



Ethanollic Extract of *Triganella Foenum-grcacum L.* (Fenugreek) Mitigates Hypothyroidism-Induced Male Reproductive Dysfunction in Rats

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Abstract

Background: Hypothyroidism, a common endocrine disorder, adversely affects various physiological processes, including male reproductive health. Fenugreek (*Triganella foenum-graecum L.*), a traditional herbal remedy, is known for its therapeutic properties but also exhibits potential protective effects on reproductive function. This study aims to evaluate the protective effect of ethanollic extract of fenugreek seeds on sperm characteristics in hypothyroid male albino rats. **Methods:** Forty adult male albino rats (200–250 g) were divided into four groups, each containing ten rats. The negative control group received normal saline daily. Hypothyroidism was induced in the remaining three groups using 0.05% 6-propyl-thiouracil (PTU) for 30 days. Post-induction, the groups were treated as follows: the positive control group received normal saline, the third group received ethanollic extract of fenugreek seeds (15 mg/kg body weight), and the fourth group received levothyroxine (L-T4, 0.1 mg/kg/day). Hormonal levels of TSH, T3, and T4 were measured using the ELISA method, and sperm characteristics were analyzed from left caudal epididymis

samples. **Results:** Hypothyroid positive control rats showed significantly increased TSH levels and decreased T3 and T4 levels compared to the negative control group. Treatment with either L-T4 or fenugreek extract significantly reduced TSH levels and increased T3 and T4 levels compared to the hypothyroid positive control group. Sperm analysis revealed that hypothyroidism significantly reduced sperm count, general motility, progressive motility, viability, and morphology. Both L-T4 and fenugreek treatments significantly improved all sperm parameters compared to the hypothyroid positive control group. **Conclusion:** Hypothyroidism impairs sperm characteristics, underscoring the importance of thyroid function in male fertility. The ethanollic extract of fenugreek seeds demonstrated a protective effect on sperm characteristics in hypothyroid rats, comparable to the effects of levothyroxine. These findings suggest that fenugreek may serve as a potential therapeutic agent for mitigating hypothyroidism-induced reproductive dysfunction. Further research is needed to explore the underlying mechanisms and clinical applications

Keywords: Hypothyroidism, Fenugreek, Male fertility, Thyroid hormones, Sperm quality.

Significance | The study showed fenugreek's potential to improve male fertility by enhancing sperm characteristics in hypothyroid conditions.

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1. Introduction

Hypothyroidism, a common endocrine disorder, is characterized by an insufficient production of thyroid hormones. This condition represents the most frequent form of pathological hormone insufficiency (Kaplan, 1984). The thyroid gland, which plays a

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crucial role in regulating metabolism, growth, and development, produces hormones that affect nearly every organ system in the body. A deficiency in these hormones can lead to widespread physiological disruptions, including alterations in the neuroendocrine axis. One such disruption involves the hypothalamic-pituitary-gonadal axis, essential for reproductive function. Hypothyroidism's impact on this axis is significant, leading to potential disturbances in testicular function (Kumar et al., 2014).

Fenugreek (*Trigonella foenum-graecum* L.), a well-known herbal remedy, has been extensively studied for its therapeutic properties (Zia et al., 2001; Vats et al., 2002). Belonging to the Fabaceae family, this self-pollinating annual herbaceous plant is known by several common names, including bird's foot, Greek hayseed, halba, and methi (Bashtian et al., 2013). Fenugreek is native to India and Northern Africa but is widely cultivated across Northern Africa, Europe, South Asia, Argentina, and Australia. India is the leading producer, accounting for 80% of global fenugreek production (Gu et al., 2017).

Fenugreek seeds are renowned for their medicinal properties, particularly their anti-diabetic and hypocholesterolemic effects, which have been demonstrated in animal and human models (Rasheed et al., 2015). Historically, fenugreek has been considered safe, and no significant toxicological effects have been reported (Al-Habori and Raman, 1998). However, emerging evidence suggests that fenugreek seeds may pose risks to fertility and reproductive health. For instance, studies have observed a sterilizing effect in albino rats and rabbits, evidenced by decreased testicular weight and histological changes in the seminiferous tubules (Baby et al., 2016). Furthermore, saponins isolated from fenugreek seeds exhibit in-vitro spermicidal properties against rat spermatozoa (Mishra et al., 2019). These seeds contain compounds like saponin and diosgenin, which are precursors to progesterone and possess antigonadotropic and antiandrogenic potentials (Raghuram et al., 1994).

Fenugreek's anti-hyperglycemic properties have been validated in both type I and type II diabetes across human and animal studies, though the exact mechanisms remain elusive (Setty et al., 1977). Interestingly, some research indicates that the ethanolic extract of fenugreek seeds may inhibit sex organ function and male fertility in rats (Sharma and Jacob, 2002). Fenugreek's bioactive constituents include furostanol glycosides, which are major soluble saponins. Saponins are a diverse group of substances, typically found in plants, consisting of sterol or triterpene rings with attached sugars. They possess unique properties, such as the ability to complex with cholesterol in cell membranes (Madhulika and Verma, 2019). Subchronic oral administration of purified sterol saponins from fenugreek seeds has increased food intake in rats, although it does not significantly alter plasma insulin and blood glucose levels (Price et al., 1987). Additionally, fenugreek saponins inhibit the

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absorption of taurocholate and deoxycholate in a dose-dependent manner (Petit et al., 1993).

The reproductive system, especially in rats, is particularly sensitive to thyroid dysfunction. Research involving hypothyroid pubertal rats, induced through a 0.05% propylthiouracil solution administered over 60 days, confirmed hypothyroidism via reduced plasma thyroxine levels. Surprisingly, despite the induced hypothyroidism, the spermatogenic and steroidogenic functions of the testes remained unaffected in these pubertal rats (Maia et al., 1990). Thyroid hormones (T₃ and T₄) are critical regulators of numerous biochemical processes, including lipid and carbohydrate metabolism, oxygen consumption, and essential physiological functions such as development, reproduction, and growth (Kundu et al., 2006). Both excessive and insufficient levels of these hormones can negatively impact spermatogonial development. For example, hypothyroidism is linked to reduced sperm production and impaired spermatogonial development, whereas hyperthyroidism may increase oxidative stress and DNA damage in sperm cells (Liu et al., 1999).

The effects of fenugreek seeds on sperm characteristics in male rats with hypothyroidism were investigated in this study. Given the intricate interplay between thyroid hormones and reproductive health, valuable insights into both the therapeutic and potential adverse effects of this widely used herbal remedy could be provided by understanding how this relationship was impacted by fenugreek.

2. Materials and Methods

2.1 Animals and Experimental Design:

Forty male rats, each weighing between 200-250 grams, were used in this study. The rats were randomly divided into four groups, each containing ten rats. Group 1 (C-Negative) served as the negative control group and received saline for 30 days. Group 2 (HYPO Positive) was the positive control group; these rats received 0.05% 6-propyl-thiouracil (PTU) in their water supply for 30 days to induce hypothyroidism, followed by saline administration for another 30 days. Group 3 (HYPO+FN) consisted of hypothyroid rats treated with 15 mg/kg body weight (B.W.) of fenugreek (FN) daily via oral gavage for 30 days. Group 4 (HYPO+Thyroxin) included hypothyroid rats treated with 0.1 mg/kg/day of thyroxin (L-T₄) intraperitoneally for 30 days. All procedures used in this study were reviewed and approved by the Scientific Committee of the College of Veterinary Medicine, University of Kufa, in compliance with the ethical principles of animal welfare.

2.2 Induction of Hypothyroidism:

Hypothyroidism was induced in Groups 2, 3, and 4 by administering a water supply containing 0.05% PTU for 30 days.

2.3 Preparation of Ethanolic Extracts of Fenugreek Seeds:

Fenugreek seeds were purchased from local markets in Najaf province. A total of 100 grams of powdered fenugreek seeds were extracted using a Soxhlet apparatus with 70% ethanol. The solvent

was evaporated under reduced pressure using a rotary evaporator until completely dry. The residue was stored at 4°C for further use (Singh et al., 2020).

2.4 Hormonal Analysis:

Blood samples were collected to measure serum levels of thyroid-stimulating hormone (TSH), thyroxine (T4), and triiodothyronine (T3) using the ELISA method with an Elabscience kit.

2.5 Sperm Characteristics Analysis:

Semen samples were obtained from the left caudal epididymis for the analysis of general motility, progressive motility, viability, and morphology. Semen from the right caudal epididymis was homogenized in Tris buffer (pH 7.4) to create a 15% (g/ml) solution (Lim et al., 2002).

2.6 Statistical Analysis:

Results were presented as mean \pm standard deviation (SD). Statistical analysis was performed using ANOVA (version 5), with a significance level of $p < 0.05$ considered significant (Xavier et al., 2019).

3. Result

3.1 Thyroid Gland Hormonal Tests Results

The thyroid hormone profiles exhibited distinct responses influenced by the treatments administered. As depicted in Figures 1, 2, and 3, significant variations were observed in the TSH, T3, and T4 levels across the experimental groups. The positive control group (HYPO Positive) displayed a notable increase in TSH levels but a significant decrease in both T3 and T4 compared to the negative control group. In contrast, rats treated with thyroxin (HYPO+Thyroxin) and fenugreek (HYPO+FN) showed significantly reduced TSH levels compared to the HYPO Positive group. Furthermore, both HYPO+Thyroxin and HYPO+FN treatments resulted in a significant increase in T3 and T4 levels compared to the positive control group, indicating a beneficial effect of these treatments on thyroid hormone regulation.

3.2 Sperm Characteristics Analysis Results

Table 1 summarizes the results of sperm characteristics analysis from the left testis of the experimental groups, including sperm general motility, progressive motility, viability, and morphology. The HYPO Positive group exhibited a significant decrease in all sperm parameters compared to the negative control group, suggesting impaired sperm function under hypothyroid conditions. In contrast, rats treated with either thyroxin or fenugreek (HYPO+Thyroxin and HYPO+FN) demonstrated improvements across all sperm parameters compared to the HYPO Positive group. Specifically, there was a marked enhancement in general motility, progressive motility, viability, and morphology of sperm in these treatment groups, indicating potential therapeutic benefits of thyroxin and fenugreek in alleviating the detrimental effects of hypothyroidism on male reproductive function.

These results highlight the differential impacts of thyroxin and fenugreek treatments on thyroid hormone levels and sperm characteristics. The findings underscore the potential of thyroxin and fenugreek as effective therapeutic agents for addressing hypothyroidism-associated male infertility, warranting further investigation into their mechanisms and clinical applications in reproductive health.

4. Discussion

Thyroid hormones regulate various physiological processes, including male reproductive health. Recent investigations underscore their critical involvement in reproductive processes, revealing a notable decrease in sperm viability and motility, coupled with an increase in abnormalities. This discussion aims to elucidate the implications of these findings on male reproductive function, particularly focusing on hypothyroidism and potential therapeutic interventions.

Hypothyroidism, a condition characterized by insufficient thyroid hormone production, has been shown to impact sperm quality significantly. Studies demonstrate that hypothyroidism leads to decreased sperm count, motility, and altered sperm morphology (SPSS, 2010). These alterations can reduce fertility, making it imperative for individuals with hypothyroidism to seek medical consultation for proper management. The mechanisms by which hypothyroidism affects sperm quality are multifaceted. Hypothyroidism can disrupt the hormonal balance, particularly testosterone levels, which are crucial for spermatogenesis (Jiang et al., 2000). Testosterone is essential for the production and maturation of sperm, and its deficiency can result in impaired sperm function.

Researchers propose that the influence of thyroid hormones extends beyond sperm viability and count. Biswas et al. (1994) and Buzzard et al. (2003) suggest that thyroid hormones impact sperm morphology and motility. Their research indicates that hypothyroidism can cause histological and endocrinological dysfunction in the epididymis, the site where sperm matures and gains motility. The epididymal epithelium, responsible for removing cytoplasmic droplets from spermatozoa, may be impaired in hypothyroid conditions. This dysfunction results in a higher percentage of sperm with cytoplasmic droplets, indicating poor maturation. Therefore, thyroid hormones play a vital role in ensuring proper epididymal function and sperm morphology, emphasizing the need for comprehensive thyroid health for optimal male fertility.

Fenugreek (*Trigonella foenum-graecum*), a herb traditionally used for its medicinal properties, has shown promise in enhancing male fertility, particularly in hypothyroidism. Research indicates that fenugreek supplementation can improve sperm parameters in male rats with hypothyroidism (Kiss et al., 2019). Several studies **highlight fenugreek's potential benefits. Firstly, fenugreek has been**

Table 1. Sperm general motility, progressive motility, viability, and morphology in the left testis of the experimental groups (Mean± SD)

Parameters Groups	Motility		Morphology (%)	Viability (%)
	General Motility (%)	Progressive Motility (%)		
Control (Normal saline)	87.80 ± 2.5 a	78.00 ± 1.00 a	90.00 ± 1.0a	90.48 ± 1.9a
Hypothyroidism	36.00 ± 3.3 b	35.92 ± 8.5 b	52.80 ± 1.9 c	41.80 ± 3.8 b
HYPO+FN	85.80 ± 2.1 a	74.80 ± 2.16 a	89.50 ± 1.8 a	88.00 ± 2.6 a
HYPO+Thyroxin	85.40 ± 3.0 a	73.40 ± 3.5 a	85.72 ±3.2b	87.70 ± 21.0a

Each letter represents a statistically significant difference between the groups at the ($p \leq 0.05$) level.

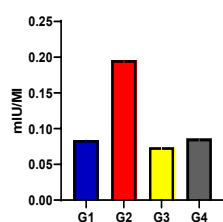


Figure 1. Thyroid Stimulating hormones (TSH) level in the experimental groups.

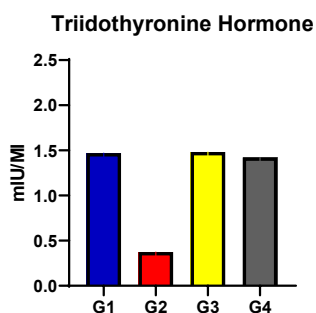


Figure 2. Thyroid hormones (T3) level in the experimental groups.

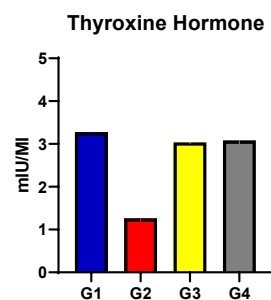


Figure 3. Thyroid hormones (T4) level in the experimental groups.

shown to improve sperm motility, essential for effective fertilization (Maheshwari et al., 2017). Secondly, fenugreek supplementation may help protect against sperm abnormalities, such as malformed sperm or those with cytoplasmic droplets, prevalent in hypothyroid conditions (Singh et al., 2022). Thirdly, fenugreek contains compounds with antioxidant properties, which can reduce oxidative stress in the reproductive system, thereby improving sperm quality (Shamim et al., 2016). Lastly, fenugreek may exert regulatory effects on hormone levels, including thyroid hormones, potentially enhancing sperm characteristics in hypothyroid conditions (Sakr et al., 2012).

The intricate relationship between thyroid hormones and male reproductive health is evident from the significant impact of hypothyroidism on sperm quality. The decline in sperm viability and motility, along with the increase in abnormalities, underscores the necessity of maintaining thyroid health for optimal fertility. Additionally, the therapeutic potential of fenugreek offers a promising avenue for mitigating the adverse effects of hypothyroidism on male reproductive function. Further research is warranted to fully understand the mechanisms involved and develop effective treatments for thyroid-related reproductive dysfunction.

5. Conclusion

The study demonstrated that hypothyroidism adversely affects male reproductive health by significantly impairing sperm parameters, including motility, viability, and morphology. The administration of thyroxin and fenugreek extracts showed beneficial effects, improving thyroid hormone levels and mitigating the negative impacts on sperm characteristics. These findings suggest that fenugreek, with its antioxidant properties and regulatory effects on hormone levels, could serve as a potential therapeutic agent for male infertility associated with hypothyroidism. Further research is necessary to fully elucidate the underlying mechanisms and to confirm the clinical efficacy of these treatments in humans.

Author contributions

T.A.A. and A.A.A. conceived the study and developed the hypothesis. A.N.A. and H.K.H. performed data analysis and interpretation. A.K.A. contributed to writing the manuscript, including the introduction and methods. S.A.M. and N.S.M. collected data and assisted with the literature review. A.A.A. supervised the project and conducted the final revision. All authors read and approved the final manuscript.

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Competing financial interests

The authors have no conflict of interest.

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