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Impact of Coriander Seeds Extract Against Thyroidectomy Induced Testicular Damage and DNA Replication in Male Rats

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Abstract: An important target organ for thyroid hormone activity is the testis and hypo or hyperthyroidism causes noticeable alterations in testicular function. This study aimed to investigate the therapeutic effect of Coriander Seeds Extract (CSE) against thyroidectomy induced toxicity, oxidative stress, injury, and proliferation in male testes rats. 40 male rats were equally divided into 4 groups [Gp1, control; Gp2, CSE; Gp3, thyroidectomies rats (Thy); Gp4, treated thyroidectomies rats with coriander (Thy + CSE)]. Current results revealed after 3 weeks of thyroidectomy; a significant ($p<0.05$) elevation in TSH, total T_4, serum AST, and serum ALP, non-progressive motility and immotile sperms, testicular MDA, testicular injury, and a significant ($p<0.05$) reduction in total T_3, sexual hormones (testosterone, FSH, LH, and prolactin), sperms parameters (count, morphological index, vitality, total and progressive motility), testicular GSH, testicular SOD, and testicular GST and PCNA expressions when compared with control. Thy + CSE modulates most of changes parameters and recovery the testicular injury. We can conclude that; coriander seed extract could enhance the testis against thyroidectomy produced toxicity and oxidative stress in testes through its positive effects in scavenging free radicals.

Keywords: Thyroidectomy, Coriander, Testes Toxicity, Oxidative Stress, PCNA Immunoreactivity

Introduction

Thyroid Hormones (TH) control the bulk of metabolic activities, such as the growth rate, Na/K pump, heart rate, blood pressure, as well as the operations of other endocrine glands (Ichiki, 2010; Ibrahim *et al*., 2012; Massoud *et al*., 2012; Salama *et al*., 2013; Hafez and Tousson, 2014). A thyroidectomy is a procedure that removes completely or fragment of the thyroid gland (Tousson *et al*., 2012a; 2014). A thyroidectomy led to hypothyroidism and a shortage of TH (Tousson *et al*., 2014).

TH levels are essential for the development of the testicles in boys (Choksi *et al*., 2003). Studies show that the Sertoli cells are the primary T_3 binding targets in the testis (Tousson *et al*., 2011; 2012b). Previous studies conducted *in vitro* indicate that T_3 activation of TR1 contributes to the differentiation and growth of the testes. Recent studies have examined how altered thyroid status on the testes histostructure in different animal models (Beltagy *et al*., 2016; Sharma *et al*., 2020).

Previous researches show that; hypothyroidism negatively impacts spermatogenesis, indicating that thyroid hormone may be crucial for upholding typical testicular functions and spermatogenesis as well as managing proper testicular development (Tousson *et al*., 2012a).

In order to cure a range of diseases, medicinal plants produce a variety of chemical components (Mutar *et al*., 2020; El-Aarag *et al*., 2021; Elbandrawy *et al*., 2022). Herbal medicine is becoming more and more well liked among both laypeople and medical professionals due to advances in our understanding of the mechanisms through which herbs effect health and quality of life (Elgharabawy *et al*., 2021; Abd Eldaim *et al*., 2021; Hasan *et al*., 2022).

Coriander (*Coriandrum sativum*) is known as Chinese parsley and cultivated for seeds (fruits) and leaves. Due to some of its qualities, including its antioxidant, antifungal,

antibacterial, and digestive agent in the digesting process, coriander is used medicinally (Mechchate *et al*., 2021; Moustafa *et al*., 2014).

With the discovery of several polyphenolics and antioxidant elements found in it, the coriander plant has a significant protective function against the development of various diseases (Mahmoud *et al*., 2022).

TH is widely considered to be a significant hormonal regulator of testis physiology throughout the development phase.

Consequently, the current investigation was conducted to examine the therapeutic advantages of coriander seed extract against thyroidectomy induced testicular toxicity.

Materials and Methods

Coriander Seeds Extracts Production

According to Moustafa *et al*. (2014), coriander seeds were ground into a powder, cooked in water for 24 h at 37°C, extracted, and kept at -30°C in the dark until usage (2014).

Thyroidectomy

According to the Tousson *et al.* (2012b); (2014) procedure, thyroidectomy was done on rats that had been intraperitoneally injected with sodium pentobarbital to induce anaesthesia. The rats were then submitted to a thorough necropsy.

Animals and Ethical Considerations

At the age of 10-12 weeks and weighing around 150 g, 40 male albino rats (*Rattus norvigicus*) were transported from the Egyptian NRC. The rats were divided into 4 groups of 10 at random before the experiment began. The rats were housed in elastic boxes for a week and fed a typical rodent meal with water accessible ad libitum after a week of acclimating to new room conditions. The institution's animal care and use ethical committee gave its approval to the study's design with the code IACUC-SCI-TU-0241.

Experimental Groups (Gps)

Rats were similarly distributed into the following four Gps.

GpI, control Gp (rats didn't obtain any therapy).

Gp2, coriander Gp [CSE; rats treated with coriander (50 mg/kg body weight) for 3 days weekly for 2 weeks] after Moustafa *et al*. (2014).

Gp3, thyroidectomized Gp (Thy; Thyroidectomies and dissections of rats were performed surgically after three weeks) according to Tousson *et al*. (2014).

Gp4, Thy + CSE (Thyroidectomies of rats were performed surgically and after 3 weeks treated with CSE for another 2 weeks).

Blood and Serum Samples

Rats were starved for the whole night at the conclusion of the experiment. Rats from each group were completely dissected after being put to death with sodium pentobarbital.

Centrifugation at 3000 rpm for 15 min was used to pull out and separate the serum from the inferior vena cava. The serum was stored at a temperature of -18°C for analysis and estimation of blood parameters.

Biochemical Analysis

According to the approach of Tiirats (1997); Thakur *et al.* (1997) total T_3 and total T_4 in sera were estimated respectively, while the approach of Peterson *et al*. (1997) was used to estimate TSH in sera.

Hormone Assay

According to the approach of Altwaijry *et al*. (2020); total testosterone levels was estimated in sera while according to Odell *et al*. (1967; 1974); serum FSH and LH levels were estimation respectively.

Sperms Morphometric Analysis

The caudal section of the epididymis was carefully detached from the testis for estimated different sperm parameters after (Tousson *et al*., 2018).

Estimations of Oxidative and Antioxidants Parameters in Testicular Homogenate

According to Mesbah *et al.* (2004); Aldubayan *et al.* (2019) Malondialdehyde (MDA) and Glutathione (GSH) activities in homogenate were appraised respectively. Superoxide Dismutase (SOD) and catalase activities were assessed according to Mahgoob *et al*. (2022); Saggu *et al*. (2014) methods respectively**.**

Histopathological Examination

Testicular tissue should be prepared for paraffin sectioning and stained with H&E after being fixed in neutral 10% formalin for two days (Tousson, 2016).

PCNA Detection

The rest of testicular paraffin sections were used for PCNA expression detection after (El-Masry *et al*., 2020).

Statistical Analysis

0.05 served as the cut-off for the biochemical data indicating the standard for statistically significant data and an unpaired t-test was used to analyse the significant variances across treatment groups. Data were communicated as average values SE.

All statistical analyses were performed using the SPSS statistical version 21 software programe from SPSS® Inc in the United States.

Results

Thyroid Hormones Variation

Table (1) shows that; a significant elevation in serum TSH and T_4 while a significant reduction in total T_3 levels in Thyroidectomies rats (Thy) in comparison to control and CSE groups.

Treatments of thyroidectomies rats with coriander (Thy + CSE) significantly increase total T_3 and significantly decrease TSH and total T_4 levels in comparison to thyroidectomy Gp (Table 1).

Coriander Reversed Thyroidectomy Altered Sperms Dynamics Morphology of Rats

Sperm dynamics in Thyroidectomies (Thy) male rats were exposed in Table 2. Non-progressive motility and immotile sperms were significantly increased in Thy Gp while sperm count, normalcy, morphological index, vitality, total motility, and progressive motility were significantly decreased in Thy Gp in comparison to the control Gp.

However, compared to Thy; treatments of thyroidectomies rats with coriander (Thy + CSE) increased sperm count, normality, vitality, total motility, and progressive motility while significantly reducing immotile sperms and non-progressive motility.

Coriander Ameliorated Thyroidectomy Reduced Serum Levels of Sexual Hormones

Sexual hormones (testosterone, FSH, prolactin, and LH) levels revealed significant reduction in comparison to control and CSE Gps. However, when thyroidectomies rats treated with CSE; the levels of sexual hormones were elevated in comparison to Thy (Table 3).

Coriander Ameliorated Thyroidectomy Elevation Testicular Enzymes

Table 4 show that; thyroidectomies rats (Thy) had significantly higher levels of AST and ALP than the control and coriander (CSE) groups. However, when thyroidectomies rats treated with CSE; the levels of AST and ALP were much lower as compared with thyroidectomies rats (Thy).

Antioxidant Defense of Coriander

In comparison to the control Gp; Thy Gp showed significant elevation in testicular MDA and a significant reduction in GSH and GST and SOD in testicular tissues (Table 5).

In comparison to Thy Gp; treatments of thyroidectomies rats with coriander (Thy + CSE) dramatically reduced testicular MDA and elevated GSH and GST and SOD in testicular tissues.

Table 1: Variation in the levels of T_3, T_4, and TSH levels in different groups

	Control	CSE	Thy	Thy + CSE
TSH (µIU/ml)	$1.21^{\#}\pm0.08$	$1.34^{\#}\pm0.15$	$4.98^{*}\pm0.37$	$2.74^{*\#}\pm0.15$
T_3 (ng/dl)	$126.8^{\#}\pm6.180$	$126.5^{\#}\pm6.090$	$62.7^{*}\pm3.52$	$81.4^{*\#}\pm5.05$
T_4 (ng/mL)	$2.13^{\#}\pm0.16$	$2.26^{\#}\pm0.21$	$3.72^{*}\pm0.24$	$2.86^{*\#}\pm0.29$

Data are expressed as mean ± SE. of 10 observations. *p<0.05 and #p<0.05 significant differences from control and thyroidectomy groups respectively

Table 2: Changes in rat's sperm count, morphology index, vitality, and sperm morphology in different groups

	Control	CSE	Thy	Thy + CSE
Count (million/ml)	$120.2^{\#}\pm6.35$	$121.5^{\#}\pm5.48$	$84.70^{*}\pm5.29$	$100.0^{\#*}\pm5.57$
Morphology index (%)	$46.5^{\#}\pm1.89$	$47.1^{\#}\pm2.45$	$30.8^{*}\pm1.960$	$36.2^{\#*}\pm1.64$
Vitality (%)	$75.2^{\#}\pm2.68$	$77.0^{\#}\pm2.95$	$64.9^{*}\pm1.830$	$75.1^{\#}\pm3.450$
Total motility	$66.2^{\#}\pm2.18$	$68.0^{\#}\pm3.05$	$55.9^{*}\pm2.150$	$66.1^{\#}\pm 2.62$
Progressive motility	$46.2^{\#}\pm1.34$	$51.2^{\#}\pm1.99$	$33.4^{*}\pm1.350$	$45.5^{\#}\pm2.440$
Non progressive	$20.0^{\#}\pm0.39$	$16.8^{\#}\pm0.65$	$22.5^{*}\pm1.210$	$21.6^{\#*}\pm0.89$
Immotile	$33.8^{\#}\pm0.85$	$32.0^{\#}\pm1.35$	$44.1^{*}\pm2.560$	$33.9^{\#}\pm0.950$

Data are expressed as mean ± SE. of 10 observations. *p<0.05 and #p<0.05 significant differences from control and thyroidectomy groups respectively

Table 3: Changes in sexual hormones levels in different groups

	Control	CSE	Thy	Thy + CSE
Testosterone (ng\ml)	$3.22^{\#}\pm0.110$	$3.35^{\#}\pm0.140$	$2.06^{*}\pm0.070$	$2.55^{\#*}\pm0.180$
FSH (mIU\ml)	$2.40^{\#}\pm0.150$	$2.44^{\#}\pm0.210$	$1.19^{*}\pm0.090$	$1.79^{\#*}\pm0.090$
LH (mIU\ml)	$1.13^{\#}\pm0.048$	$1.20^{\#}\pm0.008$	$0.95^{*}\pm0.051$	$1.00^{\#*}\pm0.029$
Prolactin (ng\ml)	$0.55^{\#}\pm0.021$	$0.56^{\#}\pm0.009$	$0.44^{*}\pm0.012$	$0.50^{\#*}\pm0.014$

Data are expressed as mean ± SE. of 10 observations. *p<0.05 and #p<0.05 significant differences from control and thyroidectomy groups respectively

Table 4: Changes in testicular enzymes activities in different groups

	Control	CSE	Thy	Thy + CSE
AST(U\l)	146.5$^{\#}$±7.82	155.1$^{\#}$±5.85	212.5*±8.06	192.4$^{\#}$*±8.56
ALP (U\l)	101.0$^{\#}$±5.66	98.5$^{\#}$±5.31	184.5*±6.25	135.5$^{\#}$*±6.04

Data are expressed as mean ± SE of 10 observations. *p<0.05 and $^{\#}$p<0.05 significant differences from control and thyroidectomy groups respectively

Table 5: Activities of Malondialdehyde (MDA); nmol/g protein) Glutathione (GSH; µmol/g tissue), Superoxide Dismutase (SOD; U\mg protein) and glutathione *S*-transferase (GST; µmol\h\mg protein), in testicular tissue

	Control	CSE	Thy	Thy + CSE
MDA	10.05$^{\#}$±0.890	9.62$^{\#}$±1.040	23.26*±1.310	18.61*$^{\#}$±1.590
GSH	3.79$^{\#}$±0.210	3.98$^{\#}$±0.290	1.44*±0.220	2.49*$^{\#}$±0.400
SOD	61.8$^{\#}$±2.4500	61.7$^{\#}$±2.9200	37.1*±2.0100	48.40*$^{\#}$±2.350
GST	0.71$^{\#}$±0.011	0.74$^{\#}$ ±0.012	0.40* ±0.001	0.56*$^{\#}$ ±0.009

Data are expressed as mean ± SE of 10 observations. *p<0.05 and $^{\#}$p<0.05 significant difference from control and Thyroidectomy (Thy) groups respectively

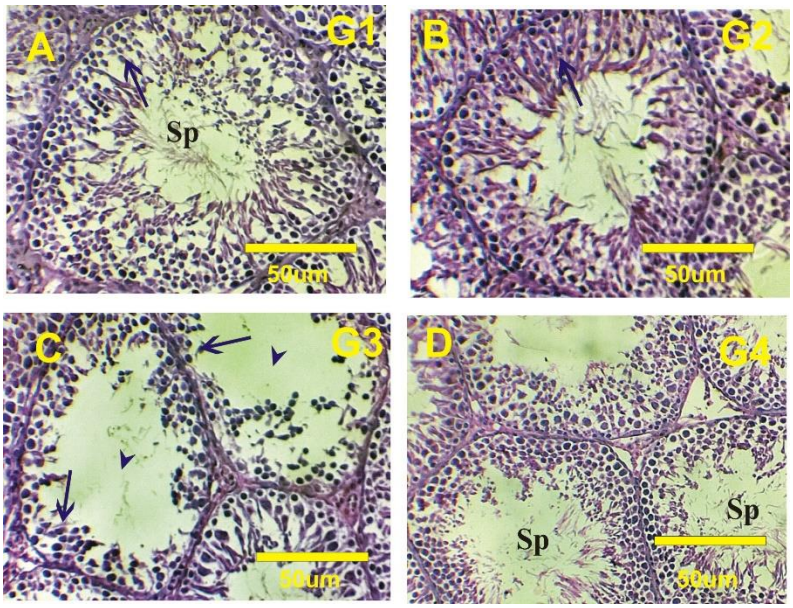

Fig. 1: HE-stained testes slices photographed under a microscope. A and B: In control (G1) and coriander (G2) testicular slices, normal seminiferous tubule structure was seen along with a typical cycle of spermatogenesis, completely packed sperms (Sp) in the lumen and Leydig cells (arrowheads). C: Spermatogenic cell configurations were disturbed (arrows) in the testes of thyroidectomy-affected rats (G3) and there were less sperms overall (arrowheads). There were also Leydig cells present. D: In testes sections from thyroidectomies rats treated with coriander (Thy + CSE), there were good arrangements of spermatogenic cells (arrows), as well as an increase in the quantity of sperm (Sp) and Leydig cells

Coriander Ameliorated Effect of Thyroidectomy on Testicular Tissue Architecture

Figure 1(A-D) showed the variation in testicular structure in different Gps. In testicular sections from controls and coriander, normal seminiferous tubule anatomy and a typical spermatogenesis cycle were seen Fig. 1(A-B).

Testes sections in thyroidectomies rats presented depletion in sperm counts and Leydig cells, with disturbance in spermatogenic cell arrangements (Fig. 1C).

Tested sections of thyroidectomies rats with coriander (Thy + CSE) presented spermatogenic cells with good arrangements and increased sperm numbers and Leydig cells (Fig. 1D).

Effect of Thyroidectomy and Coriander on PCNA-ir

The detection and distribution of PCNA in testicular tissues of the different groups were revealed in Figs. 2-3).

Testicular tissues of the control and CSE-Gps presented strong positive reactions for PCNA expression contrasted with the other spermatogenic cell types and Sertoli cells showed negative reactions (Figs. 2A-B and 3).

Testicular tissues showed mild positive PCNA expressions in the thyroidectomy rats while moderate positive PCNA expressions in Thy + CSE were observed (Figs. 2C-D and 3).

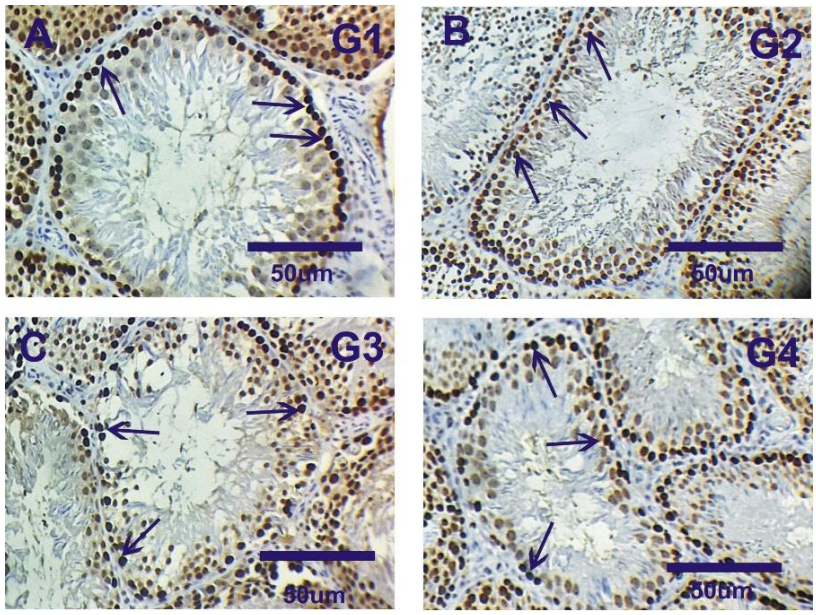

Fig. 2: Several groupings of testicular sections stained with PCNA. A and B: Both the control (G1) and coriander (G2) groups showed a significant increase in PCNA expression in testes sections. C and D: Testes sections from thyroidectomized rats (G3) had a weak positive reaction for PCNA expressions, but thyroidectomized rats treated with coriander (Thy + CSE) exhibited a more pronounced reaction

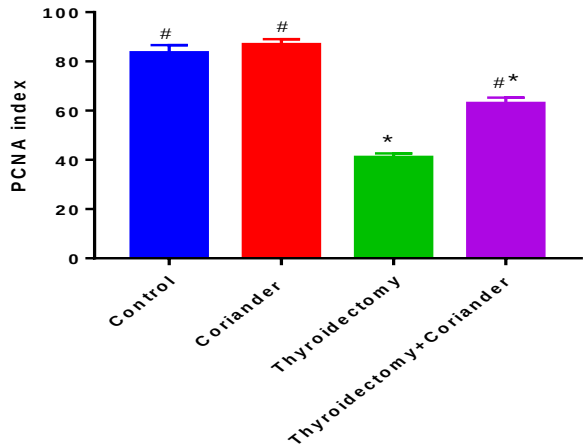

Fig. 3: The expression level of the PCNA protein in various groups is represented by the data. (*) & (#) significant $p<0.05$ compared to control and to thyroidectomy Gps respectively

Discussion

In the testis, thyroid hormone controls a variety of processes, including sperm motility, steroidogenesis, and the proliferation and differentiation of non-germ cells (Tousson *et al*., 2011; Beltagy *et al*., 2016). Current investigation aimed to investigate how Coriander Seed Extract (CSE) may help reduce the testicular damage and oxidative stress caused after thyroidectomy in male rats. Current results revealed that; thyroidectomy induced an increase in TSH and a decrease in T_3 levels, which results in a hypothyroid condition when compared to control rats. Coriander (Thy + CSE) therapy improved these variations in thyroid hormone levels and brought euthyroid condition to thyroidectomies rats. This results is consistent with those of Tousson *et al*. (2012c, 2014); Francisco *et al*. (2013), who employed thyroidectomy to induce hypothyroidism and who found that hypothyroidism was biochemically demonstrated in thyroidectomized rats by a substantial rise in TSH and depletion in T_3 levels.

La Vignera *et al*. (2017) reported that; thyroid dysfunction induced changes in semen quality. Current results revealed that; thyroidectomy induced reduced sperm count, normality, morphological index, vitality, total motility, and progressive motility, while dramatically increasing non-progressive motility and immotile sperms. A treatment of thyroidectomies rats with coriander modulates and improved these changes in semen parameters. Our results agree with Jalilvand *et al.* (2019) who find that; hypothyroidism induced testicular damage and depletion in sperm counts. Current study indicated that; rats thyroidectomy induced depletion in serum levels of reproductive hormones (FSH, LH, total testosterone, and prolactin). This striking decrease in sexual hormones may be explained by the harm that thyroidectomy caused to Leydig and Sertoli cells by producing free radicals. According to Ibrahim *et al*. (2011); Badr *et al*. (2021), who showed that hypothyroidism causes reproductive toxicity and oxidative stress, this conclusion was in line with their findings.

The key regulator of mitochondrial energy metabolism and oxygen utilization is thyroid hormone. Highly Reactive Oxygen Species (ROS) are normally produced in minute levels as byproducts of oxidative metabolism in mitochondria. They can assault nearby biomolecules and damage cellular activities if they are not rapidly eliminated (La Vignera *et al*., 2017). In the current investigation, thyroidectomy significantly altered the oxidant/antioxidant balance and this is in consistence with the previous results reported by Ibrahim *et al*. (2011); Tousson *et al*. (2014).

It is well-recognized that increased ROS production alters the redox equilibrium of cells, causing oxidative stress and healthy cell damage (El-Masry *et al*., 2019). Oxidative stress has been shown to harm healthy cells in the bone marrow, gastrointestinal tract, kidney, urine bladder, lung, neurological system, and vascular system (Cano-Europa *et al*., 2011). Current results revealed that; thyroidectomy induced elevation MDA content and depletion in GSH content and GST and SOD activity in testicular tissues and the treatments of thyroidectomies rats with coriander improve these changes.

Our results agree with Ibrahim *et al*. (2011) who reported that; hypothyroidism induced elevation MDA and depletion in GSH, catalase, and SOD activity in testicular tissues. According to Mogulkoc *et al*. (2005); Hamza and AL-Saeed (2022) who reported that; hypothyroid rat testis led to a decrease in lipid peroxidation, which may have been caused by metabolic depression brought on by hypothyroidism, which acts as a protective factor against lipid peroxidation. Our results agree with (Moustafa *et al*., 2014; Mechchate *et al*., 2021) who find that; administration of Coriander seeds and leaves extract decrease oxidative stress in liver tissues after TAA-induced hepatotoxicity. Current results agree with Sadasivan *et al*. (2006) who suggested that; the extract from coriander seeds works by maintaining the plasma membrane and strengthening tissues' resistance to toxicity.

Current results revealed that; thyroidectomy induced testicular damage; depletion in PCNA expression in spermatogonia; depletion in sperm counts and Ledig cells. Our findings are consistent with several studies that showed hypothyroidism had a negative impact on testes (Tousson *et al*., 2011; 2012b; Fadlalla *et al*., 2017). Treatment of thyroidectomies rats with CSE significantly increased PCNA immunoreactivity and decrease testicular damage. Our results agree with de Almeida Melo *et al*. (2005); Moustafa *et al*. (2014) who find that; due to the large amount of polyphenolics and antioxidant components found in coriander seeds and leaves extract, taking it reduces tissue damage and is effective in preventing the development of many lesions.

Conclusion

Testicular stucture and function changed as a result of thyroidectomy. By lowering cellular damage and increasing sperm counts, treatment of thyroidectomies rats with coriander seed extract improved these abnormalities in the testis and helped reverse these modifications to testicular structure and functioning following thyroidectomy.

Highlights

- Hypothyroidism brought on by thyroid surgery and linked to oxidative stress
- The observed metabolic changes may be a factor in testicular dysfunction
- The extract from coriander seeds improved spermatogenesis and raised the antioxidant status
- Coriander seeds extract might be applied as adjuvant treatment following thyroidectomy

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Author's Contributions

Azhar Azher Alankooshi: Wrote the first drafted of the manuscript and performed the statistical analysis. All authors managed the analysis of the study, managed the literature search, and read and approved the final manuscript.

Ahmed F. Hasan, Afaf El-Atrsh and Tarek M. Mohamed: All authors managed the analysis of the study, managed the literature search, and read and approved the final manuscript.

Ehab Tousson: Designed the study and wrote the protocol. All authors managed the analysis of the study, managed the literature search, and read and approved the final manuscript.

Data Availability

Where necessary, the appropriate author can provide access to the data that support our study's findings.

Conflict of Interests Statement

No possible conflicts of interest were disclosed by the authors with regard to the research, writing, or publishing of this study.

Ethics

The institutional ethical committee for animal care and use approved the study's design (code: IACUC-SCI-TU-0241).

References

Abd Eldaim, M. A., Tousson, E., Soliman, M. M., El Sayed, I. E. T., Abdel Aleem, A. A. H., & Elsharkawy, H. N. (2021). Grape seed extract ameliorated Ehrlich solid tumor-induced hepatic tissue and DNA damage with reduction of PCNA and P53 protein expression in mice. *Environmental Science and Pollution Research*, *28*, 44226-44238. https://doi.org/10.1007/s11356-021-13904-8

Aldubayan, M. A., Elgharabawy, R. M., Ahmed, A. S., & Tousson, E. (2019). Antineoplastic activity and curative role of avenanthramides against the growth of ehrlich solid tumors in mice. *Oxidative Medicine and Cellular Longevity*, *2019*. https://doi.org/10.1155/2019/5162687

Altwaijry, N., El-Masry, T. A., Alotaibi, B., Tousson, E., & Saleh, A. (2020). Therapeutic effects of rocket seeds (*Eruca sativa* L.) against testicular toxicity and oxidative stress caused by silver nanoparticles injection in rats. *Environmental Toxicology*, *35*(9), 952-960. https://doi.org/10.1002/tox.22931

Badr, G. M., Algefare, A. I., & Alfwuaires, M. A. (2021). Antioxidant Potential of Parsley Leaf (Petroselinum crispum) Essential Oil on Hypothyroidism and Testicular Injury in Mice Intoxicated by Carbon Tetrachloride. *BioMed Research International*, *2021*. https://doi.org/10.1155/2021/9989174

Beltagy, D. M., Mohamed, T. M., El Said, A. S., & Tousson, E. (2016). Beneficial role of ascorbic and folic acids antioxidants against thyroxin-induced testicular dysfunction in hyperthyroid rats. *Environmental Science and Pollution Research*, *23*, 17246-17254. https://doi.org/10.1007/s11356-016-6876-x

Cano-Europa, E., Blas-Valdivia, V., Franco-Colin, M., Gallardo-Casas, C. A., & Ortiz-Butrón, R. (2011). Methimazole-induced hypothyroidism causes cellular damage in the spleen, heart, liver, lung and kidney. *Acta Histochemica*, *113*(1), 1-5. https://doi.org/10.1016/j.acthis.2009.07.004

Choksi, N. Y., Jahnke, G. D., St. Hilaire, C., & Shelby, M. (2003). Role of thyroid hormones in human and laboratory animal reproductive health. *Birth defects research part B: Developmental and Reproductive Toxicology*, *68*(6), 479-491. https://doi.org/10.1002/bdrb.10045

de Almeida Melo, E., Mancini Filho, J., & Guerra, N. B. (2005). Characterization of antioxidant compounds in aqueous coriander extract (*Coriandrum sativum* L.). *LWT-Food Science and Technology*, *38*(1), 15-19. https://doi.org/10.1016/j.lwt.2004.03.011

El-Aarag, B., Attia, A., Zahran, M., Younes, A., & Tousson, E. (2021). New phthalimide analog ameliorates CCl4 induced hepatic injury in mice via reducing ROS formation, inflammation and apoptosis. *Saudi Journal of Biological Sciences*, *28*(11), 6384-6395. https://doi.org/10.1016/j.sjbs.2021.07.014

Elbandrawy, M. M., Sweef, O., Elgamal, D., Mohamed, T. M., & Elgharabawy, R. M. (2022). Ellagic acid regulates hyperglycemic state through modulation of pancreatic IL-6 and TNF-α immunoexpression. *Saudi Journal of Biological Sciences*, *29*(5), 3871-3880. https://doi.org/10.1016/j.sjbs.2022.03.016

Elgharabawy, R. M., El Tantawy El Sayed, I., Abd-Allah Rezk, N., & Tousson, E. (2021). Therapeutic impact of costus (Saussurea lappa) against Ehrlich solid tumor-induced cardiac toxicity and DNA damage in female mice. *Frontiers in Pharmacology*, *12*, 708785. https://doi.org/10.3389/fphar.2021.708785

El-Masry, T. A., Al-Shaalan, N. H., Tousson, E., Buabeid, M., & Alyousef, A. M. (2019). The therapeutic and antineoplastic effects of vitamin B17 against the growth of solid-form Ehrlich tumours and the associated changes in oxidative stress, DNA damage, apoptosis and proliferation in mice. *Pak. J. Pharm. Sci*, *32*(6), 2801-2810. https://www.pnu.edu.sa/ar/Faculties/Pharmacy/Documents/badria2412/published%20research%202.pdf

El-Masry, T., Al-Shaalan, N., Tousson, E., Buabeid, M., & Al-Ghadeer, A. (2020). Potential therapy of vitamin B17 against Ehrlich solid tumor induced changes in Interferon gamma, Nuclear factor kappa B, DNA fragmentation, p53, Bcl2, survivin, VEGF and TNF-α Expressions in mice. *Pakistan Journal of Pharmaceutical Sciences*, *33*. https://doi.org/10.36721/PJPS.2020.33.1.SUP.393-401.1

Fadlalla, M. B., Wei, Q., Fedail, J. S., Mehfooz, A., Mao, D., & Shi, F. (2017). Effects of hyper-and hypothyroidism on the development and proliferation of testicular cells in prepubertal rats. *Animal Science Journal*, *88*(12), 1943-1954. https://doi.org/10.1111/asj.12883

Francisco, J. C., Cunha, R. C., Cardoso, M. A., Simeoni, R. B., Guarita-Souza, L. C., & Miyague, N. I. (2013). The effects of total thyroidectomy on cardiac function in old rats using echocardiographic measures. *J Clin Exp Cardiolog S*, *11*, 2. https://doi.org/10.4172/2155-9880.S11-006

Hafez, E., & Tousson, E. (2014). Thyroxine-induced cardiac hypertrophy: Role of ascorbic acid in treatment. *Biomedicine & Aging Pathology*, *4*(2), 161-167. https://doi.org/10.1155/2020/1436858

Hamza, F. Z., & AL-Saeed, M. (2022). Effect of Ghrelin on Epididymal Sperm Analysis and Antioxidant System in Hyperthyroidic Adult Male Rats. *Basrah Journal of Veterinary Research*, *21*, 141-153.

Hasan, A. F., Hameed, H. M., Tousson, E., Massoud, A., Atta, F., & Youssef, H. (2022). Role of Oral Supplementation of Damiana (*Turnera diffusa*) Reduces the Renal Toxicity, Apoptosis and DNA Damage Associated with Amitriptyline Administration in Rats. *Biomedical and Pharmacology Journal*, *15*(3), 1245-1253. https://dx.doi.org/10.13005/bpj/2460

Ibrahim, W., Tousson, E., Ali, E. M., & Mansour, M. A. (2011). Folic acid alleviates oxidative stress and hyperhomocysteinemia involved in testicular dysfunction of hypothyroid rats. *General and Comparative Endocrinology*, *174*(2), 143-149. https://doi.org/10.1016/j.ygcen.2011.08.012

Ibrahim, W., Tousson, E., El-Masry, T., Arafa, N., & Akela, M. (2012). The effect of folic acid as an antioxidant on the hypothalamic monoamines in experimentally induced hypothyroid rat. *Toxicology and Industrial Health*, *28*(3), 253-261. https://doi.org/10.1177/0748233711410913

Ichiki, T. (2010). Thyroid hormone and atherosclerosis. *Vascular Pharmacology*, *52*(3-4), 151-156. https://doi.org/10.1016/j.vph.2009.09.004

Jalilvand, N., Hosseini, M., Beheshti, F., & Ebrahimzadeh-Bideskan, A. (2019). Protective effect of PPARγ agonist pioglitazone, on testicular tissue and sperm parameters in hypothyroid rats. *Toxin Reviews*. https://doi.org/10.1080/15569543.2018.1564775

La Vignera, S., Vita, R., Condorelli, R. A., Mongioì, L. M., Presti, S., Benvenga, S., & Calogero, A. E. (2017). Impact of thyroid disease on testicular function. *Endocrine*, *58*, 397-407. https://doi.org/10.1007/s12020-017-1303-8

Mahgoob, A. A. E., Tousson, E., Abd Eldaim, M. A., Ullah, S., Al-Sehemi, A. G., Algarni, H., & El Sayed, I. E. T. (2022). Ameliorative role of chitosan nanoparticles against silver nanoparticle-induced reproductive toxicity in male albino rats. *Environmental Science and Pollution Research*, 1-10. https://doi.org/10.1007/s11356-022-23312-1

Mahmoud, M. F., Ali, N., Mostafa, I., Hasan, R. A., & Sobeh, M. (2022). Coriander oil reverses dexamethasone-induced insulin resistance in rats. *Antioxidants*, *11*(3), 441. https://doi.org/10.3390/antiox11030441

Massoud, A. A., El-Atrash, A., Tousson, E., Ibrahim, W., & Abou-Harga, H. (2012). Light and ultrastructural study in the propylthiouracil-induced hypothyroid rat heart ventricles and the ameliorating role of folic acid. *Toxicology and Industrial Health*, *28*(3), 262-270. https://doi.org/10.1177/0748233711410915

Mechchate, H., Costa de Oliveira, R., Es-Safi, I., Vasconcelos Mourão, E. M., Bouhrim, M., Kyrylchuk, A., ... & Grafov, A. (2021). Antileukemic activity and molecular docking study of a polyphenolic extract from coriander seeds. *Pharmaceuticals*, *14*(8), 770. https://doi.org/10.3390/ph14080770

Mesbah, L., Soraya, B., Narimane, S., & Jean, P. F. (2004). protective effect of flavonides against the toxicity of vinblastine cyclophosphamide and paracetamol by inhibition of lipid-peroxydation and increase of liver glutathione. *Haematol*, *7*(1), 59-67.

Mogulkoc, R., Baltaci, A. K., Oztekin, E., Ozturk, A., & Sivrikaya, A. (2005). Short-term thyroxine administration leads to lipid peroxidation in renal and testicular tissues of rats with hypothyroidism. *Acta Biologica Hungarica*, *56*(3-4), 225-232. https://doi.org/10.1556/abiol.56.2005.3-4.6

Moustafa, A. H. A., Ali, E. M. M., Moselhey, S. S., Tousson, E., & El-Said, K. S. (2014). Effect of coriander on thioacetamide-induced hepatotoxicity in rats. *Toxicology and Industrial Health*, *30*(7), 621-629. https://doi.org/10.1177/0748233712462470

Mutar, T. F., Tousson, E., Hafez, E., Abo Gazia, M., & Salem, S. B. (2020). Ameliorative effects of vitamin B17 on the kidney against Ehrlich ascites carcinoma induced renal toxicity in mice. *Environmental Toxicology*, *35*(4), 528-537. https://doi.org/10.1002/tox.22888

Odell, W. D., Ross, G. T., & Rayford, P. L. (1967). Radioimmunoassay for luteinizing hormone in human plasma or serum: Physiological studies. *The Journal of Clinical Investigation*, *46*(2), 248-255. https://www.jci.org/articles/view/105527

Odell, W. D., Swerdloff, R. S., Bain, J., Wollesen, F., & Grover, P. K. (1974). The effect of sexual maturation on testicular response to LH stimulation of testosterone secretion in the intact rat. *Endocrinology*, *95*(5), 1380-1384. https://doi.org/10.1210/endo-95-5-1380

Peterson, M. E., Melian, C., & Nichols, R. (1997). Measurement of serum total thyroxine, triiodothyronine, free thyroxine, and thyrotropin concentrations for diagnosis of hypothyroidism in dogs. *Journal of the American Veterinary Medical Association*, *211*(11), 1396-1402. https://europepmc.org/article/med/9394888

Sadasivan, S., Latha, P. G., Sasikumar, J. M., Rajashekaran, S., Shyamal, S., & Shine, V. J. (2006). Hepatoprotective studies on Hedyotis corymbosa (L.) Lam. *Journal of Ethnopharmacology*, *106*(2), 245-249. https://doi.org/10.1016/j.jep.2006.01.002

Saggu, S., Sakeran, M. I., Zidan, N., Tousson, E., Mohan, A., & Rehman, H. (2014). Ameliorating effect of chicory (Chichorium intybus L.) fruit extract against 4-tert-octylphenol induced liver injury and oxidative stress in male rats. *Food and Chemical Toxicology*, *72*, 138-146. https://doi.org/10.1016/j.fct.2014.06.029

Salama, A. F., Tousson, E., Ibrahim, W., & Hussein, W. M. (2013). Biochemical and histopathological studies of the PTU-induced hypothyroid rat kidney with reference to the ameliorating role of folic acid. *Toxicology and Industrial Health*, *29*(7), 600-608. https://doi.org/10.1177/0748233711432577

Sharma, A., Mollier, J., Brocklesby, R. W., Caves, C., Jayasena, C. N., & Minhas, S. (2020). Endocrine-disrupting chemicals and male reproductive health. *Reproductive Medicine and Biology*, *19*(3), 243-253. https://doi.org/10.1002/rmb2.12326

Thakur, C., Saikia, T. C., & Yadav, N. (1997). Total serum levels of triiodothyronine (T. *Indian J Physiol Pharmacol*, *41*(2), 167-170. https://www.ijpp.com/IJPP%20archives/1997412/167-170.pdf

Tiirats, T. (1997). Thyroxine, triiodothyronine and reverse-triiodothyronine concentrations in blood plasma in relation to lactational stage, milk yield, energy and dietary protein intake in Estonian dairy cows. *Acta Veterinaria Scandinavica*, *38*, 339-348. https://doi.org/10.1186/BF03548480

Tousson, E. (2016). Histopathological alterations after a growth promoter boldenone injection in rabbits. *Toxicology and Industrial Health*, *32*(2), 299-305. https://doi.org/10.1177/0748233713500821

Tousson, E., Alghabban, A. J., & Abou Harga, H. (2014). Thyroidectomy induced hepatic toxicity and possible amelioration by Ginkgo biloba leaf extract. *Biomedicine & Preventive Nutrition*, *4*(3), 391-397. https://doi.org/10.1016/j.bionut.2014.06.001

Tousson, E., Ali, E. M., Ibrahim, W., & Mansour, M. A. (2011). Proliferating cell nuclear antigen as a molecular biomarker for spermatogenesis in PTU-induced hypothyroidism of rats. *Reproductive Sciences*, *18*(7), 679-686. https://doi.org/10.1177/1933719110395401

Tousson, E., Bayomy, M. F., & Ahmed, A. A. (2018). Rosemary extract modulates fertility potential, DNA fragmentation, injury, KI67 and P53 alterations induced by etoposide in rat testes. *Biomedicine & Pharmacotherapy*, *98*, 769-774. https://doi.org/10.1016/j.biopha.2018.01.025

Tousson, E., Beltagy, D. M., El-Gerbed, M. S., Gazia, M. A., & Akela, M. A. (2012a). The ameliorating role of folic acid in rat hippocampus after propylthiouracil-induced hypothyroidism. *Biomedicine & Aging Pathology*, *2*(3), 104-110. https://doi.org/10.1016/j.biomag.2012.07.004

Tousson, E., Ibrahim, W., Arafa, N., & Akela, M. A. (2012b). Monoamine concentrations changes in the PTU-induced hypothyroid rat brain and the ameliorating role of folic acid. *Human & Experimental Toxicology*, *31*(3), 282-289. https://journals.sagepub.com/doi/pdf/10.1177/0960327111405863

Tousson, E., Ali, E. M., Ibrahim, W., & Mansour, M. A. (2012c). Treatment with folic acid ameliorated the histopathological alterations caused by propylthiouracil-induced hypothyroid rat testes. *Toxicology and Industrial Health*, *28*(6), 566-576. https://doi.org/10.1177/0748233711420469

Tousson, E., Ali, E. M., Ibrahim, W., & Ashraf, R. M. (2012d). Histopathological and immunohistochemical alterations in rat heart after thyroidectomy and the role of hemin and ketoconazole in treatment. *Biomedicine & Pharmacotherapy*, *66*(8), 627-632. https://doi.org/10.1016/j.biopha.2012.08.009