Hilla University College Journal For Medical Science

Manuscript 1108

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ORIGINAL STUDY

Hilla Univ Coll J Med Sci

The Effect of Flaxseed Oil on Fertility

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Abstract

Background: Infertility can be defined as the inability to conceive pregnancy when sexually active and not having used any contraception in 12 months. Flaxseed oil has wide-spectrum applications in health. It has been receiving special interest in infertility treatment.

Objectives: This research aimed to determine the impact of flaxseed oil on the fertility of mice.

Methods: It involved seventy-five mice. These mice were sex-separated and randomly classified into three groups; one group served as a control group, and the other two groups were exposed to flaxseed oil extract at a dose of 60 mg/Kg body weight/day or 120 mg/Kg body weight/day for 2 weeks. The animals were redistributed at the end of the treatment period, whereby each female group was exposed to male mice from the three male groups for four weeks to investigate reproductive efficiency by calculating the pregnancy rate among females. In males, sperm count was performed with histopathological examination of the testes and epididymis.

Results: No pregnancies occurred in the flaxseed oil-treated groups, and azoospermia was observed in all the treated male groups, with marked histological alterations in the testes and epididymis.

Conclusion: Flaxseed oil had a negative influence on reproduction in both male and female mice in terms of pregnancy percentage, sperm count, with histological changes in the testis and epididymis.

Keywords: Fertility, Infertility, Sperm count, Pregnancy, Flaxseed oil

1. Introduction

Infertility is defined as the inability to conceive after twelve months of sexual intercourse in the absence of contraception [1]. It is a popular health issue that afflicts millions of people around the globe [2]. Infertility in males is caused by different factors compared to females. Among men, varicocele, asthenozoospermia, and oligospermia are the most common etiology of infertility. Although in women, it is typically a result of polycystic ovary syndrome (PCOS), fallopian tube diseases, or pelvic inflammatory diseases (PID) [3, 4]. Dietary habits influence reproductive function [5, 6]. Among various dietary components, flaxseed oil, which is an oil that is highly concentrated in alpha-linolenic acid [7], had gained wide-spectrum applications in health aspects such as liver, kidney, brain, bone, and cardiovascular disease as well as cancer [8, 9].

Recently, flaxseed oil has received special consideration in the treatment of infertility. Some studies have stated that it is helpful in reproductive health due to its effects on hormonal balance, anti-inflammatory effect, beneficial effects on sperm quality and motility, positive ovulation, and its antioxidant activity [10–12] that helps in safeguarding the reproductive

Received 25 November 2025; revised 15 February 2026; accepted 18 February 2026.
Available online 20 June 2026

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https://doi.org/10.62445/2958-4515.1108

cells against oxidative stress [13]. While other studies have mentioned that flaxseed oil not only impairs fertility by inducing hormonal imbalance and defects in the uniformity of sperm, but also contains variable amounts of protease inhibitors, cadmium, and cyanogenic compounds. These compounds have adverse consequences for health [14–16]. This study aimed to evaluate how flaxseed oil impacts the fertility of mice since mice are regarded as the most commonly used model globally due to their ability to reproduce in a short period and their close physiological similarities to human beings.

2. Material and methods

2.1. Study design

This study was a controlled laboratory experimental study in which seventy-five mice (Bulbe C) of reproductive age (6–8 weeks) from animal houses were included. They were fed ad libitum. Animals were sex-separated and kept at a normal temperature (22–25 °C), 12 hours of light and 12 hours of dark. They were provided with water and diet daily and left without treatment for 2 weeks before starting the experiment for acclimatization and to ensure that all female mice were not pregnant.

Males were randomly allocated into three experimental groups and females were also allocated into three groups. Each male group consisted of 10 mice, while each female group consisted of 15 mice.

Group 1 was a control group, which was fed olive oil.

Group 2 was treated with an oral dose of 60 mg/Kg BWT/day of flaxseed oil for 2 weeks.

Group 3 was treated with an oral dose of 120 mg/Kg BWT/day of flaxseed oil for 2 weeks.

At the end of the treatment period, the animals were redistributed in a manner such that each female group was mated with male mice from the three male groups for four weeks to investigate the effect of flaxseed oil extract on reproductive efficiency.

2.2. Preparation of flaxseed oil

We extracted flaxseed oil by grinding clean flaxseed seeds with an electric grinder, placing it in a Soxhlet thimble and subjecting them to defatting with a hexane solvent at a boiling temperature of 55 ° C for four hours. The oil was then separated from the hexane by evaporation at 50 C ° for one hour. The extracted oil was left to dry at room temperature for five days. Thereafter, it was kept in the refrigerator in a dark container at 4 °C in order to preserve the flaxseed oil stability [17].

2.3. Animal sacrifice and specimen collection

At the end of the experiment, all mice were sacrificed. Before sacrifice, they were first weighed and thereafter anaesthetized by exposure to chloroform vapor in a closed jar. a midline abdominal incision was performed to obtain the samples, which included the testis and epididymis. They were weighed using an electronic analytical precision balance. The epididymis was placed in a Petri dish with normal saline solution in order to use it for sperm counting and for the assessment of sperm viability.

2.4. Assessment of reproductive efficiency

1- The percentage of pregnancy:

It was obtained by dividing the number of pregnant females in a group by the total number in that group.

2- seminal analysis:

A. Sperm count: It was performed according to the method of Evan and Maxwell, which includes the use of a Neubauer hemocytometer chamber usually used for counting red blood cells and white blood cells [18]. The epididymis was sliced into 5–9 pieces and we filtered the suspension obtained by gauze into a test tube. Then, we placed a drop from the filtrate on a Neubauer chamber to calculate the total number of sperms.

B. Sperm viability: A drop of diluted semen was placed on a slide, followed by eosin-nigrosin stain. Thereafter, they were mixed gently together with a glass rod. The smear was examined under a light microscope. Live sperm remain unstained and appeared transparent or white, and the dead sperm had red discoloration.

3- Histological study:

Sorted fragments of testes and epididymis were histologically studied. The sample was fixed with 10% buffered formalin. Slide preparation included sequential dehydration with ascending concentrations of alcohol, cleaning with xylene, the use of paraffin, followed by sectioning with a microtome. We stained the slides with hematoxylin and eosin and thereafter examined them by light microscope [19].

2.5. Statistical analysis

Statistical analysis was performed using the SPSS program, version 26 (SPSS, IBM Company, Chicago,

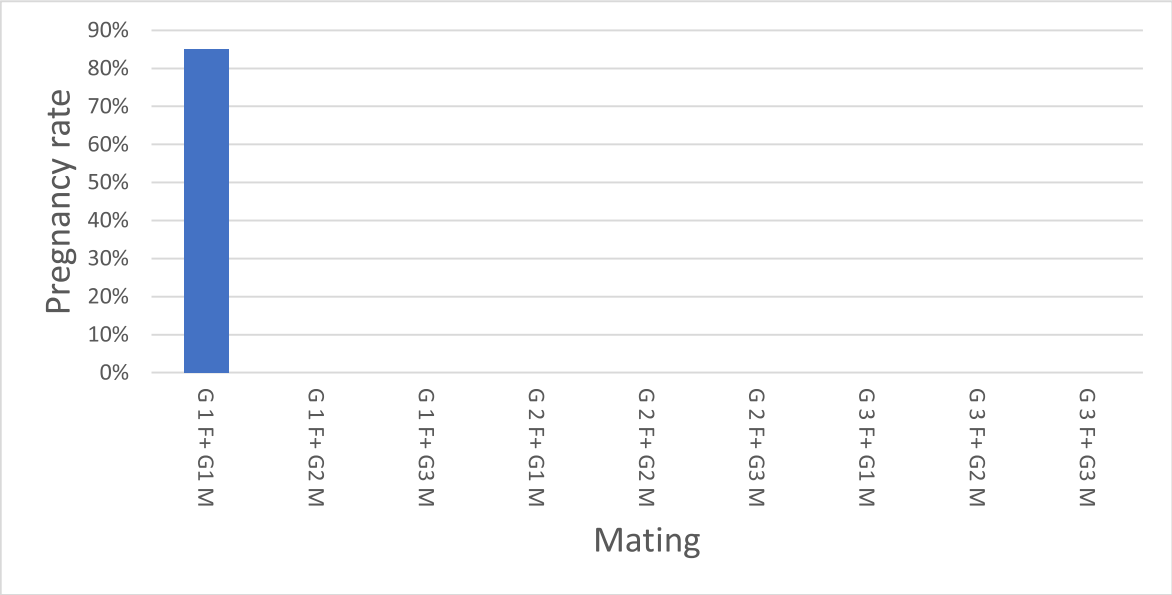

Fig. 1. The rate of pregnancy among female mice after mating with males from different studied groups for four weeks. F: female, M: male, G1: Group 1 (control group), G2: Group 2 (mice treated with oral dose of 60 mg/Kg BWT/day of flaxseed oil for 2 weeks), G3: Group 3 (mice treated with oral dose of 120 mg/Kg BWT/day of flaxseed oil for 2 weeks).

IL 60606, USA). The rate of pregnancy among different groups was evaluated using Fisher's exact test.

3. Results

3.1. Pregnancy rate

The comparison of the percentage of pregnancy in group 1 (control group) and groups two and three (treated groups) after four weeks of mating showed that the pregnancy rate among female and male mice from the control group was 80% while there was no pregnancy among treated female mice, even though they were mated with untreated males from the control group, as shown in (Table 1 and Fig. 1).

Table 1. The rate of pregnancy among female mice after mating with males from different studied groups for four weeks.

Mating among groups (n = 75)	Pregnancy %
Group 1 female + Group 1 male	80%
Group 1 female + Group 2 male	0%
Group 1 female + Group 3 male	0%
Group 2 female + Group 1 male	0%
Group 2 female + Group 2 male	0%
Group 2 female + Group 3 male	0%
Group 3 female + Group 1 male	0%
Group 3 female + Group 2 male	0%
Group 3 female + Group 3 male	0%

Group 1: control group, Group 2: mice treated with oral dose of 60 mg/Kg BWT/day of flaxseed oil for 2 weeks, Group 3: mice treated with oral dose of 120 mg/Kg BWT/day of flaxseed oil for 2 weeks.

3.2. Sperm count

The sperm count of the semen obtained from the epididymis of the control males was found to be 166 $\times 10^6$/ml of semen (the range was between 158×10^6 and 177×10^6), while it was zero in specimens of all groups of males treated with flaxseed oil as indicated in (Table 2 and Fig. 2).

3.3. Histological findings

3.3.1. Testes

Histological examination of the testes revealed atrophied or irregular shape of seminiferous tubules with inhibition of spermatogenesis in mice fed flaxseed oil 60 mg/Kg BWT/day for 2 weeks as demonstrated in (Fig. 3). and excessive inhibition of spermatogenesis and necrosis of supporting cells in mice fed flaxseed oil 120 mg/Kg BWT/day for 2 weeks, as demonstrated in (Fig. 4).

3.3.2. Epididymis

The histological features of the epididymis of male mice fed flaxseed oil 60mg/Kg BWT/day for 2 weeks included hemorrhage in the interstitial tissue and vacuolation of epithelial cells depicted in (Fig. 5). Besides that, thickening of the capsule was evident in male

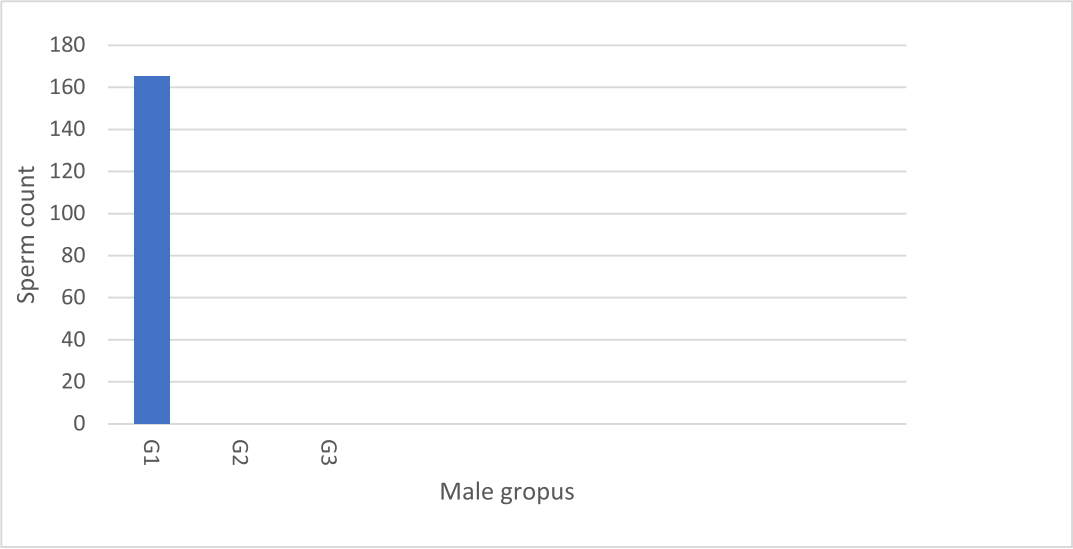

Fig. 2. Sperm count among different male groups. G1: Group 1 (control group), G2: Group 2 (mice treated with oral dose of 60 mg/Kg BWT/day of flaxseed oil for 2 weeks), G3: Group 3 (mice treated with oral dose of 120 mg/Kg BWT/day of flaxseed oil for 2 weeks)

Table 2. Sperm count among different male groups.

Male groups (n = 30)	Sperm count (means ± SD)
Group 1	$166\times10^6 \pm 5.33$
Group 2	0
Group 3	0

Group 1: control group, Group 2: mice treated with oral dose of 60 mg/Kg BWT/day of flaxseed oil for 2 weeks, Group 3: mice treated with oral dose of 120 mg/Kg BWT/day of flaxseed oil for 2 weeks.

mice fed 120mg/Kg BWT/day of flaxseed oil for 2 weeks, as observed in (Fig. 6).

4. Discussion

Most studies affirm the positive impact of flaxseed oil on reproduction due to its influence on spermatogenesis, ovulation, and hormonal balance [20, 21]. In contrast, in this study, the number of sperm was completely reduced after the intake of flaxseed oil. This discrepancy might be attributed to the use of high doses of flaxseed oil in the experiment. Flaxseed oil contains phytoestrogens [22]. These compounds are known to interfere with the male reproductive system [23]. Specifically, they attach to estrogen receptor α and β because of their structural similarity to estradiol [24]. Consequently, the growth of Leydig cells is suppressed by estradiol. It suppresses Leydig cells' regeneration and testosterone biosynthesis enzymes, leading to testosterone deficiency [25]. Since testosterone is crucial for the production of sperm and its deficiency leads to a decrease in sperm count [26]. Moreover, estrogen-like substances act against the proliferation of Sertoli cells and influence the process of spermatogenesis [27]. These mechanisms together may account for the complete reduction of sperm in treated groups.

Histological analysis of the testes revealed that the intake of flaxseed oils resulted in histopathological alterations in the testes, such as abnormal shape or atrophied seminiferous tubules with inhibition of spermatogenesis (Figs. 3 and 4). Similarly, there are histopathological alterations in the epididymis in the form of vacuolation of the epithelial cells, thickening of the capsule, and hemorrhage of the interstitial tissue (Figs. 5 and 6). These results are in agreement with Helal et al. [16] who concluded that flaxseed causes significant decrease in the concentration of sperms, and reduce their viability and motility with a rise in sperm abnormalities. Also, flaxseed showed a significant decline in serum testosterone levels, along with a significant rise in serum prolactin, FSH, and LH levels. Thus, the findings of this study support the view that excessive intake of flaxseed oil impairs reproductive organs through structural and hormonal mechanisms.

Even though some studies have concluded that flaxseed oil enhances ovulation [10, 21, 28], contrary results were observed in this study. We reported that there were no pregnancies in the treated female mice even after mating with non-treated male mice, as illustrated in Table 2 and Fig. 2. The zero percentage of pregnancy rate can be attributed to several mechanisms. Flaxseed is rich in lignans [29], which are very strong anti-estrogens. It can alter the activity of enzymes, estrogen production, and receptor functions [30, 31]. furthermore, flaxseed reduces prostaglandin E2 [PGE2] [32]. Which is a key regulator of ovulation

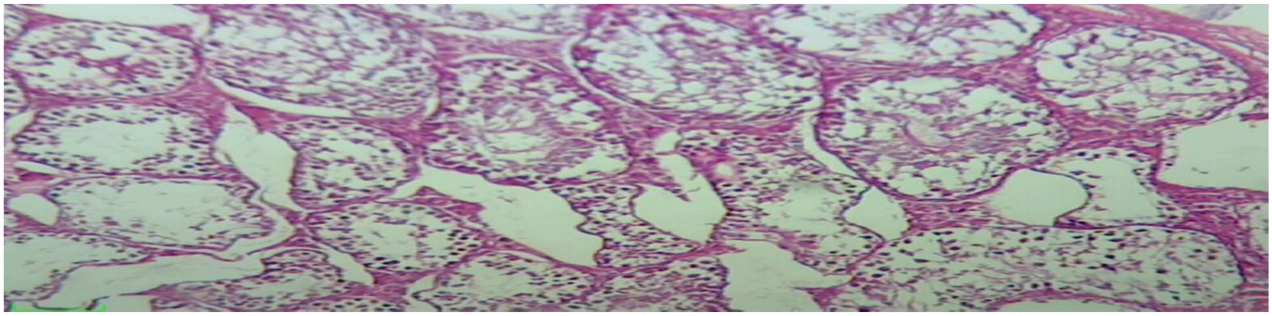

Fig. 3. Section of group 2 mice testes, shows suppression of some seminiferous tubules and atrophy of other tubules. 10x H&E.

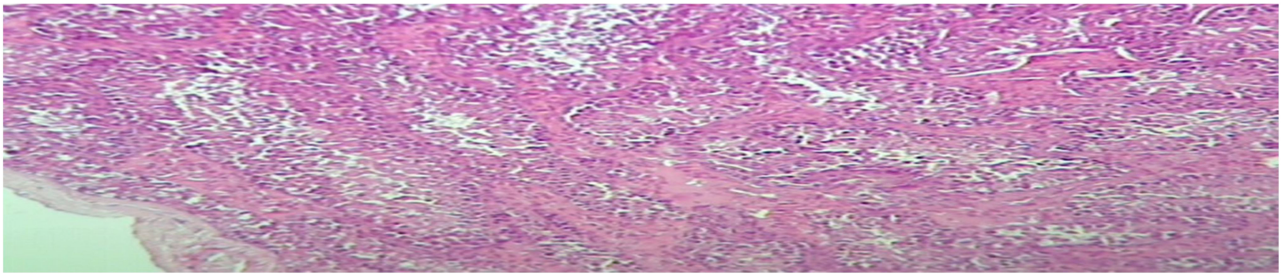

Fig. 4. Section of group 3 mice testes, shows chronic suppression of spermatogenesis, but there are spermatids with irregular capsule. 10x. H&E.

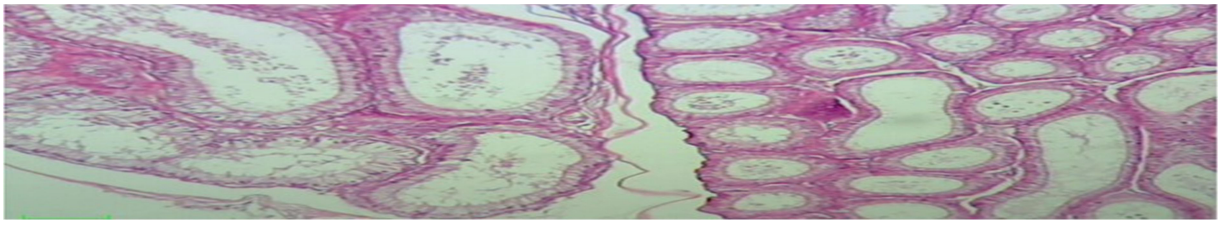

Fig. 5. Section of group 2 mice epididymis, shows vacuolated epithelial cells of tubule, the lumen contains few or no spermatids. 10x. H&E.

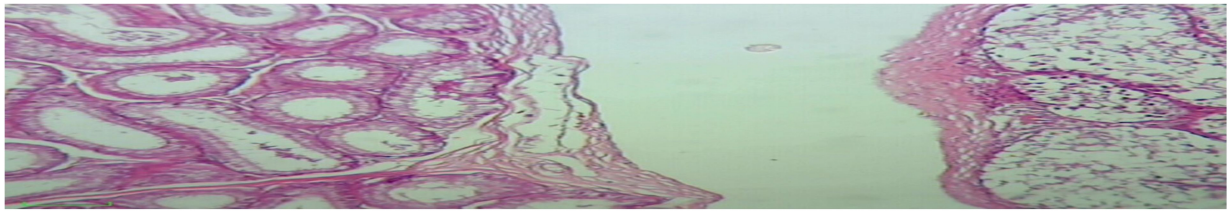

Fig. 6. Section of group 3 mice epididymis shows vacuolation of epithelial cells, thickening of capsule and hemorrhage in interstitial tissue. 10x. H&E.

and oocyte release [33]. So, suppression of PGE2 production may result in ovulatory failure. In addition, omega-3 fatty acids and lignans also promote ovarian cell death [34]. finally, flaxseed has a negative effect on the penetration rate of the sperm [35], supporting the multifactorial reproductive toxicity observed in this study.

5. Conclusion

In male and female mice, the flaxseed oil extract demonstrated a clear adverse impact on reproduction in terms of the percentage of pregnancy, the number of sperm, and histological alteration of the testis and epididymis. The presented findings suggest that excessive intake of flaxseed oil impairs reproductive physiology. Further studies are recommended to elucidate the underlying biochemical pathways, and the safe therapeutic limits of ingestion of flaxseed oil should be determined.

Conflict of interest

None

Funding

None

Ethical approval

This study was approved by the ethics committee of Al-Zahraa College of Medicine, University of Basra.

Author contributions

Mohammad F. Albadran, Ahmed B. Abdulwahid, and Assad H. Eissa designed the study. Mohammad F. Albadran, Nehaya M. Al-Aubody, and Shaymaa F. Abbas performed the flaxseed oil extraction and conducted the experiments on mice, including histological and sperm analysis. Zainab M. Mohammed and Assad H. Eissa assisted with data collection and processing. Mohammad F. Albadran, Ahmed B. Abdulwahid, and Assad H. Eissa analyzed the results. Mohammad F. Albadran, Ahmed B. Abdulwahid, and Assad H. Eissa drafted the manuscript, and all authors reviewed and approved the final version.

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