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Thymus Vulgaris As A Regulatory Effect On Induced Hyperprolactenemia In Male Albino Rats

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ABSTRACT

The purpose of this study was to induce hyperprolactenemia in adult male albino rats and determine the regulatory effect of *Thymus vulgaris*. Methods: Thirty male albino rats 180-200gr, were used in this study group (1) (n=15) hyperprolactenemia was induced with S/Cinjections of 5 mg rat prolactin, biopotency (25IU/mg) in to divided doses daily for one week, group (2) (n=15) control group, were administered 0.1 ml saline S/C for one week, in two divided doses daily. *Thymus vulgaris* was administered orally 250mg/kg/bw for two months in Experimental group, while control administered placebo for two months. Prolactin, Testosterone, Nitrite were evaluated in all albino rats, before and after prolactin injections and after Thyme and placebo administration. Results: Prolactin injections induced hyperprolactenemia, decreased testosterone and nitric oxide, Thyme administration revealed improvement in testosterone and nitrite and decreased prolactin. Conclusion: Thyme could improve the fertility, sexual function of the male albino rats

KEYWORDS: *Thymus vulgaris*, prolactin, testosterone, nitrite, fertility, hyperprolactenemia, male albino rats.

INTRODUCTION

Hyperprolactinemia can suppress reproduction in male and female human and laboratory animals [1]. Researchers indicated some negative effects in male including dimished libidos and inability to maintain or obtain a normal erection, with a reduction in testosterone concentration [2,3]. Hyperprolactinemia, is a clinical hypothalamic- hypoplysis disorder, defined as an abnormally high level of prolactin in blood ($\geq$ 25ng/ml) for women and ($\geq$ 20 ng/ml formen) and is a no table effect of anti psychotic drugs [4] due to dopamine blocking action[5].

Clinical trials have demonstrated the beneficial effects of some drugs like Peony-Glycirrhiza Decoction (PGD) in alleviating antipsychotic induced hyperprolactinemia in schizophrenic patients [6], AS PGD suppress prolactin levels in MMQ cells, in volving modulating the expression of D_2 receptor (Dr D2) and dopamine transporter (DAT)./ The herbal medicine PGD is made from paeonia (Pr) and glycyrrhiza radices (GR) has been used to treat female ovulation disorders [7,8,9].

It is known that prolactin increase with age and testosterone levels decrease at the same time [10,11,12].

This is an indication that the role of prolactin may induce some adverse diseases in old ages. As Navalainen *et al* [13] showed that prolactin induces differentiation and proliferation in rat and human prostate.

So this study is a trial to use a herbal product *Thymus vulgaris*, as a regulatory effect on induced hyperprolactinemia in male albino Rats.

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As it is hypothesized that *Thymus vulgaris* might induce a regulatory effect on hyperprolactinemia male albino rats.

MATERIALS AND METHODS

1- Thymus vulgaris Preparation:

The raw *thymus vulgaris* was extracted and prepared in an extract solution of 250mg/kg body weight daily for administration for two months, to the albino rats.

Thirty adult male albino rats 180-200gr. were used in this study. Animals were housed in groups of two in plastic boxes and maintained on a 12h. light /dark cycle at 25°c +1°c with water and food available ad libitum

The rats were divided to two equal group. Control group (n=15) were administered 0.1 ml of saline subcutaneously for one week, in two divided doses daily. Experimental group (n=15), hyperprolactinemia was induced with subcutaneous injection of 5mg rat prolactin, biopotency (25IU/mg) in two divided doses daily for one week. After one week, blood was drawn from tailvein for hormonal prolactin and testosterone determinations together with nitrite level determination. *Thymus vulgaris* was then administered orally 250 mg/Kg body weight for two months. At the end of *Thymus vulgaris* administrations. Blood sample were collected and used to determine the concentration of prolactin, testosterone and nitrite concentration for each group.

Hormonal Assay:

Serum prolactin level was done by Elisa technique determined by commercial kit roche diagnostics. Data is expressed in ng/ml.

Serum testosterone was detected by enzyme linked immunosorbent assay method by commercial kit from Roche diagnostics. Data is expressed in ng/ml.

Serum Nitrite level was determined by Elisa method, nitrite is the stable oxidation of nitrite oxide, which correlates with the amount of nitric oxide.

Statistical analysis:

The obtained data were analyzed using the statistical analysis system SPSS program.

Mean and standard deviation were determined. Significance was assessed using student "t" test for analysis of hormonal differences. Significance was established at levels of $P<0.05$.

Table 1: Prolactin, Testosterone and nitrite before prolactin administration in control and experiment albino rats

Variables	Control		Experiment		"T"
	M	SD	M	SD	
Prolactin ng/ml	11.6	2.53	10.7	3.1	NS
Testosterone ng/ml	0.20	0.06	0.17	0.04	NS
Nitrite uμ	29.2	3.2	30.6	2.6	NS

P<0.05 The data revealed non significant changes in prolactin, testosterone and nitrite before prolactin administration

Table 2: Hormonal prolactin, Testosterone and nitrite determination after S/C prolactin injections for one week and in control albino rats

Variables	Control		Experiment		"T"
	M	SD	M	SD	
Prolactin ng/ml	11.8	24.3	61.3	21.6	S
Testosterone ng/ml	0.25	0.06	0.12	0.05	S
Nitrite uμ	26.5	1.3	17.6	1.8	S

P< 0.05 The data revealed a significant changes in prolactin, testosterone and nitrite.

Discussion:

The abnormal elevation of serum prolactin, referred as hyperprolactenemia, produces alteration in several reproductive parameters of male rats as penile erection or decreased tendency to reach ejaculation [14,15]. One of the main causes affecting prolactin levels and induced hyperprolactinemia is excessive stress, stress and the stress hormone cortisol increase inflammation which further increases free radical production [16].

Table (2, 3) revealed an elevated prolactin hormone concentration after prolactin administration for one week, where as the administration of thyme regulate prolactin levels and led to or decreased concentration after Thyme administration for two months.

Hyperpolactinemia was induced using different method namely prolactin, sulpiride, antipsychotic drugs therapy, a transplant of adenohypophysis (ADH) to the renal capsule, and other methods including stress. As stress situation increases stress hormones ACTH, catecholamines and cortisol which affect reproduction in turn and reproductive hormones [17,18,19]. Thyme also named oregano, is a plant herb rich in antioxidants, have been used in many research procedures that affect growth and reproductive stimulant of male and female human and lab animals [20,21]

Antioxidants, by ameliorating stress, produces a positive effect to different organs of the body, which decreases the oxidative stress, and regulate the normal body function through the control of the brain and hormonal action. So, oxidative stress may be encountered by antioxidants which affect health, growth and body functions including reproduction. Our finding supports Thyme as an effective agent against hyperprolactinemia and help to control reproductive hormones and help restoration of the reproductive system and hormones through improve health and decrease stress. This in turn help in restoration of testosterone and other reproductive agents as Nitricoxide. [22,23,24,25,26].

Table (2) revealed a decrease level of nitrite after induced hyperprolactinemia, then there was an observed elevation of nitrite after Thyme administration for two months, this indicated that thyme administration affect positively the elevation of nitrite.

This is in agreement with Chen and Lee [27] who suggested that Thyme might stimulate the release of nitric oxide from the endothelial cells and perivascular nitrergic nerves of the corpuss cavernosum. Nitric oxide activates guanylate cyclase in the cytoplasm of smooth muscle producing CGMP, which is the actual molecule responsible for relaxation of corpus cavernosum in a dose dependent manner. The relaxing effect of Thyme on corpus cavernosal tissue could be mediated by multiple action mechanisms including increasing the release of nitric oxide from corporal sinusoids, increasing the intracellular calcium sequestration that hyperpolarizing action [28].

Also, it is suggested that thyme, act as a nitric oxide donor induce the relaxation of rat corporal smooth muscle through L-arginine/nitriceoxide pathway. Moreover, it is confirmed that long action and administration of thyme potentiates the cavernosal relaxation provoked by acetylcholine and enhances erectile capacity.

That action is mediated by endothelium derived relaxing factor and peripheral neurophysiologic enhancement with an increase in intra cavernosal pressure, which is considered as a complex result of thyme on various systems of vascular endocrine and neural net work supplying the male reproductive organ [29].

Leaf *et al*. [30] reported that endogenous metabolism of nitric oxide in mammals has long been known to give rise to plasma and urinary nitrate and nitrite. As nitrite is the stable oxidation product of nitric acid, it is correlated with the amount of nitric oxide produced. The level of nitrite is considered as an indicator for nitric oxide concentration.

Many studies consider the thyme administration as an effective stimulant of the male reproductive system help in better semen quality and stimulate male reproductive organs secretion and help to reduce the negative effect of hyperprolactinemia through a natural and safe product [31,28].

Table (2) Revealed that prolactin administration induced hyperprolactinemia in albino rats and decreased testosterone secretion, while Thyme administration elevated testosterone concentration in hyperprolactenemia induced albino rats (Table 3).

Rehman *et al*. [32] reported that hyperprolactinemia is both diminished libido and inability to either obtain or maintain a rigid erection. Although testosterone levels are usually reduced in hyperprolactinemia state correction of the low testosterone with administration of intramuscular testosterone does not correct the erectile abnormality. hyperprolactinemia stimulates dopamine and oxytocin release that may have a role in orgasm. However, it is known that hyperprolactinemia markedly increased dopamine synthesis, turnover, and release, from neurons of the hypothalamus [33,34].

Hyperprolactinemia also caused marked increases in the expression of tyrosine hydroxilasem RNA in the hypothalamus arcuate and periventricular nuclei and the zona incerta [35]. The hypothalamus is the region of the brain associated with sexual and erectile function [36]. Yuan *et al*. [8] stated that a great proportion of patients show improvements on risperone – induced adverse effects associated with hyperprolactinemia after Peony-Glycyrrhiza Decoction (PGD) administration. Further in Vitro and in Vivo experiments demonstrate that the hyper level of prolactin in mmQ cells and hyperprolactinemia rat model is significantly reduced after PGD administration [37].

Vekeman and Robyn [38] reported the prolactin increase in men with old age together with decreased testosterone. Some researches has demonstrated the same changes in rat prolactin [39,40]. These results are in agreement with the data presented in our study, which link a relationship between the hyperprolactinemia induced rat with the decreased testosterone level. The data presented in our study, also revealed that thyme administration for two months correct the testosterone levels and induce a significant increased in testosterone which help in restoration of the reproduction ability of the lab animals. This may confirm the effectively suppression effects of thyme on hyper level of prolactin in vivo experiments. Some reports indicated the effectiveness of thyme in reproduction of male animals, which may help as antiprolactin action [19].

Conclusion:

It might be concluded that *Thymus vulgaris* (Thyme) can act as a regulatory agent on induced hyperprolactinemia in male albino rats leading to suppression effects of thyme on hyperprolactin level, which seems to be used as an effective agent against hyperprolactinemia.

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