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ROLE OF SOME COMPOUNDS IN AMELIORATING SOME HEMATOLOGICAL PARAMETERS AND LACTIC DEHYDROGENASE ACTIVITY IN RATS TREATED WITH ROSIGLITAZONE

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ABSTRACT

The present study was carried out to evaluate some cardiovascular effect of Rosiglitazone, *Nigella sativa*, silymarin each alone and the combination of Rosiglitazone with either *Nigella sativa* or Silymarin in order to get the best combination to avoid the possible side effects produced by Rosiglitazone. This was done through studying the effect of the test plant drugs and their combination on some hematological parameters and hormone control on heart activity (Lactic dehydrogenase enzyme) (L.D.H) .seven groups of adult male rats each of 10 (200-250 gm / b. wt) were used in this study. Hyperglycemia was induced in six groups of rats. Whereas, the 7th group was left as normal control group. All treatments were given orally daily for successive 28 days .The 1st group was left without treatment and kept as STZ diabetic. The 2nd group was administered Rosiglitazone (0.58mg/100gm.b.wt) , The 3rd group was given *Nigella sativa* (0.25gm/100gm.b.wt) , the 4th group was given Silymarin (50mg/100gm.b.wt), the 5th and 6th groups were administered the combination of Rosiglitazone with either *Nigella sativa* or Silymarin respectively in the same recommended doses. Blood samples were collected after the 1st, 2nd, 3rd and 4th week post drug administration. Serum was separated and used for determination of various variables. The results showed that Rosiglitazone afforded a marked non significant changes in RBCs, WBCs with significant decrease in hemoglobin percent in Rosiglitazone treated group with marked increase in LDH hormone which reflect the activity of the heart when compared with diabetic non treated group and diabetic group treated with Rosiglitazone drug + Silymarin and Rosiglitazone drug + *Nigella sativa* .

INTRODUCTION

Diabetes was described more than 2000 years ago . Since the discovery of insulin, work on diabetes at the cellular and clinical levels has expended as fast as new laboratory and diagnostic technique allow [1].

Diabetes mellitus is a syndrome characterized by chronic hyperglycemia and disturbances of carbohydrate fat and protein metabolism associated with absolute or relative deficiencies in insulin secretion and /or insulin action [2].

Diabetes mellitus is associated with very subtle disorders, affects either directly or indirectly, various functions as the reproductive system. Sexual dysfunction in all its forms (reduced erection, impotence, and other libido dissociations) is an accompanying phenomenon of the diabetic disease .These disorders are related to the regulation of carbohydrates metabolism and to the duration of disease, they are not necessary correlated with sexual dysfunction [3].

The WHO expert committee on diabetes mellitus recommendations of 1980[4] included investigation of hypoglycemic agents from plants used in traditional medicine. *Nigella sativa* oil have been used for treatment of experimentally induced diabetes in animals based on its combined hypoglycemic and immunopotentiating effects that help in ameliorating the impaired immunity and infections associated with diabetes [5, 6].

A whole range of pharmacological agents are available to ameliorate the T2DM (Type two dibetes mellitus) symptoms by different mechanisms. A reduction in insulin resistance at any stage of T2DM will improve glucose metabolism by allowing the endogenous insulin to be more effective. The use of different insulin sensitizers and secregatogues, either in single therapy or in combination, would help to improve glycemic control, either by increasing peripheral glucose uptake, improving insulin secretion, decreasing hepatic glucose output or reducing the influx of glucose to the body [7].

Rosiglitazone came under heavy security after 21 May 2007, when the NEjM published online a Meta analysis of other studies into the drug's efficacy and safety .The results showed that the drug increased the risk of heart attack by 43 %in people who took it for at least 24 weeks [8].

Rosiglitazone manufactured by Glaxo Smithkline (GSK), was approved as an adjunct to diet and exercise to improve control of blood sugar levels .Rosiglitazone is approved to be used as a single therapy or used in combination with metformin and sulfonylurea, or with other oral anti-diabetes treatments [9]. In the third quarter of 2007, sales of Rosiglitazone were down 38 % from a year earlier worldwide and down 48% in the United States [10].

A number of natural products exhibit properties that could be used as remedies to improve glucose metabolism [11] some plants extract can significantly reduce blood glucose levels and lipids, improving insulin sensitivity [12].

Nigella sativa has a great potential in the treatment of diabetic animal because of its combined hypoglycemic [13] and immunopotentiating properties [14] it is cheap and readily available.

Nigella sativa is known for its hypotensive [15, 16], hepatoprotective [17-19] and immunomodulatory effects [20, 21]. Many studies have also examined the antidiabetic effect of *Nigella sativa*.

Traditional antidiabetic plants provide useful source of new oral hypoglycemic compounds for development as pharmaceutical entities, or as simple dietary adjuncts to existing therapies. A scientific investigation of traditional herbal remedies for diabetes

in ability of current therapies for many rural populations, particularly in developing countries [22].

Silymarin has been used for more than 2000 years as a natural remedy for treating hepatitis and cirrhosis and to protect liver from toxic substances .Silymarin acts by anti-oxidative, anti-lipid peroxidative, antifibrotic, and anti-inflammatory, membrane stabilizing, immunomodulatory and liver regenerating mechanisms in experimental liver diseases .Furthermore, silymarin has been extensively studied, both *in vivo* and *in vitro*, for its cancer chemopreventive potential against various cancers [23].

We therefore planned to investigate the insulinotropic effects of extract of natural product of *N. sativa* seeds and silymarin on some hematological parameters and heart activity parameters.

EXPERIMENTAL

This study was carried out on 70 mature male albino rats weighing 200-250 gm. each. They were divided into 7 equal groups (each of 10) as follows:-

Induction of diabetes:

Streptozotocin diabetic groups: After induction of diabetes by injecting rats with STZ I.P in a dose of 50 mg/kg, rats with fasting blood glucose level more than 250mg/dl were considered diabetic.

I- The 1st group (STZ group)

These animals were served as diabetic non treated group for other diabetic groups.

II- The 2nd group (STZ+Rosiglitazone treated group)

Animals of this group were given a daily oral dose of AVA (0.58 mg/100g.b.wt) dissolved in 1 ml tragacanth gum as suspension for 4 weeks.

III- The 3rd group (STZ+ *Nigella sativa* extract treated group)

These animals were received a daily oral dose of *Nigella sativa* extract (0.25gm/100g b.wt) for 4 weeks.

VI- The 4th group (STZ+ silymarin extract treated group)

Animals of this group were given dose of silymarin extract (50mg/kg.b.wt) suspended in 1 ml CMC suspension orally for 4 weeks daily.

V- The 5th group (STZ + AVA + *Nigella sativa* extract treated group)

Animals of this group were received a daily oral dose of AVA (0.58mg/100g b.wt) as previously mentioned combined with *Nigella sativa* extract (0.25gm/100 b.wt), for4 weeks.

VI- The 6th group (STZ + AVA + Silymarin extract treated group)

Animals of this group were received a daily oral dose of AVA (0.58mg/100g. b.wt) as prepared as mentioned above with a daily dose of Silymarin extract (50mg/kg.b.wt) for 4 weeks.

VII- The 7th group (control group)

These animals were served as normal control group given 1ml citrate buffer (PH=4.5) (The vehicle in which STZ was dissolved) daily orally for4weeks.

Blood sampling

At the end of the experiment, blood samples were collected by the end of 1st, 2nd, 3rd and 4th week post drugs administration from the retro orbital plexus using microhaematocrit capillary tubes into centrifuge tubes. Serum was harvested from blood without anticoagulant and used for determination of serum (Follicle stimulating hormone) F.S.H, (Leutinzing hormone) L.H and testosterone.

After 4 weeks post drug administration, animals were sacrificed and samples from heart, liver, pancreas and testis were fixed in 10% formalin for histopathological studies.

Statistical analysis

Data were collected and analyzed using the computer program SPSS / Pc+ (2001). The statistical method used was one way ANOVA test (F-Test) according to [24].

After 4 weeks post drug administration, animals were sacrificed and samples from testis were fixed in 10% formalin for histopathological studies.

RESULTS AND DISCUSSION

The results of experiment revealed the following observations.

(1) Effect on some Hematological parameters

(A) Effect on RBCs

On the 4th week post-treatment the diabetic treated group with Rosiglitazone and Rosiglitazone + *N. sativa* showed a significant decrease in RBCs count compared with diabetic non-treated group. While the diabetic groups treated with silymarin, *N. sativa* and Rosiglitazone + silymarin exhibited a marked increase in RBCs count when compared with STZ treated group.

(B) Effect on total leucocytic count (WBCs count):

In diabetic treated groups, the total WBCs count of STZ group (diabetic non treated group) was significantly elevated when compared with buffer group after 1st and 2nd weeks post treatment. The same effect was noticed in the diabetic group treated with Rosiglitazone along the course of the study when compared with both buffer and STZ diabetic group.

All treatments elicited a significant decrease in WBCs count along the first and second weeks, post treatment together with non-significant changes along

the 3rd and 4th weeks post-treatment when compared with STZ-diabetic group.

(C) Effect on Hemoglobin (Hb) content

The diabetic group treated with silymarin exhibited a non-significant increase in Hb content along the course of the experiment except after the 2nd week showed a significant increase when compared with diabetic non-treated rats. While a marked elevation in Hb content was recorded in diabetic group treated with *N. sativa* along the course of the study.

Diabetic group treated with Rosiglitazone + *N. Sativa* and Rosiglitazone + silymarin showed a non-significant changes in Hb content along the course of the study except after the 1st week in the group treated with Rosiglitazone + silymarin which showed a significant decrease compared with STZ diabetic group.

(D) Effect on Packed cell volume (PCV%)

Treatment of all diabetic group with various treatments afforded significant elevation ($p < 0.05$) in PCV% along the entire course of the experiment when compared with STZ treated group except diabetic group treated with Rosiglitazone which revealed a significant decrease in PCV% along the entire period of the study and group treated with silymarin +Rosiglitazone after the 3rd and 4th week which showed non-significant increase. The same non-significant decrease was observed after the 3rd and 4th week post-treatment with Rosiglitazone+*N. sativa* as the experiment.

(E)Effect on serum lactic dehydrogenase enzyme (LDH) activity

STZ diabetic group showed significant increase in serum LDH activity along the entire period of the experiment when compared with buffer group.

Whereas all treatments of diabetic rats for 28 days afforded a marked decrease ($P < 0.05$) in serum LDH activity along the course of the study when compared with STZ treated group except the group treated with Rosiglitazone drug showed highly marked increase in LDH level along the course of the experiment .

(F) Histopathological sections in heart confirming side effects of:

(Group AI): Rosiglitazone treated group

Microscopically, showing cardiac muscles with fatty change with large area of necrosis and severe congestion (Figure 1) and the coronary blood vessels showed high grade of congestion (Figure 2).

(Group B-I): Rosiglitazone+Nigella *sativa*

Microscopically, congestion of the cardiac blood vessels, with some lesion (Figure 3).

(GROUP CI) :(Rosiglitazone+silymarin)

Microscopically congestion of the cardiac blood vessels in between the cardiac muscles (Figure 4).

Histopathological Sections in Heart Confirming Side Effects of Rosiglitazone Drug.

(Group AI): *Rosiglitazone* treated group

The Heart

Microscopicaly, showing cardiac muscles with fatty change with large area of necrosis and severe congestion and the coronary blood vessels showed high grade of congestion.

Fig. (1). Cardiac muscles with fatty change with large area of necrosis.

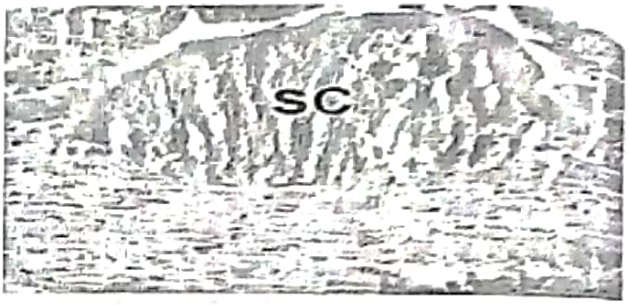

Fig. (2). Severe congestion and the coronary blood vessels showed high grade of congestion. (SC: Sever congestion) (MC: Muscle congestion).

(Group B-I): Rosiglitazone+*Nigella sativa*

The Heart

Microscopically, congestion of the cardiac blood vessels, with some lesion.

Fig. (3). Congestion of the cardiac blood vessels with some lesion.

(GROUP CI) :(Rosiglitazone + silymarin)

The Heart

Microscopically congestion of the cardiac blood vessels in between the cardiac muscles.

Fig. (4): Congestion of the cardiac blood vessels in between the cardiac muscles.

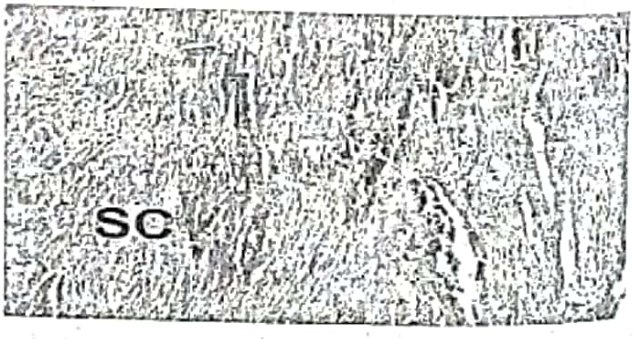

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Table (1): Effect of Rosiglitazone drug, *Nigella sativa*, silymarin and their combination on red blood cells (RBCs) count ($\times 10^6$ Cell / mm^3) in diabetic male albino rats (mean ± SE). (N = 7)

Groups	Week1	Week2	Week3	Week4
1. STZ (diabetic non treated group)	$3.24+0.18^{f}$	$3.89+0.07^{d}$	$4.16+0.12^{e}$	$4.26+0.11^{d}$
2. STZ + Rosiglitazone Group	$4.25+0.02^{d}$	$4.57+0.08^{c}$	$2.02+0.35^{g}$	$2.55+0.30^{f}$
3. STZ + silymarin Group	$5.25+0.22^{b}$	$5.91+0.27^{a}$	$4.84+0.28^{c}$	$5.60+0.32^{b}$
4. STZ + *Nigella sativa* Group	$4.75+0.24^{b}$	$5.59+0.26^{b}$	$5.63+0.15^{ab}$	$6.54+0.09^{a}$
5. STZ + Rosiglitazone + *Nigella sativa* Group	$5.09+0.23^{c}$	$5.44+0.09^{b}$	$3.28+0.27^{d}$	$3.84+0.34^{de}$
6. STZ + Rosiglitazone + silymarin Group	$3.97+0.11^{e}$	$4.29+0.15^{cd}$	$5.74+0.27^{ab}$	$5.40+0.35^{b}$

Means within the same column in each category carrying different letters are significant at ($P \leq 0.05$).

Table (2): Effect of Rosiglitazone drug, *Nigella sativa*, silymarin and their combination on total leucocytes counts (WBCs) ($\times 10^3$ Cell / mm^3) in diabetic male albino rats (mean ± SE). (N = 7).

Groups	Week1	Week2	Week3	Week4
1. STZ (diabetic non treated group)	$9.63+0.22^{b}$	$8.76+0.23^{b}$	$7.72+0.21^{b}$	$8.08+0.16^{ab}$
2. STZ + Rosiglitazone Group	$11.76+0.30^{a}$	$12.62+0.62^{a}$	$12.16+1.08^{a}$	$10.35+0.99^{a}$
3. STZ + silymarin Group	$7.41+1.26^{c}$	$6.40+0.52^{c}$	$7.28+0.22^{b}$	$8.59+0.53^{ab}$
4. STZ + *Nigella sativa* Group	$6.77+0.21^{c}$	$7.36+0.28^{c}$	$7.16+0.15^{c}$	$7.69+0.18^{b}$
5. STZ + Rosiglitazone+ *Nigella sativa* Group	$6.45+0.26^{c}$	$7.88+0.90^{c}$	$7.87+0.44^{b}$	$7.74+0.31^{b}$
6. STZ + Rosiglitazone+ silymarin Group	$6.78+0.30^{c}$	$7.80+0.30^{c}$	$8.08+0.35^{b}$	$7.19+0.39^{b}$

Means within the same column in each category carrying different letters are significant at ($P \leq 0.05$).

Table (3): Effect of Rosiglitazone drug, *Nigella sativa*, silymarin and their combination on hemoglobin (HB) concentration (g/dl) of and diabetic male albino rats (mean ± SE). (N = 7).

Groups	Week1	Week2	Week3	Week4
1. STZ (diabetic non treated group)	13.81 ± 0.16^{bc}	13.70 ± 0.22^{b}	13.52 ± 0.39^{b}	14.28 ± 0.37^{bc}
2. STZ + Rosiglitazone Group	15.55 ± 1.37^{b}	14.78 ± 1.28^{ab}	13.67 ± 0.99^{b}	12.70 ± 1.01^{c}
3. STZ + silymarin Group	14.31 ± 1.37^{bc}	16.46 ± 0.73^{a}	15.42 ± 0.88^{ab}	16.14 ± 0.82^{ab}
4. STZ + *Nigella sativa* Group	16.31 ± 0.71^{a}	16.01 ± 0.79^{a}	16.14 ± 0.55^{a}	16.79 ± 0.38^{a}
5. STZ + Rosiglitazone+ *Nigella sativa* Group	14.01 ± 0.76^{bc}	15.77 ± 0.31^{ab}	15.31 ± 0.69^{ab}	14.45 ± 0.95^{b}
6. STZ+Rosiglitazone+silymarin Group	11.76 ± 0.36^{d}	12.74 ± 0.56^{b}	13.79 ± 0.71^{b}	15.86 ± 0.84^{ab}

Means within the same column in each category carrying different letters are significant at ($P \leq 0.05$).

Table (4): Effect of Rosiglitazone drug, *Nigella sativa*, silymarin and their combination on hematocrit (PCV %) in diabetic male albino rats (mean ± SE). (N = 7).

Groups	Week1	Week2	Week3	Week4
1. STZ (diabetic non treated group)	$33.78+0.69^{c}$	$35.10+0.66^{d}$	$35.69+1.07^{c}$	$37.49+1.12^{c}$
2. STZ + Rosiglitazone Group	$27.84+0.79^{d}$	$29.38+0.56^{e}$	$27.51+2.35^{d}$	$24.66+2.65^{d}$
3.STZ +silymarin Group	$57.46+1.99^{a}$	$61.49+2.28^{a}$	$50.46+2.93^{ab}$	$47.86+2.53^{b}$
4. STZ +*Nigella sativa* Group	$46.45+2.65^{b}$	$48.30+2.32^{c}$	$53.61+0.83^{a}$	$57.38+0.82^{a}$
5.STZ+Rosiglitazone+ *Nigella sativa* Group	$46.12+2.10^{b}$	$47.56+0.95^{c}$	$35.74+3.23^{c}$	$38.58+2.91^{c}$
6.STZ+Rosiglitazone+silymarin Group	$36.40+1.41^{c}$	$38.20+1.73^{d}$	$42.12+2.65^{bc}$	$43.89+2.84^{bc}$

Means within the same column in each category carrying different letters are significant at ($P \leq 0.05$).

Table (5): Effect of Rosiglitazone drug, *Nigella sativa*, silymarin and their combination on serum lactate dehydrogenase enzyme activity (LDH) (µIU/ml) in diabetic male albino rats (mean ± SE). (N = 7).

Groups	Week1	Week2	Week3	Week4
1. STZ (diabetic non treated group)	805.00+106.45^{e}	769.33+101.00^{c}	736.66+97.80^{bc}	704.66+80.80^{bc}
2. STZ + Rosiglitazone Group	2526.66+365.48^{a}	2855.00+286.84^{a}	3266.66+414.86^{a}	3394.33+300.98^{a}
3.STZ +silymarin Group	406.66+22.01^{d}	373.33+26.19^{d}	350.00+27.23^{d}	1141.33+121.74^{b}
4. STZ +*Nigella sativa* Group	372.00+30.68^{d}	341.00+19.85^{d}	314.16+23.46^{d}	286.83+18.83^{d}
5. STZ+Rosiglitazone+ *Nigella sativa* Group	847.33+76.85^{c}	804.16+81.95^{c}	746.33+91.74^{bc}	706.83+54.87^{bc}
6. STZ+Rosiglitazone+silymarin Group	1437.66+200.15^{b}	1381.66+279.19^{b}	1296.66+274.7^{b}	1141.33+121.74^{b}

Means within the same column in each category carrying different letters are significant at ($P \leq 0.05$).
a: The highly significant value.(b) : The 2nd significant value, (C) The 3rd significant value, (d) The 4th significant value ,(E) The 5th significant value, (F) The 6th significant value.

DISCUSSION

The present study was an attempt to evaluate the hypoglycaemic effect of Rosiglitazone, *Nigella sativa*, silymarin each alone and the combination of Rosiglitazone with either *N. sativa* or silymarin when given to normal and diabetic rats for 28 successive days. Their effects on Some haematological parameters as well as the effect on L.D.H hormone was also investigated.

Because of low cost, traditional medicinal plants raise significant interest to prevent morbidity and mortality from chronic diseases where low or middle income populations are important [25].

Effect on blood picture parameters

Concerning the effect on some blood picture parameters, the obtained results revealed that all the tested plant drugs and their combinations afforded non significant changes in the total RBCs count of normal rats. Whereas STZ- diabetic rats showed a significant decrease in RBCs along the entire course of the experiment when compared with buffer group. All treatments when given to diabetic rats failed to revert the RBCs count to the buffer group except sliymarin treated group after first week post treatment which showed a significant increase and after 2nd week which revealed a non- significant change (table 1). Yet, the various treatments induced a significant elevation in RBCs counts of the diabetic treated groups when compared with STZ-treated group except Rosiglitazone after last two weeks , *N.sativa* after the 3rd and 4th week post drug administration which showed a significant decrease when compared with STZ-treated group.

Concerning the effect on total WBCs count, our results revealed that STZ elicited a significant increase in WBCs count after the first two week post-treatment along with non-significant changes on the last two weeks post STZ administration when compared with buffer group (Table 2). Meanwhile, treatment of STZ-diabetic group with Rosiglitazone elicited a significant elevation in total WBCs count along the entire period of the experiment when compared with both buffer and STZ – treated diabetic group. Whereas, treatments of other diabetic groups afforded significant decreases along the first and second week post-drugs administration when compared with STZ-treated group. However the previous effects obtained after the first and 2nd week post drugs administration were nonsignificant when compared with buffer group.

On normal rats, all treatments afforded nonsignificant changes in total WBCs counts along the entire course of the experiment except the group given N.sativa which showed a significant decrease along the entire course of the experiment as well as the group treated with Rosiglitazonenida + *N.sativa* after the 4th week post-drug administration which revealed a significant decrease when compared with normal control group. While a significant increase in WBCs count was observed after the 1st week post-drug administration in the group treated with silymarin (Table 2).

Regarding the effect of the tested plant drugs on Hb content, different treatments exhibited non-significant changes along the entire period of the experiment when compared with normal control group (Table 3).

While on diabetic group, it was clear that STZ elicited a significant decrease in Hb content along the entire period of the experiment when compared with buffer group. The same effect was noticed in the diabetic group treated with Rosiglitazone + silymarin after the end of the first week post drugs administration when compared with STZ – diabetic group, together with non-significant changes along the 2nd, 3rd and 4th week post treatment. On the other hand, the treatments of other diabetic groups with Rosiglitazone, silymarin, *N.sativa* and Rosiglitazone + *N.sativa* for 28 successive days induced significant elevations in Hb contents when compared with STZ – diabetic grops along the course of the study, Except 3rd and 4th weeks for the diabetic group treated with Rosiglitazone and after the 1st week for the group treated with silymarin and the group treated with Rosiglitazone + silymarin after 1st and 4th week post drug administration which showed non-significant changes when compared with STZ – diabetic group (Table 4) .

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Concerning the effect on PCV% of normal control groups, the various treatments elicited non-significant changes along the entire period of the experiment when compared with normal control group. Induction of diabetes with STZ caused significant decrease in PCV% along the course of the study when compared with buffer group. The same previous effect was obtained with the group treated with Rosiglitazone when compared with STZ-diabetic group. Meanwhile, the other treatments of diabetic rats afforded a significant increase in PCV% except on the 3rd and 4th week post Rosiglitazone + *N.sativa* administration and on the first two weeks for the group treated with Rosiglitazone + silymarin which showed non-significant changes when compared with STZ – treated group alone (Table 4).

The obtained decrease in RBCs count in STZ diabetic group could be possibly attributed to degenerative changes induced in haemopoietic system. Our results were supported with that reported by [24]. She reported degenerative changes in the liver represented by swollen hepatic cells with cytoplasmosis of their cytoplasm (severe hydropic degeneration) beside hyperplastic kuffer's cells. Some portal areas revealed leucocytic aggregations mainly lymphocytes beside hyalinized wall of the hepatic arterioles and proliferation of bile duct epithelium. In addition to a possible depressing of bone marrow and other haemopoietic organs. Rosiglitazone induced a marked increase in RBCs count after the first two weeks followed by a marked decrease after 3rd and 4th weeks post – drug administration to diabetic rats. Our result after last two weeks were in full agreement with [25] who reported that thiazolidinediones causes anaemia, weight gain and oedema. Indicating that Rosiglitazone failed to reverse the effect of STZ after last two weeks however, it succeeded in reverting the effect of STZ after first two weeks post drug administration. This could be attributed to dose of the drug, route and duration of administration as well as animal species. The previous response was also observed with the combination of Rosiglitazone + *Nigella sativa*. The other treatments given to diabetic rats afforded a significant elevation in RBCs count along the entire period of the study when compared with STZ treated group alone. An effect which might be possibly attributed to stimulation of bone marrow and other haemopietic system organs as increased release of RBCs from spleen or stimulation of erythropoietin hormone. silymarin induced a significant increase in WBCs count after 1st week post drug administration Moreover, it decreased significantly the WBCs counts in STZ – diabetic group along the first two weeks post-administration when compared with the elevated count caused by STZ reverting its value to nearly the control level.

The decreased WBCs count induced by *N. sativa* in normal rats as well as in diabetic rats (succeeded in reverting high count induced by STZ to nearly normal values) disagree with [26]. They reported that total WBCs in rats treated with *N. sativa* increased due to impairment of the immune system in diabetic rats. This discrepancy might be attributed to differences in doses, route and duration of drug administration.

The same previous effect was obtained with the combination of *N.sativa* and Rosiglitazone + silymariarin with Rosiglitazone in diabetic rats along the first two weeks post administration also.

Rosiglitazone elicited a significant elevation in WBCs count of diabetic rats along the entire course of the experiment when compared with buffer group and STZ diabetic group. This might be due to inflammatory changes induced in the liver induced in diabetic rats as previously discussed.

Effect on serum lactic dehydrogenase activity

At the meantime, it was obvious that STZ afforded a significant elevation in serum LDH activity when compared with buffer group along the entire period of the experiment. The administration of Rosiglitazone for 28 successive days afforded also a more profound elevation in serum LDH level when compared with both buffer and STZ group. The combination of Rosiglitazone with either *N.sativa and* silymarin afforded non-significant changes in case of it's combination with N.sativa and a marked increase in the enzyme activity after first two weeks. together with a slight increase after last 2 weeks in case of its combination with silymarin when compared with STZ treated group. However, *Nigella sativa* or silymarin each alone induced a significant decrease in serum LDH activity along the entire course of the study when compared with STZ treated group (table 5).

CONCLUSIONS

From the obtained results, Rosiglitazone drug is not an ideal anti diabetic drug, since it showed many side effects represented by high level of L.D.H hormone in groups treated with Rosiglitazone .Therefore we recommended the use of the combination of Rosiglitazone + Silymarin and Rosiglitazone + *N. sativa* which is known as a hepatoprotective drug in treatment of diabetic patients to avoid the proven hazardous effect of Rosiglitazone on cardiovascular system and to overcome the side effects of Rosiglitazone on heart.

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دور بعض المركبات فى تعديل بعض قيم صورة الدم ونشاط إنزيم اللكتيك ديهيدروجينيز فى الجرذان المعالجة بعقار الروزيجليتازون

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لقد تم تقسيم الجرذان إلى سبعة مجموعات فرعية كل واحدة 10 جرذان.

(1) المجموعة الأولى: أعطيت محلول متعادل وتركت كمجموعة ضابطة.

(2) المجموعة الثانية: أعطيت استربتوزوتوسين عن طريق الحقن داخل الغشاء البريتوني وذلك لإحداث مرض السكر تجريبياً وتركت بدون علاج كمجموعة ضابطة.

(3) المجموعة الثالثة: مصابة بمرض السكر تجريبياً وتم علاجها بالروزيجليتازون بجرعة قدرها 0.58مجم/100 جرام من وزن الجسم يومياً ولمدة 28 يوماً متتالية عن طريق الفم.

(4) المجموعة الرابعة: مصابة بمرض السكر تجريبياً وتم علاجها بالسليمارين يومياً ولمدة 28 يوماً متتالية عن طريق الفم بجرعة قدرها 50مجم/100 من وزن

(5) المجموعة الخامسة: مصابة بمرض السكر تجريبياً وتم علاجها بحبة البركة بجرعة قدرها 0.25جرام/100جرام من وزن الجسم يومياً ولمدة 28 يوم.

(6) المجموعة السادسة: مصابة بمرض السكر تجريبياً وتم علاجها بخليط الروزيجليتازون مع حبة البركة بنفس الجرعات السابقة ولنفس المدة.

(7) المجموعة السابعة: مصابة بمرض السكر وتم علاجها بخليط الروزيجليتازون مع السليمارين بنفس الجرعات السابقة ولنفس المدة.

تم تجميع عينات دم من كل فار بعد نهاية الأسبوع الأول، الثاني، الثالث والرابع من نهاية العلاج. وذلك لقياس نسبة الدهون المختلفة فى النصل وكذا قياس نسبة الهرمونات وأظهرت نتائج الدراسة الآتي:

التأثير على كرات الدم الحمراء:

لم يؤد إعطاء العلاجات المختلفة وخليط منها إلى إحداث تغيرات معنوية في عد كريات الدم الحمراء خلال فترة التجربة في الجرذان الطبيعية الغير مصابة بمرض السكر بينما أدت إصابة الجرذان بمرض السكر إلى حدوث نقص معنوي في عدد كريات الدم الحمراء طوال فترة التجربة (4 أسابيع من نهاية العلاج) وذلك عند مقارنتها بالمجموعة الضابطة (التى عولجت بالمحلول المتعادل) كما أدى علاج المجموعات المختلفة المصابة بمرض السكر بالعلاجات المختلفة إلى حدوث زيادة معنوية في عدد كريات الدم الحمراء عند مقارنتها بمجموعة الضوابط (المصابة معملياً بالسكر والغير معالجة) وذلك على مدار مدة التجربة فيما عدا

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الأسبوع الثالث والرابع للمجموعة المعالجة بالروزيجليتازون وكذا بعد الأسبوع الثالث في المجموعة الضابطة المعالجة بالروزيجليتازون + حبة البركة والتى أظهرت نقصاً معنوياً في عدد كريات الدم الحمراء عند مقارنتها بالمجموعة المصابة بمرض السكر.

التأثير على كرات الدم البيضاء:

أما بالنسبة للتأثير على كريات الدم البيضاء فلم تؤدي العلاجات المختلفة إلى حدوث أي تغيير معنوي في عدد كريات الدم البيضاء في مجموعات الجرذان الطبيعية طوال فترة التجربة فيما عدا المجموعة المعالجة بحبة البركة والذي حدث لها نقص معنوي في عدد كريات الدم البيضاء على مدار الأسابيع الأربعة عند مقارنتها بمجموعة الضوابط. بينما أدى إحداث مرض السكر إلى حدوث زيادة ملحوظة في عدد الكريات البيضاء على مدى الأسبوع الأول والثاني بالإضافة إلى حدوث تغيير غير معنوي على مدار الأسبوع الثالث والرابع بعد العلاج.

أدى علاج المجموعة المصابة تجريبياًٌ بمرض السكر بالروزيجليتازون إلى حدوث زيادة معنوية في عدد الكريات البيضاء طوال فترة التجربة. بينما أدى علاج المجموعات الأخرى بالعلاجات الأخرى إلى حدوث نقص معنوي في عدد كريات الدم البيضاء بعد نهاية الأسبوع الأول والثاني من نهاية العلاج علاوة على عدم حدوث تغييرات معنوية بعد نهاية الأسبوع الثالث والرابع من العلاج عند مقارنتها بمجموعة الضوابط (المصابة بمرض السكر).

التأثير على نسبة الهيموجلوبين فى الدم:

أما بالنسبة لتركيز الهيموجلوبين فلم يحدث أي تغيير معنوي بالنسبة لجميع المجاميع الطبيعية المعالجة بالعلاجات المختلفة طوال فترة التجربة عند مقارنتها بمجموعة الضوابط الطبيعية الغير معالجة. بينما حدث نقص غير معنوي في تركيز الهيموجلوبين في مجموعة الجرذان المصابة بمرض السكر تجريبياًٌ طوال فترة التجربة فيما عدا بعد الأسبوع الثالث من العلاج والذي أظهر نقصاً معنوياً في تركيز الهيموجلوبين عند مقارنته بمجموعة الضوابط (المعالجة بالمحلول المتعادل). بينما أدى علاج جميع المجاميع المصابة بمرض السكر بالعلاجات المختلفة إلى حدوث تغيرات غير معنوية في نسبة الهيموجلوبين طوال فترة الأسابيع الأربعة فيما عد المجموعة المعالجة بحبة البركة طوال فترة التجربة، وكذا بعد نهاية الأسبوع الثاني في المجموعة المعالجة بالسليمارين وكذا المعالجة بخليط من الروزيجليتازون مع حبة البركة والتى أظهرت زيادة معنوية في تركيز الهيموجلوبين.

التأثير على حجم الخلايا المضغوطة:

أما بالنسبة لحجم الخلايا المضغوطة فلم يحدث أي تغيير معنوي طوال فترة التجربة في الجرذان الطبيعية طوال فترة التجربة عند مقارنتها بمجموعة الضوابط.

بينما أدت الإصابة بمرض السكر إلى حدوث نقص معنوي في حجم الخلايا المضغوطة طوال فترة التجربة عندما قورنت بالمجموعة الضابطة (المعالجة بالمحلول المتعادل). أدى علاج جميع المجموعات المصابة بمرض السكر معملياً بالعلاجات المختلفة إلى حدوث ارتفاع كبير في حجم الخلايا المضغوطة طوال فترة التجربة عند مقارنتها بالمجموعة المصابة بمرض السكر تجريبياًٌ فيما عدا المجموعة المعالجة بالروزيجليتازون بمفردها أ، خليط منه مع السيليمارين حيث أظهرت نقصاً معنوياً وغير معنوياً على التوالي طوال فترة التجربة وكذا بعد نهاية الأسبوع الثالث والرابع بعد نهاية العلاج بالروزيجليتازون + حبة البركة والتى أظهرت تغييراً غير معنوياً.

التأثير على نشاط إنزيم اللاكتات ديهيدروجينيز:

أما بالنسبة لنشاط خميرة اللاكتات دي هيدروجيناز في الجرذان الطبيعية فقد أحدثت العلاجات المختلفة تأثيراً غير معنوياً طوال فترة التجربة عند مقارنتها بمجموعة الضوابط ماعدا المجموعة المعالجة بالروزيجليتازون بمفرده والتى أظهرت زيادة معنوية في نشاط خميرة اللاكتات دي هيدروجيناز طوال فترة الدراسة.