given represent the mean \pm standard deviations (* P < 0.05 significant as compared to controls) of three independent experiments carried out in triplicates.

is kept almost unchanged during the experimental conditions (upper curve). Such an induced tension in those arterial rings with an intact endothelium (lower curve) is reduced to 460 ± 28 ($p < 0.01$) by the addition of a low concentration of the product extract (0.2 mg/ml). Incremental but slight reductions in the developed tension are seen during increased product concentrations reaching a nadir value of 310 ± 20 mg at the 1 mg/ml concentration. The induced tension in those arterial rings deprived of their endothelium (middle

curve), is reduced from 800 ± 30 mg at baseline to 710 ± 37 mg ($p < 0.01$) by a product concentration of 0.2 mg/ml. Incremental but slight reductions in the developed tension are seen during increased product concentrations reaching a nadir value of 640 ± 25 mg at the 1 mg/ml concentration. Such weakened vasodilating properties of the extract are thus non-endothel-mediated and may represent a direct action on arterial smooth muscle cells.

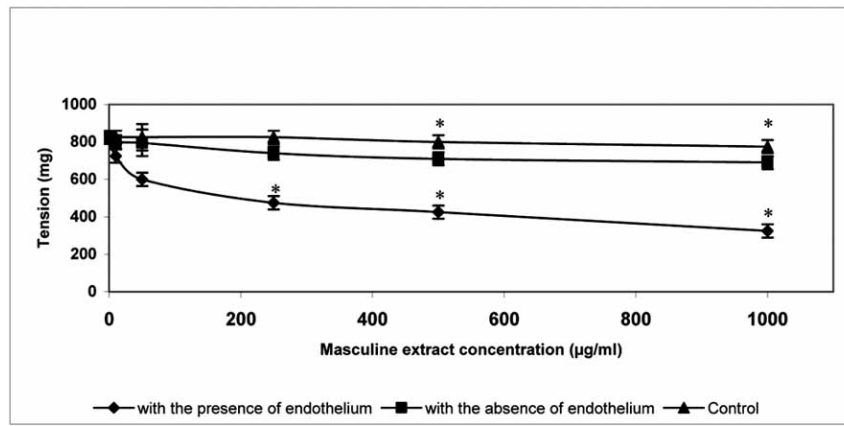


Fig. (4). The tension (mg) developed during induced contraction of arterial rings at baseline (upper curve) and during the addition of different concentrations of “Masculine” extract to intact arterial rings (lower curve) and to arterial rings deprived of their endothelium (middle curve). Values given represent the mean ± standard deviations (**P* < 0.05 significant as compared to controls) of three independent experiments carried out in triplicates.

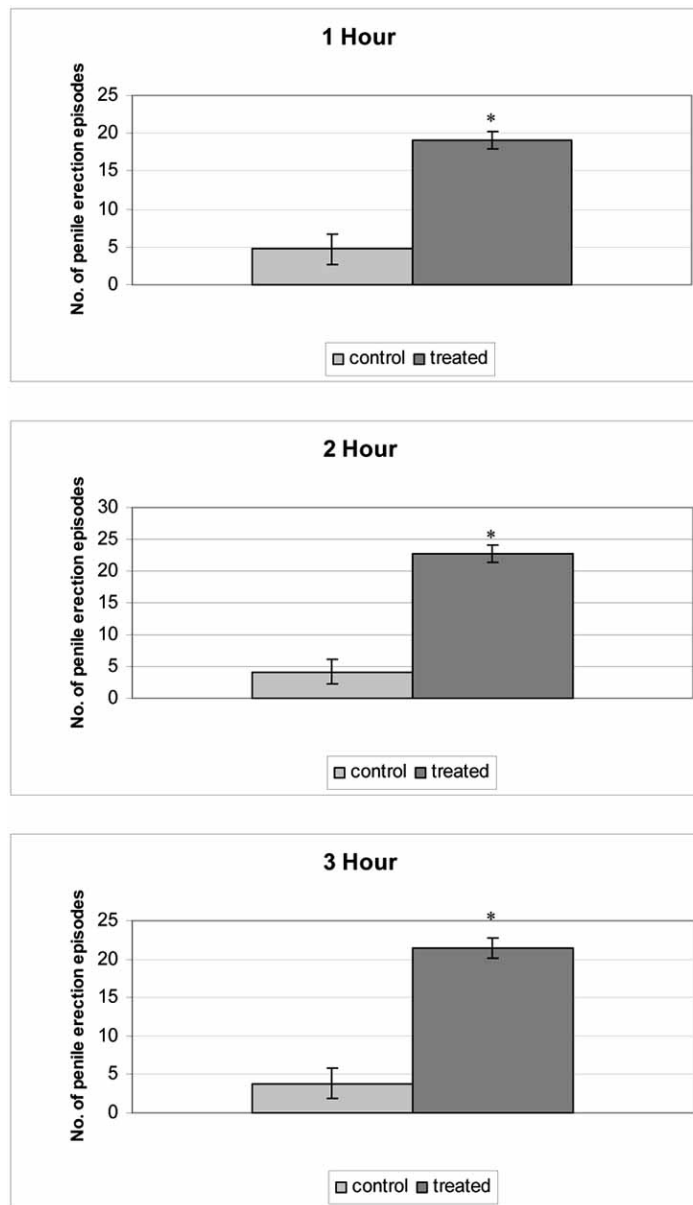


Fig. (5). Episodes of penile erection in control rats and in rats treated with plant extract within 3 hours of sexual stimulation. Values given represent the mean ± standard deviations (**P* < 0.05 significant as compared to controls).

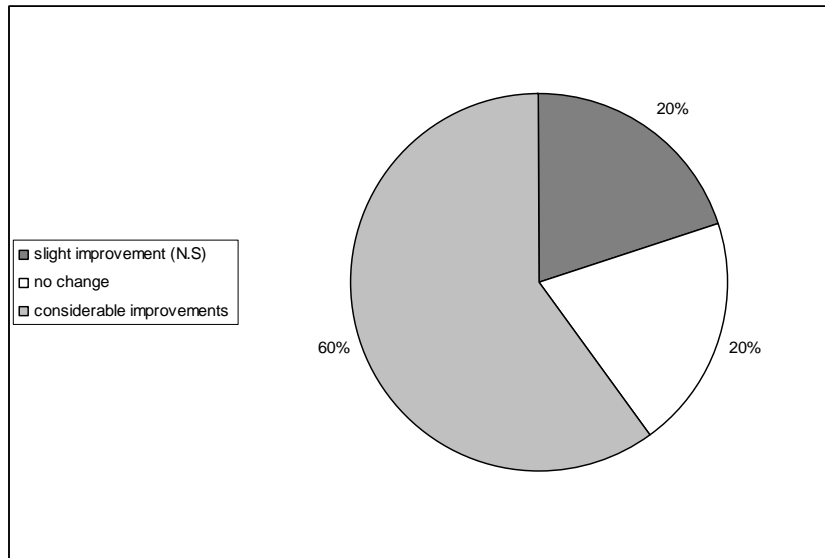


Fig. (6). Effect of Masculine consumption (1 tablet/day - for 3 months) on libido and erectile function on 25 volunteers suffering from erectile dysfunction.

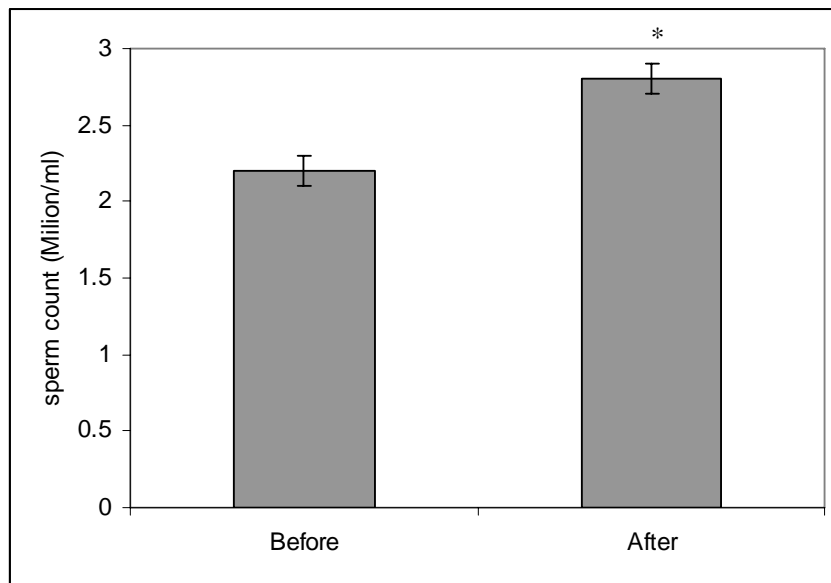


Fig. (7). Effect of Masculine consumption (1 tablet/day - for 3 months) on sperm count in 15 oligospermic volunteers.

Penile erection: Fig. (5) shows the episodes of penile erection in the control and “Masculine” treated rats within 3 hours. These episodes increase from 4.7 ± 1.7 in controls to 19.1 ± 1.5 in the treated rats within the first hour and from about 4 and 4 to about 23 and 22 episodes within the second and third hours respectively. These are highly significant differences with a mean 3-hours-increase in these episodes by 450%. The 85 young healthy males of the two groups had a mean age of 37 (range 24-47) years. One “Masculine” tablet daily for 3 months was well tolerated by all men and no adverse effect was reported. In the 60 men studied due to azospermia, who had no sexual complains, the sperm count of 50 subjects remained at 0 ± 0 at 3 months of “Masculine” consumption as it was at baseline. However the sperm count

in the remaining 10 men (17%), increased at 3 months to 0.8 ± 0.1 mil/ml ($p < 0.004$) and their sperm motility increased to $19 \pm 3.9\%$ ($p < 0.007$). At 3 months of “Masculine” dosage, 5 of the 25 men with sexual complains experienced a slight improvement in their sexual performances and 5 others experienced no change. The remaining 15 men (60%) reported considerable improvements in both libido and erectile function (Fig. 6). Ten of these 25 men had normal sperm counts while the other 15 men were oligospermic and their sperm count increased from a baseline value of 2.2 ± 0.1 to 2.8 ± 0.1 mil./ml ($p < 0.0001$) and additionally their sperm motility increased from $23.8 \pm 1.5\%$ at baseline to $43.2 \pm 1.3\%$ ($p < 0.0001$) at 3 months of masculine consumption (Figs. 7 and 8).

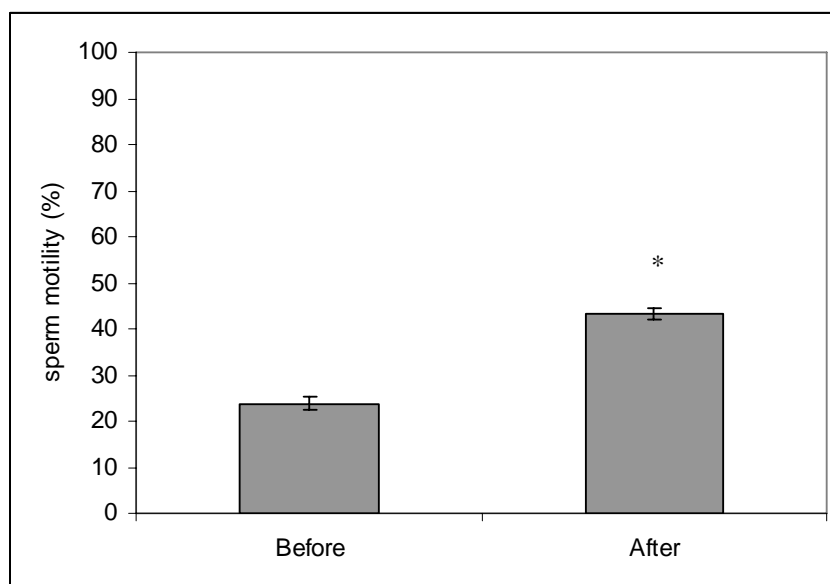


Fig. (8). Effect of Masculine consumption (1 tablet/day - for 3 months) on sperm motility in 15 oligospermic volunteers.

DISCUSSION

The results disclose that taking one daily dose of “Masculine” for 3 months is safe, well tolerated and is therapeutically efficient as improvements in both libido and erectile function were experienced by 20 (80%) of the study participants. As asafoetida is used as a spice daily by millions of people, its safety is assured.

The safety of “Masculine” active ingredient was demonstrated by the high concentrations of 5 g/kg needed to yield the LD50. Concentrations as high as 360 mg/ml did not show any sign of cellular toxicity as evidenced by LDH-release. Toxicity has been reported in rats given oil extracts of *Ferula hermonis* at daily doses above 50 mg/kg for one month [29]. Such long-term administration of high doses of *Ferula hermonis* has as well been reported to reduce testosterone and copulatory performance in rats, whereas, acute administration of the plant improved sexual functioning in these rats [30]. This is at a lower dose than that given to rats in our study; however we used a much safer *Ferula* species and a different and less concentrated extract. The paradoxical opposite effects (or side-effects) at different dosages and methods of administration of *Ferula hermonis* have also been shown in another study in rats and mice in Jordan [31, 32]. This is a well-known phenomenon in pharmacology and a familiar situation with many herbs or drugs when used at the wrong dosage in the wrong way.

The antioxidant properties of our extract were demonstrated at very low concentrations of 0.01 mg/ml, both in rat liver and in human Sperm cells. These cytoprotective effects were more significant at concentrations of 0.05 mg/ml while higher concentrations did not substantially add to these properties. Studies in Sprague Dawley rats have indicated that *Ferula asa-foetida* L. considerably augments antioxidant enzymes and detoxification in the liver and protects rats against toxins [33]. We demonstrated potent vasodilating

properties of these extracts upon intact arterial rings whereas, a weakened vasodilating effect of the extracts was shown on those arterial rings deprived of their endothelial tissue (Fig. 4). These observations, taken together, indicate that the Masculine extract has mainly an endothelial-mediated effect and a secondary direct effect on arterial smooth muscle cells. Nitric oxide is the principal product of vascular endothelial cells [34] that stimulates the production of cyclic guanosine monophosphate that relaxes vascular tone [35]. Gum extracts of asafoetida have in-vitro been shown to interfere with a variety of adrenergic, muscarinic and histaminic receptor activities [36].

Aphrodisiac effects of “Masculine” extract at high doses were demonstrated by the four- to five-fold increments in penile erection episodes observed during the controlled rat-studies. These effects and methods have been also been reported using concentrated extracts of the related species *Ferula hermonis* in rats at a dose of 12 mg/kg [29].

We demonstrated substantial antioxidant and vasodilating properties of Masculine at concentrations of 0.05 and 0.2 mg/ml respectively. Our recommended dose in man is about 1.5 mg/kg corresponding to one tablet of Masculine per day assuming an average weight of 70 kg. In good clinical practice, an optimal dose of a drug or an herb is the minimal dose that yields therapeutic efficacy with least side effects. We used a relatively small daily dose of extract and found a complete absence of side effects in the 85 men during 3 months of Masculine consumption. Improvements in both the libido and erectile function were disclosed in 80% of the studied men. Moreover, a substantial augmentation of sperm counts was noticed in all oligospermic men and in 17% of azospermic men and it was accompanied by remarkable improvements in sperm motility and microstructure.

In relation to possible mechanism of action, “Masculine” extract seems to encourage endothelial cells to release nitric

oxide which stimulates the synthesis of cyclic guanosine monophosphate in the penile corpus cavernosum. A contributing role for an effect upon prostacycline synthesis seems possible. "Masculine" contains ethanol extract from seeds and 50% water-ethanol root of asafoetida. Extracts of asafoetida contain volatile oil, resin and gum. The resinous constituents include asaresinol ferulate, free ferulic and umbellic acids as well as sesquiterpene coumarines identified as asafetidnol A and B [37]. *Asafoetida sesquiterpene* coumarines may act similar to those present in *Ferula hermonis* sesquiterpenes (ferutin, teferdin, and tenuferidine) that have been shown to have estrogenic activity, and may contribute to its aphrodisiac activity [29]. It also contains ferulic acid that is present in other plants such as *Angelica sinensis* that is used for female tonic effects.

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