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Effect of *Sesamum indicum* oil in Thyroidectomy-Induced Erectile Dysfunction in Rat

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Abstract

The aim of the present study has been to explore the effect of *Sesamum indicum* in thyroidectomy-induced erectile dysfunction in rat. The animals were anaesthetized with combination of midazolam and ketamine *i.p.,* and the thyroid gland was dissected out. The skin was then stitched and the wound was closed. Animals were treated with penicillin injection *i.p*. for 5 days postoperatively. After 45 days of surgery different groups of animals were treated with sesamum oil at dose levels 2 mL, 3 mL and 5 mL/kg *p.o*., and with standard drug sildenafil, respectively, for 28 days. At the end of the study erectile dysfunction-associated physical and biochemical parameters were evaluated to assess the effect of *Sesamum indicum* in thyroidectomy-induced erectile dysfunction. Thyroidectomy resulted in impairment of sexual function in the rat. Treatment of *Sesamum indicum* oil caused increase in testosterone level. It also produced significant positive effects on the physical parameters of sexual function such as mount latency, intromission latency, ejaculatory latency, post-ejaculatory interval, mount frequency and intromission frequency. Though the oil did not produce any significant effect on the levels of thyroid hormones, the oil at the doses of 2 mL, 3 mL and 5 mL/kg body weight restored sexual competence to a reasonable extent in which the highest dose produced the maximum response. A combination of *Sesamum indicum* oil and thyroxin may be recommended for hypothyroidism-associated sexual impairment.

Keywords: Erectile dysfunction, *Sesamum indicum*, Sesamum oil, Thyroidectomy, Thyroxine

1. Introduction

Erectile dysfunction (ED) is a common disorder involving various psychosocial and biological factors. Erectile dysfunction can be expressed as the continued inability to attain or maintain penile erection enough for satisfactory sexual performance. It is a medical condition that alters the sexual life of men world-wide [1]. Erectile dysfunction, male impotence and abnormal sperm morphology may result in infertility [2]. Erectile dysfunction is associated with lifestyle factors such as cigarette smoking, excessive alcohol consumption and age-related medical conditions [3]. Prevalence of ED is associated mainly with aging as well as one or more of co-morbiditiessuch as cardiovascular problems, diabetes, metabolic syndrome, hyperlipidemia, depression, pelvic surgery, side effects of medications, neurological disorders, trauma, symptoms of benign prostatic hyperplasia and psychological and interpersonal problems [4].

There are essentially three mechanisms of vascular changes associated with penile erection. They are, i) psychogenic, ii) reflexogenic, and iii) centrally originated (nocturnal erections). Psychogenic erections are those that occur by the stimulatory pathways (like, sound, smell, sight, touch, etc.) that frequently traverse via spinal erection centers (including T11–L2 and also S2–S4) and they are induced by dopaminergic initiation of the erection from the parts of medial pre-optic area[5]. Reflexogenic erections (RE) are induced by direct genital stimulation, which acts by transmitting ascending messages for the central erection centers (EC) and directly transmit messages to the autonomic nuclei. This explains the cause for residual erectile activity in patients suffering from upper spinal cord injuries. Nocturnal erections (NE) relate to

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the pontine reticular formation and amygdale, which can be seen during REM sleep and is believed to be the principal cause of relative reduction in sympathetic nerve inhibition by augmenting the pro-erectile centers (PEC) [6].

It is known that in the context of sexual arousal the androgens work predominantly by exerting the effects on libido and sexual behavior. Testosterone mainly functions to enhance the sexual interest of males that associates with the frequency of sexual activity. Testosterone also increases the frequency of nocturnal erections where it does not have any effect on reflexogenic or psychogenic erections [7, 8].

Disruption of thyroid gland functioning resulting in thyroid hormone imbalance would lead to changes in libido, erectile function (EF) and ejaculation. Hypothyroidism may cause decrease in the levels of testosterone and thus cause sexual dysfunction. Restoration of normal levels of thyroid hormones is associated with restoration of libido [9, 10]. In the context of thyroid dysfunction resulting in hypothyroidism, treatment with thyroid hormones up to sufficient level can restore penile erections. The multi-factorial ED which has so many etiological factors (lifestyle, androgen deficiency, aging, psychological disorders, and side effects of drugs) is managed with different strategies such as psychological/behavioral counseling, pharmacotherapy, surgical and non-surgical approaches, etc. Unfortunately, these options are too expensive with some serious side effects like aching in the penis and testes, urethral burning, pain and bleeding, implant extrusion and infections[11]. It was hypothesized that solution to ED caused due to hypothyroidism-dependent hypoandrogenic condition would lie in aphrodisiac botanicals that will not only increase libido (desire and arousal), sexual potency (effectiveness of erection) and sexual pleasure but also are cheaper, act faster and relate with less side effects.

Sesamum indicum is an annual pubescent herb with a height about 2 to 3 feet, also with branches from the base. *Sesamum indicum* oil, also known as till oil, is widely used for the preparation of various cosmetic products and in herbal medicine industry for the formulation of various proprietary medicinal oils. It contains glycolipids and phospholipids (also in flowers), globulins, cystine, histidine, p-aminobenzoic acid, ascorbic acid, tryptophan, tyrosine, valine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, biotin, choline, folic acid, inositol, pyridoxine, riboflavin, sesamol, 3 methyl butanal, niacin, nicotinic acid, pantothenic acid, octanal, phenol, 2,4-arachidicacid, hexadecenoic acid, thiamine, tocopherol, sesamolinol, linoleic acid, lignoceric acid[12], myristic acid, gallic acid, pyrogallol, caffeine, catechol, catechin, chrysin, and protocatechuic, palmitic, phytic, stearic, coumaric, caffeic, vanillic, chlorogenic, syringic, ferulic, ellagic, cinnamic, and benzoic acids [13]. *Sesamum indicum* oil is also a hypocholesterolemic agent[14]. It is also used in nasal mucosa dryness caused due to dry winter [15] especifically, linoleate in triglyceride form is a selective inhibitor of malignant melanoma growth [16]. Sesamum oil enhances oxidation of hepatic fatty acid and modulates serum triacylglycerol levels[17]. Anticonvulsant activity of sesamum seeds has also been reported[18].

The hypothesis that *Sesamum indicum* oil is useful in male infertility and/or hypothyroidism-associated ED has been tested in this study.

2. Material and Methods

2.1 Procurement of Animals

Male Albino rats weighing 200-250 g were procured from the Animal House, Department of Pharmacology, SBS PG Institute of Biomedical Sciences and Research, Balawala, Dehradun, for the present study. The animals were placed at random and allocated to treatment groups in polypropylene cages with husk as bedding. Animals were housed at a temperature of 24 ± 2 ^{0}C and relative humidity of 30-70 %. A 12:12 light:dark cycle was practiced. All animals were allowed to have free access to water, and fed with standard commercial pellet rat chow. All the experimental procedures and protocols used in this study were reviewed by the Institutional Animal Ethics Committee (IAEC) and were in accordance with the guidelines of the CPCSEA. Animal handling was performed according to Good Laboratory Practice (GLP). Ethical clearance was obtained from IAEC **(CPCSEA/IAEC/SBS/2015/01).**

2.2 Separation of *Sesamum indicum* Oil from the Seeds

The seeds of plant were collected from the hills of Garhwal Region in Uttarakhand. The seeds were dried, crushed and pressed on a wooden machine (Nautho) for oil separation. Oil was collected and stored at room temperature and directly used for the study.

2.3 Induction of Hypothyroidism (Thyroidectomy)

The animals were anaesthetized by *i.p.* administration of Midazolam @ 5 mg/kg body weight and Ketamine @ 60 mg/kg body weight. As soon as the anesthesia took its effect the animals were prepared for surgery. The hair at the site of the operation was shaved and disinfected. A skin incision of about 2 cm long was made with a scalpel in the midline axis of the neck. The wound was dilated with blunt forceps until the thyroid gland was exposed. The muscles and other adhering tissue were separated from the gland using tissue forceps, and the thyroid gland was removed with the help of scissors. The wound was carefully swabbed and penicillin powder applied. The skin was then stitched with interrupt sutures. Postoperative treatment included administration of prophylactic penicillin injection *i.p.* for 5 days [19].

2.4 Treatment Protocol

After 45 days of surgery, the animals were divided into eight groups of six animals in each group and subjected to treatment for 28 days as follows:

Group	Treatment
I	Control (Vehicle treated)
II	Positive control (Thyroidectomy without treatment)
III	Sildenafil (35mg/kg, Served as standard) oral
IV	Thyroxine (10µg /kg) po
V	*Sesamum indicum* oil (3 ml) + Thyroxine (10 µg/kg) po
VI	*Sesamum indicum* oil (2 mL/kg) po
VII	*Sesamum indicum* oil (3 mL/kg) po
VIII	*Sesamum indicum* oil (5 mL/kg) po

The doses of the drugs were selected from the previously reported studies [20]. At the end of the experiment blood was collected by retro-orbital sinus bleeding. Blood samples were allowed to clot and centrifuged at 1000 rpm for 5 min to obtain serum. The serum was used to quantitatively evaluate different biochemical parameters. Erectile dysfunction-associated different physical parameters were quantitatively checked by keeping two males and one female in each cage to assess the effect of *Sesamum indicum* oil in ED.

2.5 Statistical Analysis

The statistical significance of difference between means was calculated by ANOVA followed by *t*-test for unpaired comparison (n = 6). Values are expressed as Mean ± SEM.

3. Results

The present research involved analysis of sperm count, blood sample (serum) and tissues belonging to different treatment groups. Each sample was analyzed to estimate the effect of *Sesamum indicum* oil in hypothyroidism (throidectomy)-induced erectile dysfunction in rats.

3.1 Thyroid Hormones

Thyroidectomy caused significant decrease in T_3, and T_4 and increase in TSH levels (Positive control, Group- 2) (Table 1). Treatment with thyroxine alone and thyroxine + *Sesamum indicum* oil produced significant improvement in the T_3 and TSH levels while this treatment did not improve T_4 level. Sildenafil and *Sesamum indicum* oil at the different dose levels did not produce any effect on T_3, T_4 TSH levels as compared to the positive control group. Since there was significant improvement in the T_3 and TSH levels in the group receiving thyroxine alone or in combination with *Sesamum indicum* oil, respectively. It is suggested that the changes in T_3 and TSH levels in the thyroidectomized rats are due to thyroxine only because the groups that received *Sesamum indicum* oil alone at different dose levels showed no improvement in the T_3 and TSH levels when compared to the positive control group.

3.2 Physical Parameters (Table 2)

3.2.1 Mounting Latency

There were significant changes in all physical parameters in the different groups. Mounting latency (ML) was significantly increased in hypothyroidism-associated erectile dysfunctional rats when compared with the normal control group. Groups treated with sildenafil, thyroxine, *Sesamum indicum* oil and combination of oil and thyroxine, respectively, showed significant decrease in the ML time in minutes. The effect of oil was directly proportional to the concentration of oil. Among all the groups the maximum decrease in ML time was shown by animals that received the combination of *Sesamum indicum* oil and thyroxine (Table 2).

3.2.2 Mounting Frequency

There was significant decrease in mounting frequency (MF) in untreated sexually impaired animals (positive control). These results indicate the major relationship between hypothyroidism and ED. There was significant

Table 1. Effect of *Sesamum indicum* oil on thyroid hormones

Group	Treatment	Tnmol/l	Tnmol/l	TSH ng/mL
I	Control (Distilled water) po	3.42 ± 0.23	6.12 ± 1.02	4.66 ± 0.32
II	Positive control (Thyroidectomy without treatment)	0.52± 0.04	1.10 ± 0.11	11.72 ± 0.88
III	Sildenafil (35 mg/kg ; served as standard) po	0.48 ± 0.07	0.82 ±0.11*	13.02 ± 0.95*
IV	Thyroxine (10 µg/kg) po	3.10± 0.67***	0.64 ± 0.12**	5.26 ±0.34***
V	*Sesamum indicum* oil (3 mL) + Thyroxine (10 µg) po	2.66 ± 0.65***	1.00 ± 0.19*	6.56 ± 0.65***
VI	*Sesamum indicum* oil (2 mL/kg) po	0.46 ± 0.05	0.62 ± 0.12**	11.62 ± 0.52
VII	*Sesamum indicumn* oil (3 mL/kg) po	0.42 ± 0.05*	0.74 ± 0.14**	12.60 ± 1.14
VIII	*Sesamum indicum* oil (5 mL/kg) po	0.44 ± 0.08	0.78 ± 0.15*	12.90 ± 0.54

The statistical significance of difference between means was calculated by ANOVA followed by t-test for unpaired comparison (n=6). Values are expressed as Mean ± SEM, *P<0.05, **P<0.01, ***P<0.001 when treated groups compared with positive control group

Table 2. Effect of *Sesamum* oil on physical parameters of erectile dysfunction

Group	Mounting Latency (Min)	Mounting Frequency	Intromission Latency (Min)	Intromission Frequency	Ejaculatory Latency (Min)	Post- Ejaculatory interval (Min)
Group-1 Normal Control	7.40±0.509	11.80±0.583	10.20±0.499	14.20±0.374	13.28±0.420	20.86±1.42
Group-02 Positive control	25.00±0.32	4.40±0.75	37.40±2.21	5.60±0.75	43.26±1.57	30.56±0.69
Group-03 Sildenafil (35 mg/kg) po	10.60±0.40**	8.40±0.24**	26.40±1.288*	8.20±0.583*	26.76±0.91*	22.87±1.52*
Group-04 Thyroxine (10 µg/kg) po	8.200±0.20**	14.00±0.89**	12.20±0.37**	13.20±0.20**	15.44±0.445**	20.18±1.586*
Group-05 *Sesamum indicum* oil **(3 mL) + Thyroxine (10 µg) po**	6.900±0.56***	11.60±0.51**	7.80±0.58**	11.60±0.68**	11.10± 0.68**	13.78±0.96**
Group-06 *Sesamum indicum* oil **(2 mL/kg) po**	18.00±0.77**	14.20±0.58*	24.60±1.400*	14.80±0.324**	29.00±0.95*	26.66±0.73*
Group-07 *Sesamum indicum* oil **(3 mL/kg) po**	15.40±0.40**	16.40±0.68**	23.40±1.08*	17.20±0.49**	23.22±1.87**	22.52±1.42
Group-08 *Sesamum indicum* oil **(5 mL/kg) po**	9.00±0.77	12.00±0.32	17.00±0.55**	9.20±0.58***	18.86±0.66**	20.66±1.03*

The statistical significance of difference between means was calculated by ANOVA followed by t-test for unpaired comparison (n=6). Values are expressed as Mean ± SEM, *P<0.05, **P<0.01, ***P<0.001 when treated groups are compared with positive control group.

increase in mounting frequency in the groups treated with thyroxine, sesamum oil and combination of both, respectively, but the highest response was found in the group that received oil at the dose level 2 mL/kg body weight.

3.2.3 Intromission Latency

There was significant increase in intromission latency (IL) in untreated hypothyroid rats (positive control), whereas it was significantly decreased in groups treated with thyroxine and combination of oil and thyroxine, respectively. Groups that received sesamum oil at different dose levels showed significant decrease in intromission latency time when compared with the positive control group. Decrease in IL was observed in dose-dependent manner in these animals. Treatment with thyroxine also improved IL time in hypothyroid-based ED.

3.2.4 Intromission Frequency

The intromission frequency (IF) was significantly decreased in untreated hypothyroid rats when compared to the normal control group. Animals treated with thyroxine and thyroxine + oil showed increase in IF when compared to the positive control group. Groups receiving sesamum oil alone at different dose levels i.e., 2 mL/kg, 3 mL/kg and 5 mL/kg, respectively, showed significant increase in IF time when compared with the positive control group. The standard drug also produced increase in IF.

3.2.5 Ejaculatory Latency

Thyroidectomy produced significant increase in ejaculatory latency (EL) as compared to the normal control group. Treatment with sesamum oil produced significant decrease in (EL) in a dose-dependent manner. Sildenafil treatment also decreased the EL significantly when compared with the positive control group. The group that was treated with the combination of thyroxine and sesamum oil showed maximum decrease in EL.

3.2.6 Post-ejaculatory Interval

Post-ejaculatory interval (PEI) time in the positive control rats was significantly enhanced as compared to the normal control group. Treatment of combination of thyroxine with sesamum oil produced significant decrease in PEI time. Animals treated with sildenafil, thyroxine and sesamum oil, respectively, indicated significant decrease in PEI time compared with that of positive control group.

3.3 Testosterone

The suppressed levels of testosterone in untreated sexually impaired rats were enhanced significantly in animals treated with sesamum oil as compared to untreated rats. Sildenafil and thyroxine treatment alone also produced significant enhancement in the testosterone levels when compared to the positive control group. Sesamum oil at the three different dose levels produced significant increase in testosterone levels as compared to the positive control group. Maximum

Table 3. Effect of *Sesamum* oil on testosterone level

Group	Treatment	Testosterone (ng/mL)
I	Control (Distilled water treated)	264.80 ± 7.24
II	Positive control (Thyroidectomy without treatment)	21.67 ± 1.28
III	Sildenafil (35 mg/kg, served as standard) oral	63.86 ± 0.61**
IV	Thyroxine (10 µg/kg) oral	83.20 ± 2.52**
V	*Sesamum indicumin* oil (3 mL/kg) + Thyroxine (10 µg/kg) oral	120.8 ± 1.57***
VI	*Sesamum indicum* oil (2 mL/kg) oral	29.86 ± 2.35*
VII	*Sesamum indicum* oil (3 mL/kg) oral	34.29 ± 1.24*
VIII	*Sesamum indicum* oil (5 mL/kg) oral	36.49 ±6.70*

The statistical significance of difference between means was calculated by ANOVA followed by t-test for unpaired comparison (n=6). Values are expressed as Mean ± SEM, *P<0.05, **P<0.01, ***P<0.001 when treated groups compared with positive control group.

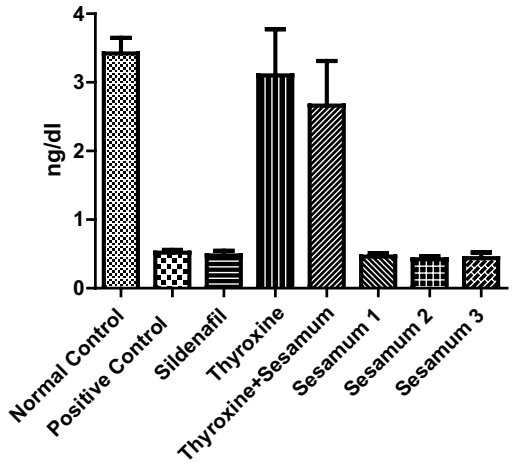

Figure 1. Effect of *Sesamum* oil on Tri-iodothyronine level in thyroidectomised rat.

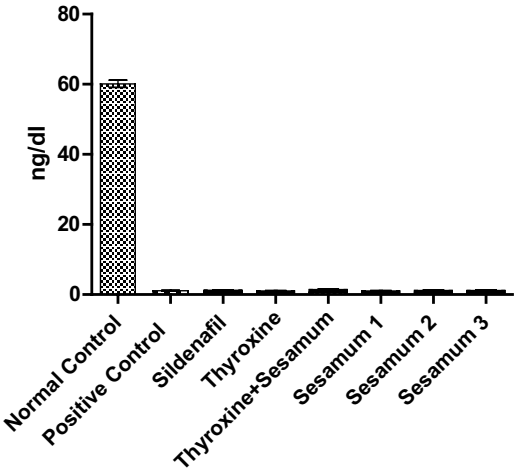

Figure 2. Effect of *Sesamum* oil on thyroxine level in thyroidectomised rats.

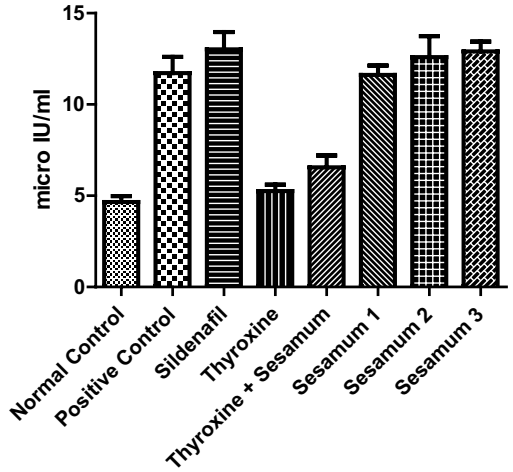

Figure 3. Effect of *Sesamum* oil on TSH level of thyroidectomized rat.

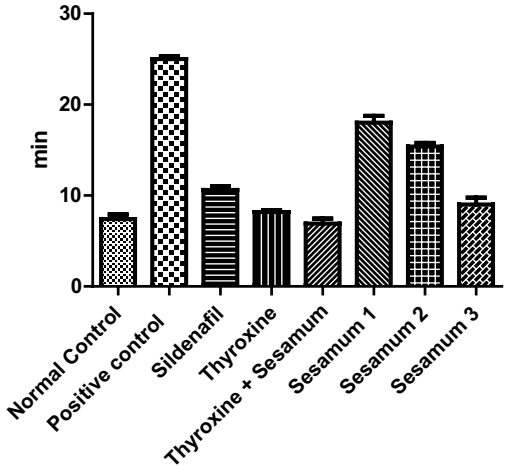

Figure 4. Effect of *Sesamum* oil on ML in thyroidectomised rat.

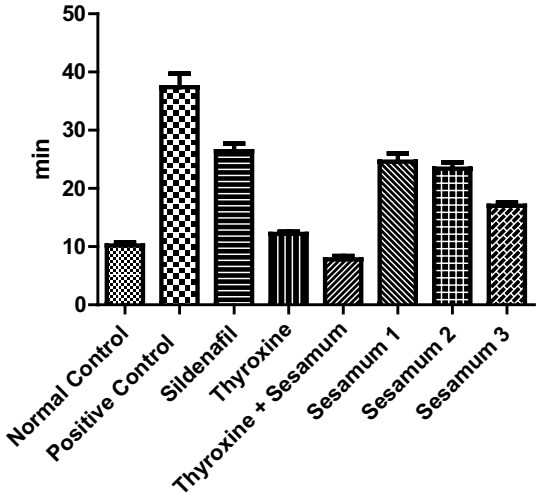

Figure 5. Effect of *Sesamum* oil on IL in thyroidectomised rat.

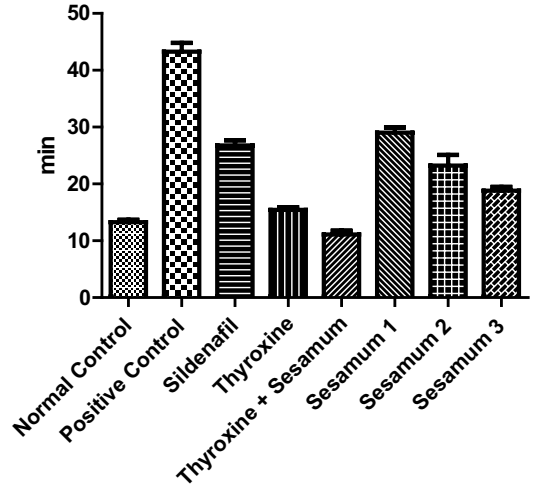

Figure 6. Effect of *Sesamum* oil on EL in tyroidectomized rat.

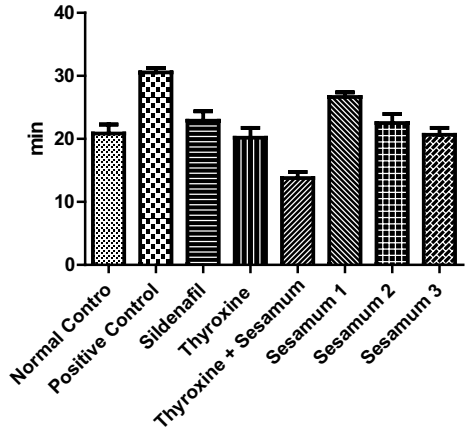

Figure 7. Effect of *Sesamum* oil on PEI in thyroidectomised rat.

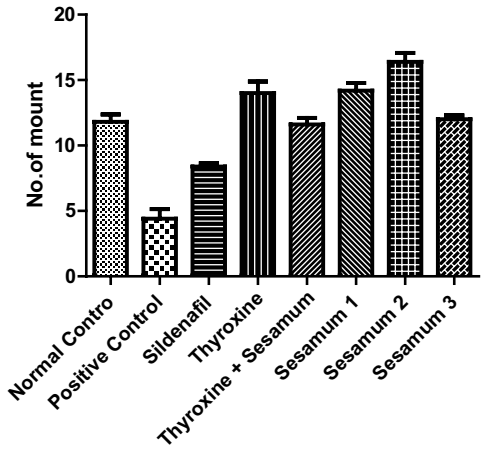

Figure 8. Effect of *Sesamum* oil on MF in thyroidectomised rat.

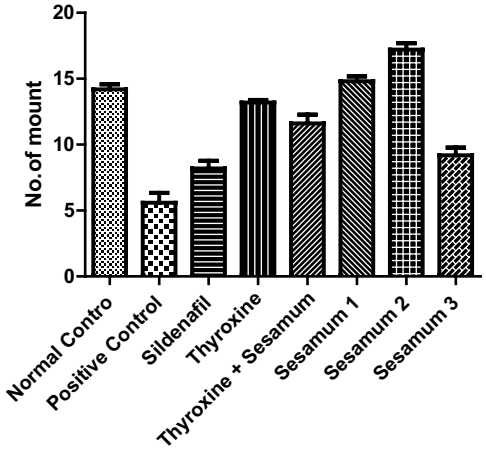

Figure 9. Effect of *Sesamum* oil on IF in thyroidectomised rat.

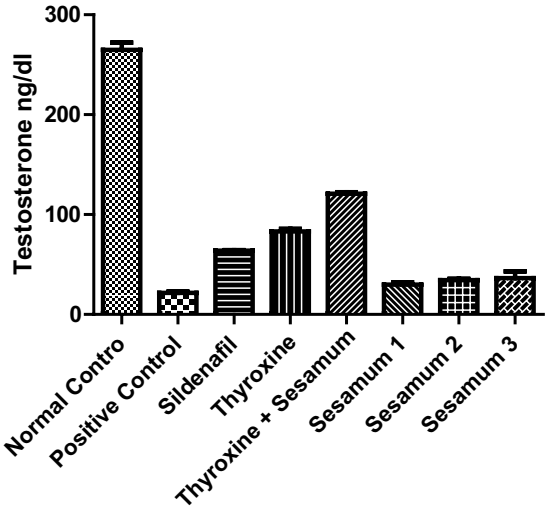

Figure 10. Effect of *Sesamum oil* on testosterone level in thyroidectomized rats.

enhancement in testosterone level was found in the group treated the combination of sesamum oil and thyroxine as compared to the positive control group (Table 3).

4. Discussion

The present study reveals that *Sesamum indicum* oil when fed to male rats induced into ED by thyroidectomy, the sexual activity was gradually improved. The oil, in combination with thyroxine, produced much better response.

During the stage of testicular development tri-iodothyronine (T3) is likely to control/send the major hormonal signals for the proliferation of Sertoli cells, and this ultimately alters the formation of adult Sertoli cell population [21]. The functions and development of Leydig cells are also regulated by thyroid hormones [22]. The above studies have shown that any major change in the status of thyroid gland will exert remarkable effects on the differentiation of Leydig cells in experimental animals [21]. The evidences obtained from different studies have suggested that thyroid hormones exert direct actions on androgen biosynthesis in Leydig cells [23, 24]

Hypothyroidism often results in decrease of luteinizing hormone (LH) levels. GnRH produced from hypothalamus induces release of LH. In conditions where the thyroid gland is hypo-active, LH is inadequate to stimulate testes to produce testosterone in males. This is the most

noticeable connection between the hypo-functioning of thyroid gland and decrease in the levels of testosterone. Therefore, in the present research thyroidectomy resulted in enhancement of ejaculatory latency and decrease of the number of ejaculations in male rats [25-28]. Therefore, there was decrease in MF, IF and EF as well as lengthening of ML, IL, EL and PEI confirming that sexual impairment of the animals has been accomplished. It has been proposed that before being declared sexually impaired the male rats must show a minimum of 25% reduction in sexual behaviors [29]. Therefore, the computed percentile alterations in these sexual behavior indices (more than 25% in each case) further suggest that sexual dysfunction was induced in the animals due to thyroidectomy. The loss of libido (as evidenced by reduction in MF, IF and EF) may be due to reduction of T3 activity. An increment in MF reflects sexual motivation, whereas a similar increase in IF and EF indicates the efficiency of erection, which involves adequate penile orientation and the ease by which ejaculatory reflexes are activated [30]. The reversal of sexual behavior as observed in control animals receiving distilled water suggest progressive enhancement of sexual behavior after administration of oil. It is worthy to note that the enhancement of sexual behavior in the oil-treated animals was more prominent with the highest dose, 5 mL/kg body weight. Best results were revealed when oil was administered in combination with thyroxine.

The pursuit of male animals towards the females suggested imminent copulation [31]. The pattern obtained for the ML and IL (indicators of sexual motivation) as well as EL (index of libido) and PEIk l (indicator of rate of recovery after exhaustion from the first series) following administration of the oil further corroborates enhanced sexual appetitive behavior in the animals. The extract progressively reversed sexual sluggishness in animals treated with sesamum oil and its combination with thyroxine altered sexual competence and may achieve complete reversal if the duration of exposure is extended beyond 28 days.

From the foregoing, it is seen that sesamum oil is capable of improving male sexual desire and arousal, potency and pleasure components of sexual behavior. The use of this model to study sexual stimulant activities of chemical compounds including plant oil may mimic disease-related sexual dysfunctions, since decrease in sexual behavior is mostly associated with reduced testosterone levels. The reduced levels of testosterone in the animals in the present study were however attenuated by the oil. Studies have shown that sexual behaviors could be enhanced by elevated testosterone levels probably via an increase in its metabolites such as Δ4-androstenedione, dihydrotestosterone and dehydroepiandrosterone and thus trigger effects enhancing libido [11, 32, 33].

Therefore, the improved sexual stimulant activity of the oil, especially the highest dose of 5 mL/kg body weight, could be attributed to the androgen increment. Overall, the present study has given credibility to the ethno-medical belief that *Sesamum indicum* seed oil would reverse sexual impairment in males. The best activity was observed with the highest dose of 5 mL/kg body weight and the activity was increased when given in combination with thyroxine.

5. Acknowledgement

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