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The Effect of Grape Leaf (*Vitis vinifera* L.)Aqueous Extract on LH FSH, PRO, and PRL Levels in Rabbit Females Having Hyperthyroidism

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Abstract
Grape leaf extract (GLE) are very potent antioxidant and exhibit numerous interesting pharmacologic activities, including an antioxidant property, and has been suggested to be of use in treatment of several disease. Our objective are to investigate the protective and therapeutic effect of GLE against levothyroxine sodium – indused hyperthyroidism in rabbit. Femal oryciolagus cuniculus rabbits were divided into four groups: the 1 st group, rabbits were orally administered (using a feeding solution)with daily dose(5 mL distilled water)for two months, the 2nd group, the rabbits were treated with levothyroxine sodium (50 µg/kg b.w, body weight)for one month. The 3rd group, the rabbits were treated with GLE(100mg/mL) for one month and group 4th the rabbits were treated with GLE(100mg/mL) for two months . The level of LH,FSH, PRO and PRL were evaluated in blood. The result indicated that the administration of levothyroxine sodium (50µg/kg b. w) induced a significant decrease in LH, FSH, PRO and a significant increase in PRL. Also the obtained data showed significant increase in LH, FSH, and PRO while PRL showed significant decrease of treated (G3) which received GLE compared with animal group that received levothyroxine sodium (G2). This is may be the presence of proanthocyanidins and procyanidins which have antioxidant and free radical scavenging activities. The result suggests that grapleaf extract may prevent levothyroxine sodium induced hyperthyroidism.
Keyword: Grape leaf extract(*Vitis vinifera* L.), Levothyroxine sodium, LH, FSH, PRO, PRL.

INTRODUCTION

Didem et al., [1] Grape leaf or *Vitis vinifera* L. (Vitaceae) is a deciduous woody climber with coiled climbing tendrils and large leaves. It has small, pale, green flowers in the summer followed by bunches of berry fruits that range from green to purple-black.

Lardos et al., and Monagas et al., [2][3] The grape has been used in folk medicine for its biological activities since ancient times.The leaves of the plant, which have astringent and haemostatic properties, are used in the treatment of diarrhea, hemorrhage, varicose veins, hemorrhoids, inflammatory disorder, pain, hepatitis, and free radical related diseases.

Nilufer et al., [4] The juice of the leaves has been also recommended as an antiseptic for eye wash.

Felicio et al., [5] Some of above cited disease could be related to viral or bacterial agents. Furthermore, in recent years, the leaves are used in the formulation of dietary antioxidant supplements.

Dimple et al., [6] Levothyroxine sodium is the monosodium salt of the levorotary isomer of thyroxine. Levothyroxine (T4) is a naturally occurring hormone produced by the thyroid gland and converted to the more active hormone triiodothyronine (T3) in peripheral tissues[6]. The precise signals controlling the conversation of T4 to T3 within the cell are not known.

Babych et al,. [7] The nervous system they increase the resting or basal metabolic rate of the whole organism and have stimulatory effects on the heart, skeletal muscle, liver and kidney. Thyroid hormones enhance lipolysis and the utilization of carbohydrate.

Nagataki et al,. [8] Thyroid hormone affect every cell in the body. Many things affect the thyroid and its hormones. Achieving thyroid balance involves consideration of ovarian and adrenal hormones, stress levels, possible antibody attacks, and inheritance of enzymes with reduced levels of efficiency.

Shilpi et al,. [9] The thyroid hormones themselves affect body temperature, energy, thinking, metabolic rate, weight, bowel function, menstrual cycles, fertility, hair growth and appearance.

Ragender et al,. [10] The possible symptoms from mild thyroid imbalance are so varied that they can often be overlooked or misdiagnosed, especially if the blood work-up is incomplete. Because of the loss of Progesterone production, as women enter the menopausal transition, they are especially susceptible to low thyroid symptoms. In many patients, very small amounts of thyroid supplementation can make a huge difference in achieving thyroid balance and health.

The aim of this report is to assess the preclinical and clinical available data on Grape leaf aqueous extract on LH, FSH, PRO and PRL hormones.

MATERIALS AND METHODS

PLANT MATARIAL

The leaves of healthy Grape under investigation were purchased from a local market at Baghdad, Iraq.

PREPARATION OF GRAPE LEAF EXTRACT

Powdered plant material (25 g) was extracted with distilled water (250 mL) by stirring in a 60 °C for 3hr.The extract was filtrated and the filtrates were pooled. The extract was stored in refrigerator until used. The Grape leaf extract was administration orally to the experimental animals in a dose of (5 mL rabbit of (1.5-2)kg).

INDUCTION OF HYPERTHYROIDISM

The Hyperthyroidism was induced in experimental rabbit females by oral administration of levothyroxine sodium (50µ/(1.5-2)kg body weight)in a freshly prepared (tablet dissolve in water or food).

CHEMICAL AND DRUG

Kosasa [11] ,Wennink et al,. [12] ,Fraser et al,. [13], Bauman[14] The levothyroxine sodium was purchased from Al-sophee Pharma, Baghdad, Iraq. The levels of LH, FSH, PRL, and PRO were assayed by using ELSA (Human Germany), supplied from Monobind Inc.

ANIMLAS

Female oryciolagus cuniculus rabbits (1.5-2 kg) were purchased from the Laboratories of city of medicine, (Baghdad, Iraq) were used in the experiments. Prior to the experiments, rabbits were fed with multivitamin, vegetables, and wheat. The animals were kept on standard laboratory dite, and under the same hygienic conditions. 9 animals were used for each group of study.

Group I: Normal control rabbits received with standard fed and water for 2 months.

Group II: Rabbits were orally fed 50µg of levothyroxine sodium once daily for one month.

Group III: Rabbits were treated with GLE (100mg/mL) for a period of one month.

Group IV: Rabbits were treated with GLE(100mg/mL) for two months

The blood samples were collected from the rabbit heart using heparinized capillary tube. Serum was separated by centrifugation at 2000 rpm for 10 min.

Statistical analysis: All statistical analysis of the study were done using SPSS version 15.0 for Windows (statistical Package for Social Science, Inc., Chicago, IL, USA).

Descriptive analysis was used to show the mean ± standard deviation of variables. The significance of difference between mean values was estimated by Student T- test. The probability $p< 0.05$ = significant.

RESULTS AND DISCUSSION

Results are given in table (1). In the present study, in hyperthyroidism group (G2) the mean value of LH, FSH, PRO and PRL were found to be 2.70 ± 0.08 U/L, 3.35± 0.41 U/L, 6.41±0.10ng/mL and 6.30±0.43 ng/mL respectively. In treatment group (G3) the LH, FSH, PRO and PRL were 4.24± 0.11 U/L, 5.66± 0.15 U/L, 7.81± 0.28 ng/mL and 2.45±0.18 ng/mL. The results show that mean LH, FSH, and PRO levels in hyperthyroidism group (G2) are significantly lower as compared to control rabbits group, but PRL level is significantly higher in hyperthyroidism group as compared with control group. The treatment group (G3) with GLE showed the significant highest of LH, just significant of FSH, and PRO but PRL showed the significant lowest mean level.

Table(1): Mean values of blood LH, FSH, PRO and PRL levels in rabbit females

	Control G1	L.Thyroxine sodium 1 month G2	L.Thyroxine sodium +Plant extract 1 month G3	L.Thyroxine sodium+Plat extract 2 month G4	p-value			
	Mean±SEM	Mean±SEM	Mean±SEM	Mean±SEM	G2vs. G1	G3,s. G1	G4vs. G1	G4vs. G2
LH U/L	5.47± 0.14	2.70 ± 0.08	4.24± 0.11	4.97 ± 0.17	0.0001**	0.0001**	0.05*	0.0001**
FSH U/L	6.13 ±0.07	3.35± 0.41	5.66± 0.15	6.23 ± 0.15	0.0001**	0.01*	N.S	0.0001**
PRO ng/mL	6.76±0.13	6.41±0.10	7.81± 0.28	8.85±0.13	0.05*	0.001*	0.01*	0.0001**
PRL ng/mL	4.05±0.22	6.30±0.43	2.45±0.18	1.37±0.12	0.0001**	0.0001**	0.0001**	0.0001**

SEM: Mean standard error,** P=<0.0001 (highly significant),* P = <0.05(significant), P=>0.05(N.S=No. significant)

Capuco et al,. [15] No other hormone affects such wide range of cells and tissues as thyroid hormones. Thyroid hormones are responsible for regulation of oxygen consumption, thermogenesis and lipogenesis[.

Paulus et al,. [16] In our study showed that the levels of LH, FSH and PRO were decrease in Hyperthyroidism as compared to control rabbits group.

Ruiz et al,. [17] These finding agree with previous studies referred to decrease LH, FSH, and PRO levels can be attributed to a direct effect of thyroid hormones on pituitary LH,FSH and PRO production.
Idris et al,. [18] Hyperthyroidism or thyrotoxicosis is characterized by an increase in serum TSH.

Jannini et al,. [19] Hyperthyroidism induced alteration in the reproductive system such as altered levels of LH and FSH and also altered ratio in laboratory animals and human.

Neepa et al,. [20] Hyperthyroidism in adult's female humans and rats is associated with altered levels of LH. Alteration in sex steroid metabolism and increased incednces of oligomenorrhea and amenorrhea also are noted in humans.

Frisch et al,. [21] In addition these findings are mentioned to administration of levothyroxine (T4) stimulate increase level of PRL from the anterior pituitary. Disorders of the hypothyalamus or the pituitary stalk (infiltrations, inflammations, mass lesions) may therefore result in increased PRL concentration.

Sathi et al,. [22] Previous reprte mentioned that the changes in serum levels of PRL and PRO may be caused the levothyroxin treatments and play a role in the alterations previously observed.

Abeer [23] The present study referred that the effect of aqueous extract of Grape leaf (GLE) on hormones shows the rise levels in LH, FSH, and PRO but low level of PRL . This changes in levels of hormones could be attributed to Grape leaf aqueous extract (GLE) contains polyphenols including proanthocyanidins and procyanidins that showed antioxidant and free radical scavengers.

Leelavinothan et al,. [24]And may be GLE play a regulatory role in sex hormones. Because GLE exhibit a wide range of biological effects, including antioxidant and enzyme-modulating action and anti-allergic, anti-atherosclertic, antithrombotic, antiviral, anticarcinogenic, antispasmodic, and diuretic effect.

Resch et al,. [25] Previous reports showed that both hyper- and hypothyrodisim are associated with increased oxidative stress.

Dobrzynska et al,. [26] Incases of thyrotoxicosis, part of sustained injury to various body tissues is attributed to oxidative damage therefore can be inhibited effect of excess of oxidative stress by treatment of Grape leaf Aqueous extract.

Puiggros et al,. [27]Recently, there is great evidence that GLE prevents oxidative injury by modulating the expression of antioxidant enzyme systems .

CONCLUSION

The results indicated that levothyroxine used for inducing hyperthyroidism was effective. Grape leaf aqueous extract has change the levels of LH, FSH, PRO ,and PRL. It has therapeutic action this may be due to including an antioxidant property, and has been suggested to be of use in treatment of several disease.

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