

Effect of *Trigonella*, *Allium Sativum* and Their Mixture on Some Physiological Parameters in Hyperthyroidimic Rats

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ABSTRACT

Background: alterations in the level of hormones including thyroid hormones lead to physiological/ clinical abnormalities. **Aim of work:** this study aimed to illustrate the protective effect of *Trigonella*, *Allium sativum* or their mixture against hyperthyroidism induced by L-thyroxin in male albino rats. **Materials and methods:** thirty albino rats were divided randomly into five groups. **Group A:** healthy rats, **Group B:** normal rats were subcutaneously injected with 500 µg/kg body weight L-thyroxin once daily for two weeks to induce hyperthyroidism, **Group C:** hyperthyroid rats received oral dose of 250 µg/kg body weight/day *Trigonella* extract. **Group D:** hyperthyroid rats received oral dose of 250 µg/kg body weight/day *Allium sativum* extract. **Group E:** hyperthyroid rats received mixture of *Trigonella* and *Allium sativum* extract. At the end of the experiment. Blood samples were collected for biochemical analysis. **Results:** hyperthyroid rats had significant increase ($P < 0.05$) in serum levels of triiodothyronine (T_3), thyroxin (T_4), TG, VLDL, AST, ALP, BUN and uric acid as well as a significant decrease in TSH, LDL, HDL, LDL/HDL and TC, total protein and percentage of body weight change compared to the normal control group. Oral administration of these extracts ameliorated most of the tested parameters.

Conclusion: This study concluded that *Allium sativum*, *Trigonella* or their mixture have a protective effect against hyperthyroidism

Keywords: hyperthyroidism, *Trigonella*, *Allium sativum*.

INTRODUCTION

Thyroid hormones regulate almost all functional aspects of the body, including metabolic, respiratory, cardiovascular, nervous and reproductive functions, either directly or indirectly⁽¹⁾. Alterations in the level of these hormones lead to physiological and clinical abnormalities, such as hypothyroidism and hyperthyroidism that alters basal metabolic rate and causes many health problems. Hyperthyroidism is the result of excess synthesis and release of thyroid hormone. Thyrotoxicosis is the hyper metabolic state associated with elevated levels of free thyroxin (fT_4) or free triiodothyronine (fT_3) or both. There has been a tendency among researchers in attempting to treat disorders by replacing chemical drugs with some natural plant components⁽²⁾. Despite the fact that day-by-day herbal drugs are gaining much importance for their affordable and safe nature, scientific investigations towards the mitigation of thyroid disorders by the plant extracts increased⁽³⁾. Therefore, this study is an endeavor to find out a plant extract that can regulate the levels of both of the thyroid hormones. As a member of the Liliaceae family, garlic is one of these plant products, traditionally used for its cytotoxic, antitumor, antifungal, antibacterial, antiviral and anti protozoal properties. Furthermore, in the ancient Indian medicine, garlic is

recommended for the treatment of hemorrhoids, rheumatism, dermatitis, abdominal pain, cough and leprosy⁽⁴⁾. *Allium sativum* (garlic), contains various substances including minerals, carbohydrates, proteins, fats and vitamins. Among many different compounds⁽⁵⁾ found in garlic, studies suggest that biological and pharmacological effects of this plant are mainly due to its sulfur compounds. Some of these organo-sulfur compounds are aliiin, alliin, ajoene, allylpropyl disulfide, diallyltrisulfide, sallylcysteine, vinylidithiines, S-allylmercaptocystein, and others⁽⁶⁾. Fenugreek is one of the most widely used plants in various indigenous systems of medicine for the treatment of different ailments. *Trigonella foenum-graecum* is used in medicine to kidneys, disperse cold and alleviate pain. Raw fenugreek seeds early in the morning with warm water before brushing the teeth has healing effect on joint pains, without any side effects⁽⁷⁾. Other medicinal uses of *Trigonella foenum-graecum* include its use as antiulcer, wound healing, CNS stimulant, antioxidant, antidiabetic, anti-neoplastic, anti-inflammatory and anti-pyretic drugs. Fenugreek seed contains 45-60 % carbohydrates, mainly mucilaginous fiber (galactomannans); 20-30% proteins high in lysine and tryptophan; 5-10 % fixed oils (lipids); pyridine-type alkaloids, mainly

trigonelline (0.2-0.3 %), choline (0.5 %), gentianine, and carpaine; the flavonoids apigenin, luteolin, orientin, quercetin, vitexin, and isovitexin; free amino acids, such as 4-hydroxyisoleucine (0.09 %); arginine, histidine, and lysine; calcium and iron; saponins (0.6-1.7 %); glycosides yielding steroidal saponinins on hydrolysis cholesterol and sitosterol; vitamins and nicotinic acid; and 0.015 % volatile oils⁽⁷⁾. It is a general belief that a synergism between two or more plant extracts enhances the physiological potential of the bioorganic substances. Therefore, a combination of different plant extracts is very often preferred over single extract. In folk medicine *Trigonella foenum graecum* (TFG) and *Allium sativum* (AS) extracts are used to treat hyperthyroidism⁽⁸⁾. So, this study aimed to evaluate the possible synergistic effects of these extracts on thyroid hormones and other physiological parameters which influence by hyperthyroidism⁽⁸⁾.

MATERIALS AND METHODS

Preparation of the extracts

1-*Allium sativum*

Fresh cloves of *Allium* were peeled, and slurry made with the help of an electrical grinder and left overnight. It was filtered through cheesecloth and lyophilized to yield a free-flowing dry powder.

2-*Trigonella*

Dry *Trigonella* seeds were pulverized with the help of an electric grinder and the powder was extracted using 20% ethanol by the cold percolation method, then filtered. Ethanol was evaporated and the extract was lyophilized to obtain a powder (Herb: Extract ratio – 8:1). The extracts were dissolved in double-distilled water for oral administration.

Animals and treatment

Experimental Animals:

This experiment was carried out on 30 male Swiss albino rats weighing 100–120 g that were obtained from the Animal Farm of El-Nile Company for Pharmaceutical Products (El-Nile, Cairo, Egypt). Rats were housed in metallic cages and maintained under standard conditions of temperature, humidity and normal light/dark cycle along the experimental period. Rats were left to acclimatize for one week before starting the experiment.

Experimental Design:

In the current study, 30 male Swiss albino rats maintained on a standard pellet diet and tap water

add libitum and divided randomly into five equal experimental groups (6 rats in each group) as follows: **Group I** (Control group) normal rats. **Group II** (hyperthyroid group): rats were injected subcutaneously with 500 µg/kg body weight of L-thyroxine daily for 15 successive days.

Group III (L-Thyroxin + *Trigonella foenum-graecum* (TFG)): rats were injected subcutaneously with L-thyroxin (500 µg/kg body weight) as group II and administered orally with 500 mg/kg body weight of TFG alcoholic extract ten minutes after L-thyroxin injection for 15 days.

Group IV (L-thyroxin + *Allium sativum*, AS): rats were injected subcutaneously with L-thyroxin (500 µg/kg body weight) as in group II and administered orally with 220 mg/kg body weight of AS alcoholic extract. Extract was administered ten minutes after L-thyroxin injection for 15 days.

Group V (L-Thyroxin + Mixture of AS + TFG extracts): rats were injected subcutaneously with L-thyroxin (500 µg/kg body weight) and orally administered a mixture of AS and TFG extracts. Mixture extracts was administered ten minutes after L-Thyroxin injection, for 15 days.

All the treatments were given between 9.00 and 11.00 a.m. of the day to avoid circadian variation and were continued for 15 days.

Body weight measurement:

Body weight was recorded weekly beginning on zero time (the time prior to treatment) and continued until the end of the treatment.

Blood sample collection:

At the end of the experimental period, rats anesthetized by ether, and blood samples were collected from retro-orbital sinus after overnight fasting. Blood was collected and serum was separated by centrifugation (at 2500 rpm for 15 minutes at room temperature) to estimate biochemical parameters.

Biochemical analysis

Assessment of biochemical parameters:

In the present study total protein (TP) and albumin concentrations were estimated, then serum globulin concentrations were calculated according to the formula:

$$\text{Globulin (g/dl)} = \text{total protein (g/dl)} - \text{albumin (g/dl)}$$

Serum concentration of aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, and BUN as well as lipid profile that includes total cholesterol, triglycerides and high-density lipoprotein

cholesterol (HDL-C). Also, concentrations of TSH and thyroid hormones (T3 and T4) and testosterone were measured. All parameters were estimated using Bio Merieux SA kits, France.

The ratio of serum albumin/ globulin was determined. However, ratios of TC/HDL (risk factor 1) and LDL/HDL (risk factor 2) were also calculated after estimation of serum LDL-C (low-density lipoprotein cholesterol) and VLDL (very low-density lipoprotein cholesterol) using the Friedwald's and Norbert formulas, respectively as following:

Friedewald's equation: $LDL \text{ (mg/dl)} = TC - \{HDL + [TG/5]\}$.

Norbert equation: $VLDL = TG/5$

Statistical analysis:

The results were expressed as Mean \pm SE. Data were analyzed by using the Statistical Package (SPSS) program, version 20 and t test. The Bonferroni test was used as a method to compare significance between groups. **The study was approved by the Ethics Board of Al-Azhar University.**

RESULTS

Body weight: animals that received L- thyroxin have a highly significant decreased in body weight ($p < 0.001$), while those treated with *Trigonella*, *Allium sativum* or the mixture showed insignificant changes as compared to control rats (Table 1).

Hormones:

The data in table (1) show that T_3 , T_4 significantly increased ($p < 0.05$), serum TSH significantly ($p < 0.05$) decreased in hyperthyroid rats, accompanied with insignificant change in testosterone level when compared to control rats. Plant extract treated rats show that T_3 , T_4 , TSH and testosterone levels recorded insignificant change in all treated groups when compared to control group.

Lipid profile:

T_4 produced a significant decrease ($p < 0.05$) in HDL level. There was a significant increase ($p < 0.05$) in TG levels while there was insignificant change in TC, LDL, VLDL, TC/HDL, LDL/HDL as compared to control group. *Trigonella* extract group recorded a highly significant decrease ($p < 0.05$) in TC, LDL and a significant increase ($p < 0.05$) in TG. Meanwhile, an insignificant change in HDL, VLDL, LDL/HDL and TC/HDL were recorded as compared to control rats. In *Allium sativum* group, there was a highly

significant decrease ($p < 0.01$) in TC and LDL as well as a significant increase ($p < 0.05$) in HDL. While, insignificant change in TG, VLDL, TC/HDL, LDL/HDL as compared to control rats. Administration of a mixture recorded a highly significant decrease ($p < 0.01$) in TC, LDL and a significant increase ($p < 0.05$) in HDL. In significant changes were obtained in TG, VLDL, TC/HDL and LDL/HDL as compared to the control group (Table 3).

Liver functions:

The data in table (4) revealed insignificant change in serum ALT activity, and significant increase ($p < 0.05$) in AST and ALP activities in hyperthyroid group as compared to the control rats. Treatment of hyperthyroid rats with *Trigonella*, *Allium sativum* and mixture extracts recorded insignificant change in ALT, AST, ALP levels when compared to control rats (table 4).

Kidney functions:

The data in table (5) showed that there was insignificant change in serum creatinine level while a significant increase ($p < 0.05$) in serum uric acid and a highly significant increase ($p < 0.01$) in serum BUN in hyperthyroid group. Treatment of hyperthyroid rats with *Trigonella* extract showed that there was insignificant change in serum creatinine while a significant increase ($p < 0.05$) in serum BUN and uric acid in comparison with control group. Treatment of hyperthyroid rats with *Allium sativum* extract showed that there was insignificant change in serum creatinine, BUN and a significant increase ($p < 0.05$) in serum uric acid in comparison with control group. Mixture of the extracts improved the disturbance occurred in the activity of these parameters, where they showed insignificant change when compared to control rats.

Protein profile:

The present study showed that administration of thyroxin to normal rats significantly ($p < 0.05$) decrease the total protein value and showed insignificant change in albumin, globulin and albumin/globulin ratio levels as compared to control rats. Administration of *Trigonella*, *Allium sativum* or mixture extracts recorded insignificant change in the concentration of these parameters as compared to control group (Table 6).

Table (1): Percentage of body weight change

Parameter	Control	hyperthyroid rat	Trigonella	Allium sativum	mixture
Body weight	2.5±0.6	-3±0.8**	2.3±0.6	2.6±0.5	2.9±0.5

Values represent mean ±SE (standard error). (P* $<$ 0.05, P** $<$ 0.001 as compared to control group).

Table (2): Changes in the TSH, T3, T4 and Testosterone levels in the control and treated groups

Group Parameter	Control	hyperthyroid rat	Trigonella	Alliumss ativum	Mixture
TSH(μ u/dl)	3±0.1	1.9 ±0.4*	2.2 ±0.4	2.6±0.3	2.9±0.5
T3(ng/dl)	1.9±0.1	6.5±1.5*	3.5±1.5	3 ±1.2	2 ±0.9
T4(μ g/dl)	5.5±0.5	11±1.6*	6.6±0.7	6±1.1	5.7±0.7
Testosterone(ng/dl)	3.6±0.3	4±0.4	3.9±0.1	3.86±0.2	3.5±0.9

Values represent mean ±SE (standard error). (P* $<$ 0.05, P** $<$ 0.001 as compared to control group).

Table (3): Changes in the lipid profile in the control and treated groups

Group Parameter	control	hyperthyroid rat	Trigonella	Allium Sativum	MIXTURE
T C (mg/dl)	74±0.9	72±0.6	69±0.5**	68±0.6**	67±0.7**
T G (mg/dl)	65±0.8	69±0.9*	67.8±0.7*	66±0.4	65±0.6
HDL (mg/dl)	40±0.9	36±1.43*	41±0.6	42±0.2*	43±0.2*
LDL (mg/dl)	21±0.5	22.2±0.2	14.6±0.7**	12.4±0.6**	10.6±0.2**
VLDL (mg/dl)	13±0.5	13.8±0.2	13.5±0.5	13.2±0.7	13±0.9
LDL/HDL (mg/dl)	0.52±0.1	0.61±0.3	0.35±0.1	0.29±0.2	0.24±0.4
TC/HDL(mg/dl)	1.85±0.4*	2±0.3	1.68±0.1	1.61±0.2	1.5±0.1

Values represent mean ±SE (standard error). (P* $<$ 0.05, P** $<$ 0.001 as compared to control group).

Table (4): Changes in the ALT, AST and ALP levels in the control and treated groups

Group Parameter	Control	hyperthyroid rat	Trigonella	Allium sativum	Mixture
ALT (U/L)	22.5±1.1	26±1.5	24.6±1.2	24.3±1.1	23±1.1
AST (U/L)	35.5±1.1	40±1.1*	38.1±1.3	37±1.5	35±1.3
ALP (U/L)	61±1.2	66±1.2*	64.3±1.2	63±1.1	61.4±1.3

Values represent mean ±SE (standard error). (P* $<$ 0.05, P** $<$ 0.001 as compared to control group).

Table (5): Changes in the BUN, creatinine and uric acid levels in the control and treated groups

Group Parameter	control	hyperthyroid rat	Trigonella	Alliums sativum	Mixture
BUN (mg / dl)	18.2 ±0.5	22±0.2**	20±0.5*	19±0.8	18.4±0.7
Creatinine (mg / dl)	0.4±0.1	0.35±0.01	0.28±0.03	0.3±0.01	0.4±0.03
Uric acid (mg / dl)	4.0±0.86	6.80 ±1.67*	5.4±0.1*	5.3±0.5*	4.6±0.35

Values represent mean ±SE (standard error). (P* $<$ 0.05, P** $<$ 0.001 as compared to control group).

Table (6): Changes in the total protein, albumin, globulin, albumin/globulin and albumin/creatinine levels in the control and treated groups

Group Parameter	control	hyperthyroid rat	Trigonella	Allium sativum	Mixture
Total protein (g/dl)	6.3±0.18	5.2±0.3*	5.9±0.1	6.1±0.3	6.4±0.59
Albumin (g/dl)	3.4±0.2	2.5±0.4	2.9±0.13	3±0.15	3.5±0.9
Globulin (g/dl)	2.9±0.2	2.7±0.01	3±0.5	3.1±0.3	3±0.1
Albumin/Globulin	1.17±0.1	0.9±0.13	0.9±0.13	0.96±0.14	1.2±0.2

Values represent mean ±SE (standard error). (P* < 0.05, P** < 0.001 as compared to control group).

DISCUSSION

Hyperthyroidism is a term for overactive tissue of the thyroid gland, resulting in overproduction and excess of circulating free thyroid hormones thyroxin (T4), triiodothyronine (T3), or both. Human hyperthyroidism is accompanied by multiple abnormalities with increased energy expenditure and excessive mobilization and utilization of metabolic substrates⁽¹⁾. *Trigonellaseed* is rich in galactomannan, young seeds mainly contain carbohydrates and sugar. Mature seeds contain amino acids, fatty acids, vitamins, saponins and large quantity of folic acid. The main chemical constituents of *T. foenum-graecum* are fibers are flavonoids, polysaccharides, saponins, flavonoids and polysaccharides, fixed oils and some identified alkaloids⁽⁹⁾. Meanwhile, garlic contains at least 33 sulfur compounds, several enzymes, 17 amino acids, and minerals such as selenium. It also contains a higher concentration of sulfur compounds than any other *Allium* species. The sulfur compounds are responsible both for garlic's pungent odor and many of its medicinal effects⁽¹⁰⁾. One of the most biologically active compounds, *allicin* (diallylthiosulfinate or diallyl disulfide) does not exist in garlic until it is crushed or cut injury to the garlic bulb, then the enzyme *allinase* is activated which metabolizes *alliin* to *allicin*. *Allicin* is further metabolized to *vinyl dithiols*. This breakdown occurs within hours at room temperature and within minutes during cooking. *Allicin*, which was first chemically isolated in the 1940's, has antimicrobial effects against many viruses, bacteria, fungi and parasites⁽¹¹⁾. Goitrogens found in many plants are hydrolyzed to ultimate goitrogens which mostly inhibit the biosynthesis of thyroid hormones by blocking the coupling of *iodotyrosine* and *iodination* of *monoiodotyrosine*. Some of these goitrogens include *sulphurated organic compounds*

such as *sodium thiocyanate*, *thioglycosides*, *cyanogenic glucosides* and *aliphatic disulphides* known to be present in *Alliums*. In this study, treatment with **L-thyr oxin** led to a significant reduction in animals body weight, however *Allium sativum* extract returned the weight nearly to the control value due to the beneficial effects of *allicin*. *Fenugreek aqueous extract* exhibited an increase in rat's body weight that may be related to its antioxidant property which protects the functional organs and increase body weight. In the present study, increased plasma T3 and T4 levels and decreased in TSH levels were observed in the hyperthyroid animals induced by thyroxin. The administration of garlic extract caused depression in the level of triiodothyronine (T₃) and thyroxin (T₄) with an increase in TSH levels in the experimental animals. *Allium* must have interfered with the oxidation and subsequent incorporation of the iodine present⁽¹²⁾. *Alliums* are known to contain chemical group, *disulphides*, *sulphur* and *thio group* that probably act through a similar mechanism to displace the *iodide ions* present in the thyroid follicle thereby stalling *iodination* and lead to a depression in the serum levels of T3 and T4⁽¹³⁾. *Trigonella* have been known to interfere with thyroid hormone homeostasis at various levels, e.g. binding of TSH-receptor, thyroid-iodide transport, thyroid hormone secretion from the gland and extrathyroidal 5'-monodeiodination of hormones that may be the cause of thyroid hormone decrease.

As thyroid dysfunction has a great impact on lipids as well as a number of other cardiovascular risk factors, our data also, referred to a significant decrease in all lipids parameters except VLDL and TG that increased in the hyperthyroid group compared to the control groups. Reduction in total cholesterol due to thyroxin treatment was due to decrease in HDL and LDL cholesterol. Garlic is a goitrogenic and hypolipidemic agent that can help

in decreasing the level of TG, TC and in increasing the level of HDL to normal pattern as in healthy group. Significant decrease in serum TG level may be due to the TG-lowering effect of garlic on fatty acid synthesis⁽¹⁴⁾. The hypocholesterolemic activities of garlic is due to the presence of allicin and allyl propyldisulphide together with their derivative compounds. This hypocholesterolemic effect is due to the abilities of the active substances to limit hepatic cholesterol biosynthesis, enhance cholesterol turnover to bile acids and its excretion through gastrointestinal tract or by inhibiting cholesterol absorption from intestinal lumen⁽¹⁵⁾. Fenugreek-treated hyperthyroid rats showed significantly reduced serum triglycerides that may be attributed to its content of lecithin which dissolve cholesterol and contains lipotropic (fat dissolving) substances that dissolve deposits of fat, prevents fatty accumulates and water retention. Also, fenugreek have hypocholesterolemic effect due to increased conversion of hepatic cholesterol to bile salts and loss of complexes of these substances in the feces with fenugreek saponins. Thus an increase in HDL-C following the treatment suggests its beneficial role in the regulation of hyperthyroidism⁽¹⁶⁾.

In particular, the elevation of ALP, an enzyme found mainly in the liver is, an indication of liver damage. L-thyroxin injection produced a significant increase in the hepatic marker enzymes (AST and ALP) as a result of leaking of these enzymes from liver cells cytosol into bloodstream since the toxic action of L-thyroxin mediated through the generation of free radicals which eventually damage the liver cells leading to the leakage of these enzymes. Once the cellular membrane integrity is disrupted the serum concentrations of these enzymes are usually proportional to the rate of damage⁽¹⁷⁾.

Reduction in the activities of these enzymes in garlic extract-treated hyperthyroid rats is an indication of their hepatoprotective activities. These protective effects of garlic extract may be associated with their inherent antioxidant properties which is believed to accelerate the regenerative capacity of the hepatocytes causing stabilization of its cell membrane and ultimately protection of the liver cells against deleterious agents and free radical mediated toxic damages. However, fenugreek extract-treated rats showed insignificant change in serum ALT and ALP that attributed to

fenugreek antioxidant property which protects the functional organs and has hepatoprotective effect⁽¹⁸⁾

Serum BUN, creatinine, uric acid are often regarded as reliable markers of renal function status. Elevations in the serum concentrations of BUN and uric acid in hyperthyroid rats are signs of renal dysfunction. Administration of garlic extract led to reduction of these kidney biomarkers. Garlic nephroprotective properties have been proposed to be mediated through antioxidant or free radical scavenging activities due to its high concentration of flavonoids and alkaloids. The garlic extract enhanced the ability of the kidneys to remove these waste products from the blood as indicated by reduction in serum urea and uric acid that confer the protective effect of garlic on the kidney of hyperthyroid rats⁽¹⁹⁾. Meanwhile, fenugreek have nephroprotective effect that may be attributed to its antioxidant and hypoglycemic properties and its constructive effect of collagen which prevent ROS-induced destruction of filtration and basement membrane of kidney⁽¹⁹⁾.

Serum total protein was significantly reduced in hyperthyroidemic rats comparable to control ones. The decrease in serum total protein was due to a reduction in ribosomal protein synthesis⁽²⁰⁾. After treatment with *Trigonella* serum total protein levels restored to normal values this because fenugreek is one of the important source of protein which can be utilized as alternative to animal proteins which influence on physiological functional properties⁽²⁰⁾. In hyperthyroid *Allium sativum*-treated rats, serum total protein and albumin levels restored to normal values. Naturally occurring goitrogens found in many plants are hydrolysed to ultimate goitrogens which mostly inhibit the biosynthesis of thyroid hormones by blocking the coupling of iodotyrosine and iodination of monoiodotyrosine. Some of these goitrogens include sulphurated organic compounds such as sodium thiocyanate, NaSCN, thioglucosides, cyanogenic glucosides and aliphatic disulphides known to be present in *Alliums*. Also, antioxidant properties of fenugreek and *Allium sativum* improve organ functions⁽²¹⁾.

CONCLUSION

This study concluded that *Allium Sativum*, *Trigonella* or their mixture have a protective effect against hyperthyroidism.

Therefore this study recommends increased dietary intake of *Allium Sativum*, *Trigonella* or their mixture that may be beneficial for patients with hyperthyroidism. Also, more toxicological studies must be done.

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