

Effect of Grape Seed Extract on Biochemical Factor and Histological Changes in Liver and the Kidney in Albino Rat Infected Hypo- Hyperthyroidism Induced Laboratory by Carbimazole and L-Thyroxine

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Abstract

The aim of the current study was showing the effect of hypothyroidism and hyperthyroidism on some physiological parameters (creatinine and urea) and the concentration of amine transfer enzymes (AST, ALT, and ALP) also the histological structure of liver and kidney in albino rat, and role of grape seed extract (GSE) in protecting the liver and kidney tissue against thyroid disorders and improve the level, creatinine, urea, AST, ALT, and ALP. Study experiment samples consist of 80 rats divided into two main groups hypothyroidism and hyperthyroidism, each group includes five treatments. Carbimazole was used in 30 mg/kg dose to induce hypothyroidism and L-thyroxine in 20 mg/kg dose to induce hyperthyroidism. Results showed that a significant increased ($P<0.05$) concentrations of creatinin, urea, AST, ALT in hypothyroidism and hyperthyroidism groups compare with control, ALP significant increased ($P<0.05$) in hyperthyroidism while showed significant decreased ($P<0.05$) in hypothyroidism compare with control, treatment with GSE in both groups showed significant differences in concentration of urea, creatinin, AST, ALT, ALP and improved liver and kidney tissue compare with hypothyroidism and hyperthyroidism treatments. It was concluded from this study that extract of grape seeds has a protective role for the liver and kidney against damage caused by thyroid disorders and its treatments.

Keywords: *Grape seed extract, Thyroid, Liver, Kidney, Carbimazole, L-Thyroxin, Hypothyroidism, Hyperthyroidism.*

Introduction

Thyroid gland by its hormones Control of the most important biological processes in the body growth, development and metabolism and any change in the level of T4 and T3 puts the body abnormally [1]. Thyroid disorder hypo- Hyperthyroidism and its treatments drugs Carbimazole and L-Thyroxin have effects on the body such as Cholesterol, lipid profile, triglyceride, lipid, oxidation, antioxidant, Malondialdehyde MDA and catalyse enzyme CAT [2,3,4], also it includes an effect on the liver and its enzyme, kidney, uric acid, urea, creatinine and histological changes in the liver and kidney[5,6]. In our study use grape seed extract to explain its role in reducing the damage which occurs in thyroid gland disorders and its treatments Carbimazole and L-Thyroxin. When the dose from carbimazole and L-Thyroxin are higher

than required for the treatment causing damage so that may be used reverse treatment and even thus causing damage [7], our study aims clarification grape seed extract role In reducing damage causing when thyroid gland disorders and comparison that when to be used a reversible treatment on AST, ALT, ALP, urea, creatinine and Histological Changes in liver and kidney.

Materials and Methods

Experiment design: In this study used 80 albino rats 200-250 g, 3-4 month age, divided into two main groups hypothyroidism and hyperthyroidism and each group includes five treatments all treatment consisted of 8 rats, to induce hyperthyroidism was used L-Thyroxin drug dose 20 mg/kg it was a drug known to treat hypothyroidism and used

carbimazole drug to induce hypothyroidism dose 30 mg/kg. Initially to be sure the hypothyroidism and hyperthyroidism occurs in this animals groups, in hypothyroidism group this was done by dosing (T1, T3, T4) treatments 30 mg/kg carbimazole daily and fifteen days later a blood samples were withdrawn to measure the concentration of (T4, T3, TSH) hormones, the results showed a low concentration of (T4, T3) hormones and a high concentration of TSH hormone, this means hypothyroidism has occurred in this treatments.

In hyperthyroidism group this was done by dosing (T1, T3, T4) treatments 200 mg/kg L-Thyroxin daily and fifteen days later a blood samples were withdrawn to measure the concentration of (T4, T3, TSH) hormones, the results showed a high concentration of (T4, T3) hormones and a low concentration of TSH hormone, this means hyperthyroidism has occurred in this treatments, after the occurrence of thyroid disorders the dosage was as follows:

In hypothyroidism group treatment(C) given oral dose of distilled water for 30 days it was control, treatment (T1) continued to give oral dose of carbimazole 30mg/kg daily for 30 days, treatment (T2) given oral dose of GSE 150 mg/kg daily for 30 days, treatment(T3) continued to give oral dose of carbimazole 30 mg/kg and GSE 150 mg/kg daily for 30 days, treatment(T4) given oral dose just L-Thyroxin 20 mg/kg for 30 days.

In hyperthyroidism group treatment(C) given oral dose of distilled water for 30 days it was control, treatment (T1) continued to give oral dose of L-Thyroxin 20 mg/kg daily for 30 days, treatment(T2) given oral dose of GSE 150 mg/kg daily for 30 days, treatment(T3) continued to give oral dose of L-Thyroxin 20mg/kg and GSE 150 mg/kg daily for 30 days, treatment(T4) given oral dose just carbimazole 30 mg/kg for 30 days.

Chemicals

To induce hyperthyroidism was used L-Thyroxin drug dose 20 mg/kg it was a drug known to treat hypothyroidism and alternative to the thyroid hormone thyroxine, and used carbimazole drug to induce hyperthyroidism dose 30 mg/kg it is a common drug for the treatment of hyperthyroidism.

Plant Extract

In the present study used local Iraqi Grapefruits It was purchased from local Iraqi markets, Seeds were isolated and drying it in the shade, then grind them into an electric mixer to get a powder for use in the Soxhlet apparatus for water extract of grape seeds.

Determination of Some Biochemical Parameters

Determination of amino carrier enzyme activity (AST, ALT) and ALP by following the method of color [8] and several tests were used (Kit) was provided by Italian Giese company.

Determination of Urea and Creatinine

The level of creatinine was measured using Colorimetric Method by kit from British company [9], urea measured using Enzymatic Method by kit from French company Bio Merieux [10].

Histological Study

Histological sections of liver and kidney were prepared according to the method [11].

Statistical Analysis

All results under study were subjected to statistical analysis to know the significant differences between the control treatment and other treatments in both groups by using F-test at 0.05 probability level [12].

Results and Discussion

Effect of Hypothyroidism and Hyperthyroidism on Level AST, ALT and ALP and the Role of GSE

Treatment T1 in hypothyroidism group showed significant increase ($P < 0.05$) in liver enzymes AST and ALT Compared with control, anti-thyroid drug such as carbimazole caused oxidative stress due damage in cell membranes in liver that causes exit enzymes into the serum [13,14], many studies agree with high enzymes ALT that means damage in liver cells [15], the AST enzyme found in the skeletal muscle, heart, lung, and kidney and increase it in serum might show the damage of these organs in addition to the liver in patients with hypothyroidism [16], the liver needs thyroid hormones to do its functions and thyroid hormones control metabolism through gene expression and its connection to the nuclear material and patients with

hypothyroidism have liver dysfunction and tissue damage due the low thyroid hormones [17]. The Significant decrease ($P<0.05$) enzyme ALP in the T1 compared with control and other groups interpreted in Studies it has because of hypothyroidism, Malnutrition, Anaemia, heart disease and decrease Mg, Zn [18,13].

Treatment T4 didn't show significant differences in ALT and ALP compared with treatment with T1 while treatment T3 showed significant differences ($P<0.05$) in AST, ALT, ALP compared with T1 and T4 treatments, that back to the protective role of the grape seed extract in preventing damage by oxidative stress due carbimazole drug [19,20], grape seed extract protective cell membranes against radial root and prevents analyzed it and exits enzymes that make decreased AST,ALT in this treatment [20]. Also treatment T3 significant increase ALP compared with T1 and T4 treatments, grape seed extracts rich compounds were treated malnutrition, anemia and contains minerals Mg, Zn The important in the activation and action of ALP [21, 22, 23].

Treatment T1 in hyperthyroidism showed significant increase ($P<0.05$) in AST, ALT, ALP compared with control and other groups this is consistent with several studies, when thyroid hormones increase the metabolism

will increase and the body will need oxygen, the blood circulation is unable to give enough oxygen and This leads to liver damage with increased programmed death of cells and enzymes to exit into the serum [24], and may be lack of oxygen in sufficient quantities lead to free radicals that cause necrosis of liver cells in patients with hyperthyroidism and this causes exit the enzymes from the liver cells [25], also rise in T3 increases the action of the mitochondria and free radicals this affects nuclear material and early cell aging [26,27].

Treatment T3 showed a significant difference ($P<0.05$) in AST, ALT, ALP compared with T1 and T4 treatments, this is dedicated to the grape seeds extract in resistance to free radicals resulting from the rise of thyroid hormones and L-Thyroxin drug [28], the phenols and flavonoids in grape seed extract have a capacity to handle H₂O₂ and get rid of free radicals that damage cells and protect cells from oxidation, inflammation and reduce liver enzymes which has increased its concentration due to liver damage [29], also quercet in which one of the compounds extract grape seeds has able to preventive and therapeutic the liver tissue which was observed in the reduction of necrosis and programmed death of cells by increasing NO and removing free radicals [30].

Table 1: The role of grape seed extract on liver enzymes in rats induced hypothyroidism

parameters treatments	AST [U/L]	ALT [U/L]	ALP [U/L]
Control	1.74±47.66 C	0.36±4966. C	0.44 ±82.00 A
T1	1.11±58.33 A	0.68±59.73 A	1.48 ±73.00 B
T2	030±46.26 C	0.37±52.20 B	2.55 ±87.66 A
T3	0.42±46.66 C	1.04±54.00 B	1.87 ±83.00 A
T4	0.49±51.33 B	0.79±58.4 A	0.49 ±75.33 B
LSD	2.36	1.96	5.61

Table 2: The role of grape seed extract on liver enzymes in rats induced hyperthyroidism

parameters treatments	AST [U/L]	ALT [U/L]	ALP [U/L]
Control	1.80±46.88 B	0.58±50.20 C	0.44 ±82.48 BC
T1	3.06±56.00 A	1.04±76.00 A	1.15±96.00 A
T2	2.62±44. 48BC	0.73±52.23 C	4.59 ±86.82 B
T3	1.49±40.33 C	1.35± 52.23 C	0.73± 78.66 DC

T4	1.77±52.33 A	2.10±57.33 B	0.63±75.00 D
LSD	5.39	3.10	5.21

Effect of Hypothyroidism and Hyperthyroidism on Level Urea, Creatinine and the Role of GSE

Urea and creatinine showed significantly increased ($P<0.05$) in T1 and T4 treatments in hypothyroidism group compared with control, this is consistent with studies that explained the reason for the lack of thyroid hormones leads to slow metabolism and irregular blood flow leading to decreasing transfers in kidney and glomerular dysfunction [5], in hypothyroidism occurs destruction of proteins that due increases' urea, liver cells were also

found to form urea in hypothyroidism [31]. In hyperthyroidism group T1 and T4 treatments showed significant increase ($P<0.05$) in urea and creatinine compared with control, the hyperthyroidism leads to renal failure because irregular blood circulation and cardiac outcomes and causes ischemia [32], the oxidative stress caused by hyperthyroidism leads to kidney tissue damage and dysfunction [33], also L-levothyroxine drug causes increased urea, creatinine, and changes in the kidney tissue [34].

Table 3: The role of grape seed extract on urea and creatinine in rats induced hypothyroidism

parameters treatments	urea [mg/dL]	creatinin [mg/dL]
Control	0.18±22.66 C	0.03±0.3667 C
T1	0.48±26.33 B	0.01±0.5067 A
	0.48±21.99 C	0.06±0.3867 C
T3	0.30±25.05 B	0.001±0.1967 D
T4	0.49±29.33 A	0.01±0.4400 B
LSD	0.98	0.020

Table 4: The role of grape seed extract on urea and creatinine in rats induced hyperthyroidism

parameters treatments	urea [mg/dL]	creatinin [mg/dL]
Control	0.32±22.23 C	0.004±0.3617 D
T1	0.48±33.66 A	0.09±0.4667 A
T2	0.13±22.00 C	0.003±0.4100 C
T3	0.94±28.00 B	0.003±0.4467 B
T4	0.49±29.19 B	0.001±0.4360 B
LSD	1.48	0.0176

Treatment T3 showed significant difference in concentration urea, creatinine and improvement in kidney tissue compared with T1 and T4 in both groups, This is due to the role of grape seed extract as an antioxidant and this is consistent with the study on mice treated with medication that causes kidney damage while the mice showed a clear improvement in kidney tissue and function after treatment with the proanthocyanidins compound from grape extract [35], Proanthocyanidins has a role in resistance to

oxidative stress and protection kidney against free radicals caused by medical drugs [36], the flavonoids and phenols in grape seeds are not limited to antioxidants but assist in gene expression and increase the effectiveness of antioxidant enzymes significantly increased [30].

Histological Study

The results microscopic test of taking histological slides from liver and kidney showed that the presence of pathogenic

tissue changes in liver and kidney tissue for T1, T4 treatments in both group's hypothyroidism and hyperthyroidism, While T3 treatment in both groups showed significant improvement in liver and kidney tissue. Treatment T1 in hypothyroidism showed clear necrosis in hepatic cells and hyperplasia of the bile duct Figure (3), so that T4 treatment in both groups showed Simple hyperplasia in the bile duct and congestion in the central vein and infiltration of inflammatory cells Figure (5,8), this consistent with the study on rats treated with carbimazole histological sections of the liver showed.

The infiltration of leukocytes and bloating in cytoplasmic liver cells, fatty degeneration, congestion of blood vessels and necrosis of liver cells and the results explained that Carbimazole caused liver cell degradation due to free radicals and the inability of antioxidants to resist the increase in free radicals [6], so that the effect of hypothyroidism on rats and people with hypothyroidism and its effect on the liver and hepatic toxicity the study showed the liver to degeneration fatty and hepatic poisoning due to lack of thyroid hormones [37].

Treatment T1 in hyperthyroidism group showed congestion and hyperplasia of the bile duct and simple infiltration in inflammatory cells with simple degeneration Figure (6), this results maybe were because of oxidative stress caused by L-thyroxine that increase metabolism and free radicals so that the body's defenses of antioxidants are unable to resist free radicals that damage liver tissue [38], in the study on hyperthyroidism induced in rats indicated that T3 hormone stimulates the gene responsible for programmed death in liver cells and it was observed in the histological study a difference in cell color and degeneration in the cytoplasm nature as well as hyperthyroidism causing ischemia in the liver [39].

While the T3 treatment in both groups which showed a clear improvement of the liver tissue Figure(4, 7), and this may return to the role of effectiveness grape seed extract compounds against oxidative stress, inflammation and programmed cell death resistance [40], the role of grape seed extract as an antioxidant in protecting cells from damage and antimicrobial activation [41], so

that grape seed extract is a strong antagonist of the free radicals on the one hand and activates the enzyme's antioxidants on the other hand[42].

Histological sections of kidney were shown in T1 treatment in hypothyroidism excessive infiltration of inflammatory cells, expansion of renal tubules, degeneration and clear necrosis of germicidal cells and clear congestion of blood vessels Figure (11), T4 treatment showed a slight expansion of the renal tubules and some of the tubules with recombinant and dissociated epithelial cells of the basal membrane within the tubules Figure (13), T4 treatment in hyperthyroidism showed a clear atrophy in the renal tubules and some of them seem to expand clearly and observed a slight degeneration in the cells lining the renal tubules Figure (16), these results were consistent with the study, the changes that occur in the tissue of the kidney of some medical properties that included anti-thyroid including carbimazole and methimazole the study showed that people with nephropathy due to these drugs showed membrane changes, vascular dysfunction and renal glaucoma[43], the hypothyroidism leads to the imbalance of gene expression of the axis renin-angiotensin-aldosterone and because of low cardiac output and blood flow and thus imbalance of regulation of the kidney and glomerular dysfunction as well as lack of thyroid hormones affect the growth and development of the kidney and the lack leads to damage to the blood vessels become the executor of proteins[44].

Treatment T1 in hyperthyroidism showed enlargement of renal tubules and minor degeneration in the living cells of the renal tubules, it was observed that intracranial hemorrhage was present and a slight infiltration of inflammatory kidney cells Figure (14), these results coincided with several studies that explained the cause of tissue changes due to the oxidative stress caused by L-thyroxine [33,34,45]. The T3 treatment in both groups hypothyroidism and hyperthyroidism showed significant improvement in kidney tissue and function Figures (12, 15), this improvement due to the role of grape seed extract in protecting the kidney from the toxicity of drugs and thyroid disorder that causing oxidative stress and these improvement back to the phenolic compounds and flavonoids and their ability to

treat inflammation and activate the body to detoxify[46], in the study explained the improvement in kidney tissue to the ability of the grape seed extract to activate the cell defenses against oxidative stress and

maintain the mitochondria thus limiting the accelerated programmed death of the renal cell and raising the level of glutathione within the cell [47].

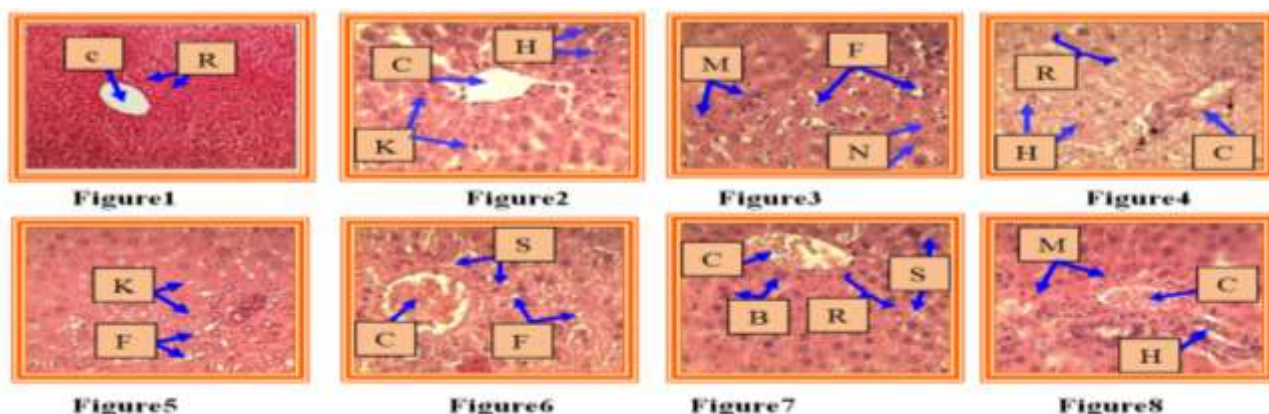


Figure1: Liver tissue in control, normal hepatic Cells(R) are arranged around the central vein(CV)10xH&E. **Figure2:** Liver tissue in treatment T2 in both groups, normal hepatic cells (H) arranged around central vein (CV) and Kupfer cells 40xH&E. **Figure3:** Liver tissue in treatment T1 in Hypothyroidism group, Necrosis in hepatic cells(N), Fatty degeneration (F) and Inflammation of inflammatory cells(M) 40xH&E. **Figure4:** Liver tissue in treatment T3 in hypothyroidism group, normal hepatic cells (H) Arranged as cords (R) and Simple hyperplasia in the bile duct (C) 40xH&E. **Figure5:** Liver tissue in treatment T4 in Hypothyroidism group, Reproduction of Kupfer cells (K) and expansion of hepatic sinuses and simple fatty degeneration (F) 40xH&E. **Figure6:** Liver tissue in treatment T1 in hyperthyroidism group, The central vein is congested (C), expansion of hepatic sinuses(S) and fatty degeneration(F) 40xH&E. **Figure7:** Liver tissue in treatment T3 in hyperthyroidism group, The Simple congestion in central vein (C), Simple bleeding(S), The cells are normal and arranged As cords (R) and Some cells contain two nuclei(B) 40xH&E. **Figure8:** Liver tissue in treatment T4 in hyperthyroidism group, The central vein is congested (C), Inflammation of inflammatory cells(M) and hyperplasia in the bile duct (H) 40xH&E.

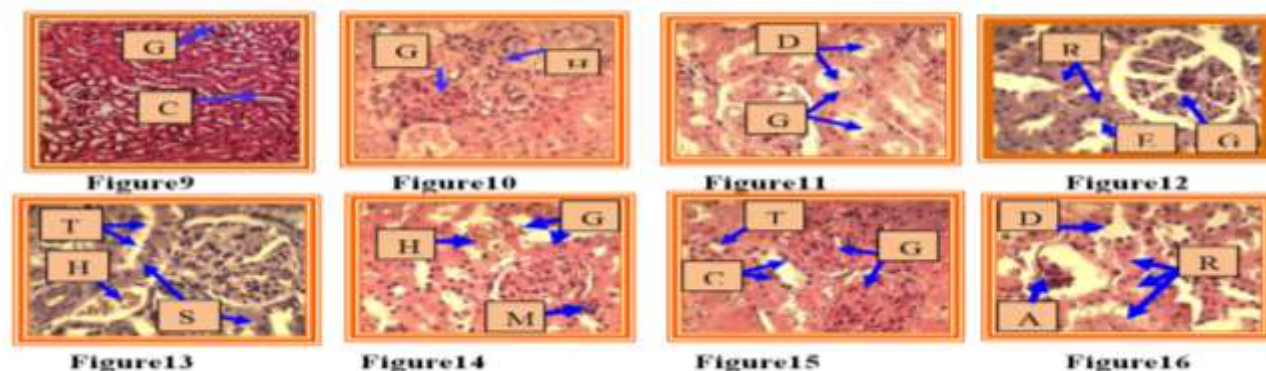


Figure 9: Kidney tissue in control, normal Glomeruli Surrounded by renal tubules (G) and The tubules are lined with natural cubic cells (C) 10xH&E. **Figure10:** Kidney tissue in treatment T2 in both groups, Enlarged natural globules surrounded by renal tubules(G) and The tubules are lined with natural cubic cells (T) 40xH&E. **Figure11:** Kidney tissue in treatment T1 in Hypothyroidism group, Congestion inside the Tubules (D) and Clear necrosis (G). 40xH&E. **Figure12:** Kidney tissue in treatment T3 in hypothyroidism group, natural glomeruli (G),natural cells lined with tubules (E) and Simple degeneration in some cells (R) 40xH&E.**Figure13:** Kidney tissue in treatment T4 in Hypothyroidism group, Tubular basophilia(T),Clear bleeding in the tissue(H) and Simple dislocation and degeneration in cells(S) 40xH&E. **Figure14:** Kidney tissue in treatment T1 in hyperthyroidism group, Degeneration of cells lining the tubes (G), Bleeding within the tissue(H) and infiltration Inflammatory cells(M)40xH&E. **Figure15:** Kidney tissue in treatment T3 in Hyperthyroidism, Natural glomeruli(G).Natural cells lined with tubules(T) and Cells repair(C) 40xH&E. **Figure16:** Kidney tissue in treatment T4 in hyperthyroidism group, Clear atrophy in glomeruli(A), enlarged tubules (D) and The degeneration of the lining cells(R) 40xH&E.

Conclusion

In this study, the grape seed extract showed a significant role in protecting the liver and kidney tissue and functions against damage caused by thyroid disorders and its drugs

Carbimazole and L-Thyroxin. We suggest using grape seed extract for patients with subclinical thyroid disorders, also using it alongside thyroid therapy for patients with thyroid disorder

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Acceptance Letter

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Dear Dr. Ahmed Jassem Al-Naely / Al-Qadisiyah University, Iraq.

Dr. Dalal Turki Shattnan / Al-Qadisiyah University, Iraq.

Greetings

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