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Original Article

Dyslipidemia and antioxidant properties of Lycopene and Vitamin E in alloxan-induced diabetes

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ABSTRACT

Cardiovascular diseases implicated in Diabetes mellitus include diabetic dyslipidemia consisting of low high density lipoprotein, increased triglycerides and postprandial lipidemia. This is resulting from high level of glucose or hyperglycemia leading to oxidative stress via glucose auto-oxidation, damaging various organs including the liver. The aim of this study is to evaluate the dyslipidemia and antioxidant properties of Lycopene and Vitamin E in the management of diabetes and its associated lipidemia. The experimental Albino rats used were divided into eight groups. The first group served as normal control and was not induced with alloxan, while Groups 2 to 8 were made to develop diabetes with 50mg/kg body weight of rats with alloxan for 72 hours. Group 2 was not treated and served as a negative control while Groups three to eight were treated with three concentrations of Lycopene (80mg, 90mg, 100mg/kg body weight) and Vitamin E (0.1mg,0.2mg, 0.3mg/kg body weight) respectively for four weeks. Blood samples were collected at weekly intervals and analyzed for glucose, triacylglyceride, cholesterol, superoxide dismutase(SOD) and catalase (CAT).The increased level of glucose(mg/dl) was significantly (($p< 0.05$) reduced from the diabetic range of 175.00 ± 6.02-173.67 ± 1.86 to that of 116.05 ± 0.33-$115.21\pm0{,}04$ and 116.16 ± 0.01-114.81 ± 0.02 after treatment with Lycopene (100mg) and Vitamin E (0.3mg).The decreases were significant as the doses were increasing. After induction of diabetes, triacylglycerides and cholesterol were significantly increased showing lipidemia, but were reduced by Lycopene and Vitamin E especially at higher doses. The diabetic level of SOD (132 ± 57.02) and that of CAT (95.33 ± 1.20) after the 4th week, were reduced by Lycopene and Vitamin E to 24.67 ± 0.67 and 26.00 ± 0.57, for SOD :24.67 ± 0.76 and 26.00 ± 0.57 for CAT respectively. This work has shown that Lycopene and Vitamin E could be used in management of lipidemia and oxidative stress in diabetes mellitus.

Keywords: Antioxidant, Diabetes mellitus, Dyslipidemia, Lycopene, Triacyglycerol, Vitamin E

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INTRODUCTION

Diabetes mellitus(DM) is an endocrine chronic disease characterized by hyperglycemia, hyperlipemia, negative nitrogen balance and sometimes ketonemia [1]. The incidence is increasing with the improving living standard, the change of eating habits and rapid development of medical examination technology, with an estimation of 323 million adults being affected and 5.1 million deaths recorded [2]. In DM, high level of glucose found in the blood can lead to oxidative stress via glucose auto-oxidation and can damage various organs [2]. The eyes, kidneys, nerves, heart, and blood vessels are organs that may undergo long term damage and dysfunction in DM [3].

Cardiovascular diseases that occurs in patients with diabetes include diabetic dyslipidemia consisting of low high density lipoprotein (HDL), increased triglycerides and postprandial lipemia [4]. The oxidative damage is kept in check by complex network of antioxidants defense and repair system, which could be synthesized in the body or obtained from diet with Vitamin E being one of the best [5]. Glycemic homeostasis in living organism is compromised in diabetes and when exacerbated leads to several complications [6]. The ability of the therapeutic agents to restore glycemic balance in hyperglycemic condition is an index of their anti-diabetic properties [6].

Health and economic burden of diabetes has become critical to warrant urgent prevention and treatment. In all, with specific components of vegetable and functional foods having proven health values, dietary intervention may become valuable in the management of diabetes mellitus [7].

Lycopene an antioxidant in red fruits and vegetables such as watermelon, tomatoes and grapes [7] have shown to have potential antioxidant properties[8]. It has been suggested that antioxidants reduce oxidative stress and scavenge free radicals in diabetes [2]. It is speculated that lycopene capability to lower blood glucose, improve insulin resistance and lipid metabolism are due to its improvement of oxidative damage and scavenging of free radicals [2]. It is reported that Lycopene therapy significantly improved the blood glucose levels and body weight of diabetic rats[9].Moreover, scientific studies provided by extensive literature survey reveals the lycopene antioxidant and anti-diabetic activities [10,11] .

There are considerable epidemiological evidence favouring an inverse relationship between vitamin E intake and cardiovascular disease as well as convincing observation in vitro and in vitamin E-supplemented animal models with a report that, the evaluation of the vitamin E status of high-risk populations with oxidative stress has been limited to the determination of total plasma levels showing its ability to block the oxidative stress [12]. Moreover, there is clinical evidence that high intake of lycopene and vitamin E may be associated with a decreased risk of coronary heart disease[13]. However the dyslipidemia and antioxidants properties of Lycopene and Vitamin E supplementation in Diabetes therapy are rarely reported and this present study is geared towards that attempt.

MATERIALS AND METHODS

Animals: The 72 albino rats used in this research were obtained from the department of Veterinary Science, University of Nigeria, Nsukka. The rats were 6-10 weeks old and weighed between 200-320g. The rats were allowed to adapt to their environment for 2 weeks before full commencement of the experiment. They were fed with feeder's chow obtained from Bendel feeds and Flour mill Ltd.

The drugs used in this work- Lycopene, Vitamin E and Alloxan were purchased from Pioneer enterprise, Emzor and BDH respectively.

The rats were divided into eight groups. Seven of the eight groups were made diabetic by injecting 50mg/kg body of alloxan. Development of diabetes was allowed for 3 days at the end of which the hyperglycemic blood level were measured and established. Then the diabetic animals were treated with lycopene and vitamin E for four weeks as follows.

Group 1: Normal Control; Non – diabetic and No Treatment with Lycopene and Vitamin E.
Group 2: - Diabetic control - Diabetic and No Treatment with Lycopene and Vitamin E
Group 3 - Diabetic and Treated with Lycopene (80mg/kg)
Group 4: - Diabetic and treated with Lycopene (90mg/kg)
Group 5 :- Diabetic and treated with Lycopene (100mg/kg)
Group 6: - Diabetic and treated with Vitamin E (0.1mg/kg)
Group 7: - Diabetic and treated with Vitamin E (0.2mg/kg)
Group 8: - Diabetic and treated with Vitamin E (0.3mg/kg)

Collection of blood samples: The rats were sacrificed painlessly under chloroform anesthesia. Blood was collected at weekly intervals by cardiac

puncture, centrifuged at 3000 rpm for 10minutes and serum was collected for further analysis.

Determination of biological variables: The serum activities were determined by spectrophotometric methods for Glucose using glucose oxidase-peroxidase method as described by Monica [14], triacyglycerol level, using glycerokinase peroxidase method of Tietz [15] and total cholesterollevel using cholesterol oxidase peroxidase (CHOA-POD) method of Roeschlau [16]. Superoxide dismutase and catalase were determined spectrophotometrically (Beckman DU 640) using commercially available kit RANSEL, Randox Lab. Ltd, UK, and Karen Reiner method [17] respectively. The serum levels were monitored after 1, 2, 3 and 4th week of treatment.

Statistical Analysis: The data obtained were expressed as Mean±Standard Error of Mean (M±SEM) of triplicate analysis. One Way Analysis of Variance (ANOVA) and pot hoc LSD were used to test for differences in the mean the treatment group using SPSS 20 package. The level of significance was set at $p < 0.05$.

RESULTS

Table 1 shows that alloxan diabetes significantly ($p< 0.05$) raised the glucose level(mg/dl) from a range of 80.14±9.15 -66.39± 3.56 for normal control rats without diabetes to a diabetic range of 173.67± 1.86- 175.00± 6.02. Both lycopene (100mg) and vitamin E (0.3mg) significantly ($p< 0.05$) reduced the glucose level to respective ranges of 116 .05 ± 0.3 - 115.21±0.04 and 116.16±0.01 – 114.81± 0.02 in the first and the last week of treatment respectively. As the doses of lycopene and vitamin E were increasing, the glucose level was decreasing with vitamin E more pronounced than lycopene.

Table 2 shows that the triacylglycerol level (mmol/l) in group I (117.44± 1.03) was increased to a diabetic level of 184.36± 0.06 in the first week and then to 181.91± 5.66 in the 4th week. lycopene and vitamin E respectively decreased the triacyglycerol level to a range of 160.38± 2.03 - 154.08± 1.29 and 129.90± 2.31 -120.17± 0.09 in the 1st and 4th weeks respectively. Vitamin E significantly reduced triacylglycerol level more than the lycopene.

Table 3 shows the effect of lycopene and vitamin E on cholesterol level (mmol/l). The induction of diabetes raised the cholesterol level from a normal level range of 97.32±0.16 - 98.67±0.04 to a diabetic level range of 129.40±0.55- 133.94±2.54 for 1st and 4th weeks respectively. Lycopene and vitamin E reduced the cholesterol level to a range of 126.66± 0.88 – 125.45±0.90 and 123.54±1.65-122.74±1.12 after 1st and the 4th weeks of treatment respectively. Vitamin E reduced the cholesterol level more than lycopene though not significantly. Table 4 shows the effect of lycopene and vitamin E on superoxide dismulase (SOD)level (U/L). The normal range of 574.67±159.00 -663.33±166.66 was reduced to 184.00± 76.00 on the 1st week and 132.00±57.22 on the 4th week of treatment. lycopene reduced the SOD level to 486.00±76.00 on the 1st week and 104.62±19.34 on the 4th week while vitamin E (0.3mg) reduced it to 354.33±7.18 and 356.67±2.40 on the 1st and 4th week respectively.

Table 5 shows that the catalase level (U/L) range of 133.67±0.88- 142.33±1.86 for group-1 were reduced to a diabetic range after induction of diabetes to 80.67±33.33 in the 1st week and 95.33±1.20 on the 4th week. Lycopene (100mg) and vitamin E (0.3mg) reduced the level of CAT to 87.33± 0.33 in the 1st and 24.67±0.67 in the 4th week while that of vitamin E was 17.33±0.33 on the 1st and 26.00+0.57 on the 4th week.

DISCUSSION

The significant increases in the glucose, triacylglycerol and cholesterol levelsin diabetic animals (Tables 1-3) are indications of diabetic conditions and lipidemia as a result of alloxan diabetes. The alloxan being a carcinogen and cytotoxic glucose analog was used here as a diabetogenic agent to destroy the pancreas and thus insulin metabolism leading to lipidemia by bocking the utilization of glucose and increasing the release of triacylglycerol and cholesterol which is consistent with the report of literature [6].

Alloxan significantly ($p<0.05$) induced a form of insulin-dependent diabetes mellitus after three days administration and raised glucose level. Triacyglycerol, cholesterol, SOD and catalase levels as makers for the accompanied abnormality in diabetes [18] were also affected likewise.

There were significant decreasesin all parameters with the administration of different doses of lycopene and vitamin E especially after the 4th week, showing that as the concentration and days of administration were increasing, levels of all the parameters analyzed were decreasing. Generally vitamin E proved more effective than lycopene. This is consistent with the report of Singh *et al* [3] which reported that Lycopene and vitamin E possessed ability to reduce lipidemia.

The reduction of lipidemia by lycopene and vitamin E was attributed to the ability of the antioxidants to balance the free radicals generated

from alloxan diabetes, hence preventing peroxidation of the lipid components of the cell membrane. Disruption of membrane integrity is a common causative factor attributed to increase in the release or leakage of cellular contents [19].This finding is consistent with the reports of Li et al. [20].While that of Catalase level is in conformity with the finding of Goth [21].

Conclusion: This work has shown that after four weeks of alloxan injection, the glucose, triacylglycerol and cholesterol levels were significantly ($p<0.05$) increased, butlater reduced by treatment with lycopene and vitamin E. Vitamin E was seen to be more effective and reduced these three parameters more significantly than lycopene. SOD and catalase were likewise reduced by Lycopene and Vitamin E showing pronounced Dyslipidemia and antioxidant properties.

Conflict of interest: No conflict of interest associated with this work.

Contribution of authors: The authors declare that this work was done by the authors named in this article and all liabilities pertaining to the claims relating to the content of this article will be borne by the authors.

Table 1 Effect of Lycopene and Vitamin E on Glucose Level (mg/dl) in Alloxan Diabetes After Four Weeks of Treatment in Albino Rats.

TREATMENT	**Wk1**	**WK 2**	**Wk 3**	**Wk4**
NOMAL	66.39	76.78	73.87	80.14
	$\pm$3.56^{ab}	$\pm$4.73^{ab}	$\pm$1.50^{ab}	$\pm$9.15^{ab}
ALLOX-INDUCED	175.00	180.10	169.00	173.67
	$\pm$6.02^{ab}	$\pm$5.35^{ab}	$\pm$1.00^{ab}	$\pm$1.86^{ab}
LYCO(80mg/kg)	117.78	117.28	117.07	116.94
	$\pm$.03^{ab}	$\pm$.05	$\pm$.03^{ab}	$\pm$.03^{ab}
LYCO(90mg/kg)	117.53	117.39	116.84	116.27
	$\pm$.06^{ab}	$\pm$.17^{ab}	$\pm$.03^{ab}	$\pm$.02^{ab}
LYCO(100mg/kg)	116.05	115.81	115.54	115.21
	$\pm$.03^{ab}	$\pm$.04^{ab}	$\pm$.06^{ab}	$\pm$.04^{ab}
VIT E(0.1mg/kg)	117.85	117.32	117.05	116.68
	$\pm$.02^{ab}	$\pm$.06^{ab}	$\pm$.03^{ab}	$\pm$.03^{ab}
VIT E(0.2mg/kg)	116.67	116.19	115.76	115.43
	$\pm$.03^{ab}	$\pm$.01^{ab}	$\pm$.02^{ab}	$\pm$.02^{ab}
VIT E(0.3mg/kg)	116.16	115.53	115.33	114.81
	$\pm$.01^{ab}	$\pm$.17^{ab}	$\pm$.02^{ab}	$\pm$.02^{ab}

Result Represents Mean $\pm$SEM of Triplicate Sample. Least Significant Difference (LSD) was used to compare the means. Values were considered significant at $p<0.05$ and superscripts with the same letter are significant.

[a] = Significant difference at $p<0.05$ when each group was considered with Normal Control

[b] = Significant difference at $p<0.05$ when each group was considered with the Diabetic Control

[c] = Significant difference at $p<0.05$ when the lycopene was compared with Vitamin C .

Table 2 Effects of Lycopene and Vitamin E on Triacyglycerol Level (mmol/l) in Alloxan Diabetes After Four Weeks of Treatment in Albino Rats.

TREATMENT	Wk1	WK 2	Wk 3	Wk4
NOMAL	117.44	118.77	116.04	121.27
	$\pm$1.03^{ab}	$\pm$.72^{ab}	$\pm$.54^{ab}	$\pm$.43^{ab}
ALLOX-INDUCED	184.36	184.80	185.07	181.91
	$\pm$.06^{ab}	$\pm$.02 ^{b}	$\pm$.04^{ab}	$\pm$5.66^{ab}
LYCO(80mg/kg)	169.35	168.13	167.90	166.93
	$\pm$.03^{abc}	$\pm$.03 ^{b}	$\pm$.65^{ab}	$\pm$.70^{ab}
LYCO(90mg/kg)	166.07	161.11	162.67	158.18
	$\pm$1.64^{abc}	$\pm$.059 ^{b}	$\pm$2.28^{ab}	$\pm$4.50^{ab}

LYCO(100mg/kg)	160.38	157.23	156.33	154.08
	±2.03^{bc}	±.06^{b}	±2.03^{ab}	±1.29^{ab}
VIT E(0.1mg/kg)	166.19	169.36	163.60	174.45
	±3.92^{b}	±.03^{b}	±4.65^{b}	±6.27^{ab}
VIT E(0.2mg/kg)	146.48	132.53	143.72	126.84
	±11.96^{b}	±.017^{ab}	±12.26^{b}	±.08^{ab}
VIT E(0.3mg/kg)	129.90	126.84	124.94	120.17
	±2.31^{b}	±3.02^{ab}	±3.25^{ab}	±.09^{ab}

Result Represents Mean ±SEM of Triplicate Sample. Least Significant Difference (LSD) was used to compare the means. Values were considered significant at $p<0.05$ and superscripts with the same letter are significant.

[a] = Significant difference at $p<0.05$ when each group was considered with Normal Control

[b] = Significant difference at $p<0.05$ when each group was considered with the Diabetic Control

[c] = Significant difference at $p<0.05$ when the lycopene was compared with Vitamin C .

Table 3 Effects of Lycopene and Vitamin E on Cholesterol (mmol/l)inAlloxan Diabetes After Four Weeks of Treatment in Albino Rats.

TREATMENT	Wk1	WK 2	Wk 3	Wk4
NOMAL	97.92	98.45	98.68	98.67
	±0.16^{ab}	±0.72^{ab}	±0.82^{abc}	±0.04^{ab}
ALLOX-INDUCED	129.40	130.70	129.53	133.94
	±0.55^{ab}	±.96^{ab}	±1.24^{abc}	±2.54^{ab}
LYCO(80mg/kg)	126.24	126.18	125.97	126.03
	±0.11^{ab}	±.09^{ab}	±0.10^{abc}	±0.03^{ab}
LYCO(90mg/kg)	125.84	125.60	125.28	125.05
	±0.07^{ab}	±.09^{ab}	±0.11^{abc}	±0.16^{ab}
LYCO(100mg/kg)	126.66	126.42	126.34	125.45
	±.88^{ab}	±.93^{ab}	±0.74^{abc}	±0.90^{ab}
VIT E(0.1mg/kg)	127.74	127.73	126.97	125.96
	±0.66^{ab}	±0.47^{abc}	±0.47^{abc}	±0.44^{abc}
VIT E(0.2mg/kg)	125.95	125.96	125.43	124.74
	±0.44^{ab}	±0.78^{abc}	±0.71^{abc}	±0.48^{ab}
VIT E(0.3mg/kg)	123.52	123.26	122.79	122.74
	±1.65^{b}	±1.23^{abc}	±1.24^{cb}	±1.12^{abc}

Result Represents Mean ±SEM of Triplicate Sample. Least Significant Difference (LSD) was used to compare the means. Values were considered significant at $p<0.05$ and superscripts with the same letter are significant.

[a] = Significant difference at $p<0.05$ when each group was considered with Normal Control

[b] = Significant difference at $p<0.05$ when each group was considered with the Diabetic Control

[c] = Significant difference at $p<0.05$ when the lycopene was compared with Vitamin C .

Table 4 Effects of Lycopene and Vitamin E on SOD X 10^{-3} (U/L) in Alloxan Diabetes After Four Weeks of Treatment in Albino Rats.

TREATMENT	Wk1	WK 2	Wk 3	Wk4
NOMAL	574.67	736.00	735.00	663.33
	±159.83^{ab}	±.577^{ab}	±.577^{ab}	±166.66^{ab}
ALLOX-INDUCED	183.00	167.67	100.33	132.00
	±76.00^{ab}	±.179^{ab}	±.333^{ab}	±57.02^{ab}
LYCO(80mg/kg)	121.00	307.33	418.67	713.00
	±8.50^{ca}	±25.66^{ac}	±1.452^{ab}	±8.66^{ab}
LYCO(90mg/kg)	258.00	396.33	837.00	64.00

	±.11	±.92 [ac]	±.50[ab]	±.57 [b]
LYCO(100mg/kg)	486.00	678.33	904.67	104.67
	±76.00 [ac]	±53.16 [ac]	±.33[ab]	±19.34[bc]
VIT E(0.1mg/kg)	364.67	799.33	924.33	125.67
	±30.17	±112.66[cb]	±10.34[cb]	±.33 [cab]
VIT E(0.2mg/kg)	435.33	471.67	471.33	152.00
	±12.35[b]	±220.16[c]	±221.36[b]	±1.15[abc]
VIT E(0.3mg/kg)	354.33	250.33	184.33	356.67
	±7.18	±.88[ab]	±35.3 [ac]	±2.40[abc]

Result Represents Mean ±SEM of Triplicate Sample. Least Significant Difference (LSD) was used to compare the means. Values were considered significant at $p<0.05$ and superscripts with the same letter are significant.

[a] = Significant difference at $p<0.05$ when each group was considered with Normal Control
[b] = Significant difference at $p<0.05$ when each group was considered with the Diabetic Control
[c] = Significant difference at $p<0.05$ when the lycopene was compared with Vitamin C .

Table 5 Effects of Lycopene and Vitamin E on Catalase X 10^{-3} (U/l)inAlloxan Diabetes After Four Weeks of Treatment in Albino Rats.

TREATMENT	Wk1	WK 2	Wk 3	Wk4
NOMAL	133.67	131.67	135.33	142.33
	±0.88[ab]	±0.33[ab]	±0.33[ab]	±1.86[ab]
ALLOX-INDUCED	80.67	54.33	86.33	95.33
	±33.33[ab]	±0.88[ab]	±0.66[ab]	±1.20[ab]
LYCO(80mg/kg)	59.33	45.33	30.00	35.00
	±0.33 [a]	±12.83 [cab]	±3.055[ab]	±13.01[abc]
LYCO(90mg/kg)	21.33	92.33	21.67	10.67
	±0.35[abc]	±0.33 [cab]	±0.66[abc]	±0.33[abc]
LYCO(100mg/kg)	87.33	40.33	33.67	24.67
	±0.33 [ac]	±0.67[abc]	±0.881[abc]	±0.67[abc]
VIT E(0.1mg/kg)	34.33	43.00	48.33	53.33
	±.03[ab]	±1.00[abc]	±0.33[ab]	±0.33[abc]
VIT E(0.2mg/kg)	60.00	78.33	16.67	31.00
	±13.50[abc]	±17.66[abc]	±0.33[ab]	±0.57[ab]
VIT E(0.3mg/kg)	17.33	62.33	45.67	26.00
	±033[abc]	±17.57[abc]	±0.66[ab]	±0.57[abc]

Result Represents Mean ±SEM of Triplicate Sample. Least Significant Difference (LSD) was used to compare the means. Values were considered significant at $p<0.05$ and superscripts with the same letter are significant.

[a] = Significant difference at $p<0.05$ when each group was considered with Normal Control
[b] = Significant difference at $p<0.05$ when each group was considered with the Diabetic Control
[c] = Significant difference at $p<0.05$ when the lycopene was compared with Vitamin C .

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