Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 10, Issue 3, September 2015 , p.p(140-154)
ISSN 1992 – 0849

Effect of Glibenclamide and Tomato lycopene extract on some biochemical parameters in serum of alloxan Induced diabetic rabbits

[1]Entedhar R. Sarhat , [2]Ayhan R. Mahmood , [3]Mohammed Sh. Abdulla
entedharr@gmail.com[1] , Ayhan4gb@yahoo.com[2] , mohammed777@yahoo.com[3]
[1,2,3]Tikrit University / Natural Resources Researches Center

Received date: 24 / 2 / 2014 **Accepted date: 8 / 3 / 2015**

ABSTRACT

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both, and occurs in almost all populations of the world a variable prevalence. In the present study we evaluated the effect of glibenclamide, and tomato lycopene extract on blood glucose, enzymatic antioxidants, glycated hemoglobin (HbA1c), and malondialdehyde (MDA) in 50 alloxan induced diabetic rabbits. The results showed a significant (P < 0.001) increase in the level of glucose, HbA1c, MDA in alloxan diabetic rabbits in comparison to the control rabbits. A Significant decrease in the level of serum glucose, HbA1c, and MDA in alloxan diabetic rabbits when received glibenclamide daily as single dose 0.5 mg/kg body weight for 20 weeks, and2and 4 mg/kg of tomato lycopene extract for 20 weeks respectively. The result of this study showed a significant (P <0.05) decrease in the mean of serum catalase in alloxan diabetic rabbits in comparison with control group after treatment with 0.5 mg/kg glibenclamide, and 2, 4 mg/kg of lycopene extract a significant (P <0.05)increase in serum catalase was observed in alloxan diabeticrabbit.

The aim of the study was to evaluate the effect of glibenclamide and tomato products on antioxidative status in alloxan induced diabetic rabbits.

Keyword: *diabetes, glibenclamide, lycopene, antioxidants.*

Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 10, Issue 3, September 2015 , p.p(140-154)
ISSN 1992 – 0849

تأثير مستخلص لايكوبين الطماطة والكلابينكلامايد على بعض المعايير الكيموحيوية في مصل الدم الارانب المحدث بها السكري بواسطة الالوكسان

انتظار رفعت سرحت[1] ، ايهان رشيد محمود[2] ، محمد شريف عبدالله[3]
entedharr@gmail.com[1] , Ayhan4gb@yahoo.com[2] , mohammed777@yahoo.com[3]
جامعة تكريت / مركز البحوث للموارد الطبيعية[1,2,3]

تاريخ استلام البحث: 24 / 2 / 2014 تاريخ قبول البحث: 8 /3 / 2015

الملخص

يعد داء السكري أحد الاضطرابات الايضية الذي يتميز بانخفاض مستوى الكلوكوز في الدم نتيجة خلل اما في افراز الانسولين ، عمل الانزيم او كلاهما ويحدث داء السكري على مستويات مختلفة في معظم دول العالم. في الدراسة الحالية تم تقييم تأثير مستخلص لايكوبين الطماطة على كلوكوز الدم والانزيمات المضادة للأكسدةالمالون ثنائي الألدهايدوالهيموكلوبين المسكرفي 50 ارنب محدث بها السكري بواسطة الالوكسان. أظهرت النتائج ارتفاعا معنويا في مستوى الكلوكوز و المالون ثنائي الألدهايدو الهيموكلوبين المسكرفي الارانب المحدث بها السكري بواسطة الالوكسان بالمقارنة مع مجموعة السيطرة. في حين لوحظ انخفاضا معنويا ($P < 0.001$) في مستويات الكلوكوز والمالون ثنائي الألدهايد،و الهيموكلوبين المسكر عندما استخدام جلابينكلامايدبتركيز 0.5 ملغم / كغم من وزن الجسم كجرعة مفردة يوميا ولمدة 20 اسبوع وعند استخدام خلاصة لايكوبين للمطاطة بتراكيز 2، و 4ملغم/كغم من وزن الجسم ولمدة 20 اسبوع مقارنة مع مجموعة السيطرة. كما وأظهرت نَتَائِجُ انخفاضا معنويا ($P < 0.05$) في معدلانزيم الكتاليز في مصل الارانب المحدث بها السكري بالمقارنة مع مجموعة السيطرة. و بعد العلاج بجلابينكلامايد بتركيز 0.5 ملغم / كغم و خلاصة لايكوبين للطماطة بتراكيز 2، و 4ملغم/كغم من وزن الجسماحدثت ارتفاعا معنويا ($P < 0.05$) في مستوى انزيم الكتاليز في مصل الارانب المحدث بها السكري مقارنة مع مجموعة السيطرة ..لذلك هدفت الدراسة الى تقييم تأثير الجلابينكلامايدواستهلاك منتجات الطماطة على الانزيمات المضادة للأكسدةفي مصل الارانب المحدث بها السكري بواسطة الالوكسان.

الكلمات الدالة: داء السكري، جلابينكلامايد، لايكوبين، مضادة الاكسدة.

Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 10, Issue 3, September 2015 , p.p(140-154)
ISSN 1992 – 0849

1.INTRODUCTION

Diabetes is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbance of carbohydrate, fat, and protein metabolism resulting fromdefects in insulin secretion, insulin action, or both. The World Health Organization estimates that over 170 million people worldwide are afflicted with this chronic condition and projects that numbers will rise to over 360 million by the year 2030[1].

Reports suggest that patients with diabetes mellitus are susceptible to increased levels of oxidative stress[2,3]. Poor intravascular substrate control is largely regarded as a factor contributing to the increase in superoxide anions ($O_2\cdot^-$) that has previously been observed in diabetic serum[4]. Other potential mechanisms relating to enhanced oxidative stress in diabetes include a compromised antioxidant defence system, glucose autoxidation, the formation of advanced glycated end-products and a change in the glutathione redox status[5].

The pharmacological agents currently employed, such as sulfonylureas (e.g., glibenclamide), biguanides (e.g., metformin), thiazolidinediones (e.g., pioglitazone) and α-glycosidase inhibitors (e.g., acarbose) act to selectively modulate a specific pathological pathway [6, 7].

Antioxidants are protective agents that inactivate reactive oxygen species (ROS) and thereby significantly delay or prevent oxidative damage. The role of dietary antioxidants including Vitamin-C, Vitamin-E and B-carotenes in disease prevention has received much attention in recent years [8]and much work has been done on them. Very recently a new carotenoid compound called Lycopene, a red pigment which is rich in tomatoes and tomato based food products which is thought to play an important role in defense against chronic diseases like cancer, coronary heart diseases has been discovered [9-12]. Lycopene is a carotenoid compound, an acyclic isomer of B-carotene and does not show any pro vitamin A activity. It is a highly unsaturated hydrocarbon containing eleven conjugated and two unconjugated double bonds. It is the most predominant carotenoid in human plasma present naturally in greater amount than B-carotene and other dietary carotenoids. This perhaps indicates its greater biological significance in human antioxidant defense system [13].

Tomatoes are a valuable source of several micronutrients and phytochemicals including carotenoids, polyphenols, potassium, folate, ascorbic acid and α-tocopherol. An extensive literature survey from all scientific sources revealed that lycopene has antioxidant and anti-

Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 10, Issue 3, September 2015 , p.p(140-154)
ISSN 1992 – 0849

diabetic activity . But the influence of lycopene on diabetic patients who are under the treatment is not clear[14,15].

This study aimed to evaluate the hypoglycaemicand antioxidant activities of glibenclamide, and tomato lycopene extract in alloxan induced diabetic rabbits.

2. MATERIAL AND METHODS

Sample Preparation

- Drugs solution: Glibenclamide 0.5 mg was dissolved in 1 ml distilled water[16].

-Extraction of Lycopene: The Tomatofruits *Lycopersicumesculentum* were used in this study as lycopene source.500 gm of tomato fruit were chopped to small pieces and mixed with distilled water (1 weight: 3 volumes). This mixture was immediately shaken vigorously in a blender for 10 minutes. The mixture then left for two hours in mixer under cooled condition, and then the thick suspension was filtered through several layers of quiz and the extract centrifuged to remove residual materials. The extract volume reduced in incubator at 25 C and crud powder extract obtained.

The lycopene content ranged from 11.47 to 53.90 mg/100 g in tomato paste, 20 mg lycopene powder was weighed and dissolved in 10 ml of distilled water to give 2 mg/ml solution. This solution was administered at a dose of 2 mg/kg and 4 mg/kg body weight using clean and dry oral feeding needle for 21 days.

Experimental animals

The experimental study was carried out on 125adult rabbits (about 1.5-2.1 kg), during the period from June 2011 to May 2012. The animals were divided into 5 groups each group consists of 25 animals:

Group 1 (G1):diabetic rabbits received an alloxan (180 mg/kg intravenous injection)[17].

Group 2 (G2):diabetic rabbits received Glibenclamide 0.5 mg/kg.

Group 3 (G3):diabetic rabbits received lycopene 2 mg/kg[15].

Group 4 (G4):diabetic rabbits received lycopene 4 mg/kg[15].

Group 5 (G5):healthy control rabbits.

Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 10, Issue 3, September 2015 , p.p(140-154)
ISSN 1992 – 0849

Induction of diabetes mellitus

The animals were Diabetes induced by injection of alloxan tetra hydrate (Koch-light laboratories, Coin brook, England -0158 Alloxan puriss) at a dose of 180 mg body weight intravenous in marginal ear vein [17] then after 6 hours the animals were injected with 10 ml of 10% glucose solution subcutaneously. The control group received an equivalent amount of normal saline.

Glucose solution 10% was given for 24 hours instead of the tap water in order to reduce alloxan hypoglycemic shock. The animals with high blood glucose concentration more than 300 mg/dl were considered as diabetic and employed in this study. Tests were performed on diabetic rabbits a week after the onset of diabetes.

Biochemical analysis

-Blood samples

At the end of experiment,5 ml of blood samples were collected by ear vein of the rabbits from(125rabbits) and 1 ml of the sera prepared through centrifuging at 2500×gfor 15 minutes at 30◦C.

- Determination of Blood Glucose

The samples collected from fasting rabbits were used to determination of the fasting blood glucose that measured by enzymatic method [18].

-Determination of glycated hemoglobin

A standard colorimetric method was used to determine the glycated hemoglobin [19].

-Erythrocyte Malondialdehyde assay

Malondialdehyde (MDA) was assayed according to the method of Ohkawa, *et al.*[20]. The reactions to form thiobarbituric acid reactive substances (TBARs) depend on condensation of two molecules of MDA to generate a reddish chromogen that absorbs light at 532 nm wave length.

-Determination of erythrocyte catalase activity (CAT)

Serum Catalase activity (CAT) was determined according to the method used by Ohkawa, *etal.*[20].

Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 10, Issue 3, September 2015 , p.p(140-154)
ISSN 1992 – 0849

-Statistical Analysis

The data for various biochemical parameters were expressed as mean ± SD and compared using one way analysis of variance (ANOVA) test. Values were considered statistically significant when $p < 0.05$,(Graph Pad Software, Inc. San Diego, CA).

3. RESULTS

In present study, serum glucose levels increased high significantly (P <0.01)in rabbits after alloxan administration (355.82±8.4 mg/dI) as compared with control group (130.14±4.3 mg/dI). Table(1) showed a high significant decrease in the level of glucose (P <0.01) in alloxan diabetic rabbits (170.9 ±1.87 mg/dI) when received glibenclamide daily as single dose 0.5 mg/kg body weight for 20 weeks as compared with group 1. The intake of 2 mg/kg of lycopene extract for 20 weeks produced high significant (P < 0.001) decrease (199.68±2.9 mg/dI) in comparison with group1, while after 20 weeks of treatment with 4 mg/kg of lycopene extract, the mean of serum glucose level decreased significantly (P < 0.01) (182.00±2.1 mg/dI)when compared with group1, as shown in. The results also showed no significant differences in glucose level in group 3 and 4 in comparison to that treated with glibenclamide 0.5 mg/kg.

The level of glycated hemoglobin increased significantly (P <0.05) in alloxan diabetic rabbits (7.02±0.49)in comparison to the control group (3.91±0.18). While Glycated hemoglobin levels increased in alloxan diabetic rabbits (4.3±0.2) %Hbreceived glibenclamide 0.5 mg/kg body weight for 20 weeksin comparison to group1.Treatment with 2 mg/kg of lycopene extract for 20 weeks caused a significant decrease(P <0.05) in the level of glycated hemoglobin in alloxan diabetic rabbits (5.87±0.32)%Hbwhen compared with control group, while after 20 weeks of treatment with 4 mg/kg of lycopene extract caused a significant decrease(P <0.05) in the level of glycated hemoglobin in alloxan diabetic rabbits (3.82±0.16)%Hbin comparison with control group . The results of this study showed significant decreases (P <0.05)in Glycated hemoglobin in alloxan diabetic rabbits treated with lycopene extract (2, and 4 mg/kg)in comparison to that treated with glibenclamide 0.5 mg/kg %Hb. The mean of serum catalase decreased significantly (P <0.05) in alloxan diabetic rabbits (7.5±1.1 U/ml) in comparison with control healthy group (12.75±1.12 U/ml). After treatment withglibenclamide0.5 mg/kg body weight for 20 weeks a significant (P <0.05) increase in serum catalase was observed in alloxan diabetic rabbits (8.46±1.4 U/ml)when compared with group 1 as shown in table1. The results also showed that level of catalase

Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 10, Issue 3, September 2015 , p.p(140-154)
ISSN 1992 – 0849

elevated significantly (P <0.05) in alloxan diabetic rabbits when treated with2 mg/kg of lycopene extract for 20 weeks, while the serum catalase increased significantly to (11.8±0.87U/ml) when alloxan diabetic rabbits intake 4 mg/kg for 20 weeks of lycopene extract when compared with theserum catalase level in group1, as shown in table (1). No significant differences (P > 0.05) found in serum catalase level in alloxan diabetic rabbits treated with lycopene extract (2mg/kg) in comparison to that treated with glibenclamide 0.5 mg/kg.

The level of erythrocyte malondialdehyde was significantly(P <0.001)increased in thein alloxan diabetic rabbits(15.17±3.83µmol/L)when compared to the group 1 (8.45±1.97 µmol/L) as shown in table (1), while the level of malondialdehyde inalloxan diabetic rabbits decreased(13.61±3.16µmol/L)significantly (P <0.05) when treated withglibenclamide 0.5 mg/kg body weight for20 weeks compared with group1. while there is no significant differences (P >0.05) demonstrated in malondialdehyde level in alloxan diabetic rabbits (15±3.8 µmol/L)treated with2mg/kg of lycopene extract for 20 weeks in comparison with group 1, also the results showed that there is no significant differences (P > 0.05) in serum malondialdehyde level in alloxan diabetic rabbits (14.41±3.61µmol/L) treated with 4 mg/kg of lycopene extract for 20 weeks of lycopene extract in comparison with group1, as shown in Table (1) .significant differences(P <0.05)observed in serum malondialdehyde level in alloxan diabetic rabbitstreated with lycopene extract (2mg/kg) when compared to that treated with glibenclamide 0.5 mg/kg,but there was no significant differences (P > 0.05) in the level of serum malondialdehyde in alloxan diabetic rabbits intake 4 mg/kg.

Table (1): Effect of Lycopene and of glibenclamide on fasting blood glucose, HbA1c, MDA and Catalase levels.

Group	Glucose (mg/dI)	HbA1c (%Hb)	Catalase (U/ml)	MDA (µmol/L)
G1	355.82±8.4	7.02±0.49*	7.5±1.1*	15.17±3.83***
G 2	170.9 ±1.87**	4.3±0.2*	8.46±1.4*	13.61±3.16*
G 3	199.68±2.9 ***	5.87±0.32*	9.94±0.96*	15±3.8
G4	182.00±2.1**	3.82±0.16*	11.8±0.87*	14.41±3
G 5	130.14±4.3	3.91±0.18	12.75±1.12	8.45±1.97

***(P < 0.05) ,** (P < 0.01), ***(P < 0.001)**

Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 10, Issue 3, September 2015 , p.p(140-154)
ISSN 1992 – 0849

4. DISCUSSION

Diabetes is a metabolic disorder characterized by chronic hyperglycaemia leading to various dysfunctions in the body. Free radical generation is currently suggested to play an important role in the causation and complications of the disease[21].

In present study, the mean serum glucose level increased in rabbits after alloxan administrationas compared with control group (tabe1). The immediate effect of alloxan is the elevation of the blood glucose [22, 23]. Alloxan is the most prominent diabetogenicchemicals in diabetes research, following its administration; alloxan is concentrated in the islets of Langerhansin pancreas and damages the β cells of the isletsin pancreas, by the liberation of oxygen free radicals,and in the liver where it is reduced to dialuric acid with a reduction in antioxidant status[24, 25]. Dialuric acid is unstable in aqueous solutions and undergoes oxidation back to alloxan, accompanied by generation of O_2, H_2O_2 and OH radicals by Fenton type reaction. Hydroxy radicals generated causes single stranded breaks in the islets cellDNA[25-28].

Ssignificantdecreasein serum glucose level observedin alloxan diabetic rabbits after treatment with glibenclamid and lycopene extract for 20 weeks as compared before treatment Table (1) . The results of this study agree with results ofother studies that found tomato products including powder, paste and tomato catchup sauce have significantly beneficial therapeutic effects in rats[29-31]. Ali and Agha [31] showed that lycopene extracted from tomatoes is able to reduce concentrations of glucose. In recent years, various plant extracts have been claimed to be useful for the treatment of diabetes mellitus. According to earlier studies, plant extracts causeantihyperglycemic effect by promoting regeneration of beta cells or by protecting the pancreas from destruction, by restricting glucose load as well as by promoting unrestricted endogenous insulin action or its effect on beta cells to release insulin and activate the insulin receptors to absorb the blood sugar [32-35].

Glibenclamide reduces serum glucose level in alloxan diabetic rabbits by stimulating insulin release from beta-cells of the pancreas. Glibenclamide is one of the sulphonylureases that are useful in the treatment of diabetes mellitus, which is produced its effect via stimulating of endogenous insulin release from pancreas, enhancing peripheral tissue utilization of glucose, or by decreasing the absorption of glucose by intestine[22, 36,37].

Lycopen, a red carotenoid pigment in tomatoes and tomato-based products, is an acyclic form of beta-carotene with a potent antioxidant effect. It has attracted substantial interest

Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 10, Issue 3, September 2015 , p.p(140-154)
ISSN 1992 – 0849

during recent times for its beneficial in reducing oxidative stressing coronary heart diseases and other chronic diseases by increasing serum total antioxidant level[14, 38].

There were a significant elevation in glycosylated hemoglobin, (P <0.05) in alloxan diabetic rabbits when compared with corresponding control group. During diabetic mellitus, the excessglucose present in blood reacts with hemoglobin to form glycosylated haemoglobin. It has been reported that various proteins, including hemoglobin, albumin, collagen, low density lipoprotein, or crystalline proteins undergo non-enzymatic glycation in diabetes. The rate of glycation is proportional to the concentration of blood glucose [39-41]. Glycosylated haemoglobin has been found to be increased over a long period time in diabetes[42].There is an evidence that glycation itself may induce the formation of oxygen-derived free radicals in diabetic condition [43]. Therefore, the measurement of glycosylated hemoglobin is supposed to be a very sensitive index for glycemic control [44].

Administration of lycopene extract to alloxan diabeticrabbits caused a significant decrease(P <0.05) in the level of glycated hemoglobin when compared with alloxan diabetic rabbits as shown in figure 2. These results are in agreement with the results of Bose&Agrawal, [44]whomimproved thatlong-termadministration of tomato that existed lycopenefortype II diabetic patients reduced Glycosylated Hemoglobin [HbA1c].The free radicals generated in this group, inaddition to protein glycation as a result of hyperglycemia could inactivate Glycosylated Hemoglobin [42]. In this studyserum catalase decreased significantly (P <0.05) in alloxan diabetic rabbits in comparison with control healthy group.These results are in agreement with the results of other studies had observed that superoxide dismutase, catalase and glutathione peroxidase decrease in liver, kidney and heart in tissues of patients with diabetesmellitus while the level of reactive oxygen species such assuperoxide anion radicals increase[29, 32]. Where the effect of supplementation withtomato lycopene extract was observed a significant(P <0.05) increased in serum catalase in alloxan diabetic rabbits compared to the control group. The results of this study conform to results of Ibrahim *et al*.[30], and Ali *et al*.,[31] showed that lycopene extracted from tomatoes isable to reduce concentrations of glucose, hydrogenperoxide, serum lipids and increase insulin concentrations, catalase, superoxide dismutase andglutathione peroxidase in diabetic rats. AlsoLycopene has a high antioxidative activity and exerts a protective effect in various diseases [45].

Lipid peroxidation indices measured in plasma-included malondialdehyde, lipid hydroperoxides, and lipoperoxides, which were significantly elevated in diabetic patients regardless of the presence of complications [46].Hydroperoxides have toxic effects on cells both directly and through degradation to highly toxic hydroxylradicals. They may also react with transition metals like iron or copper to form stable aldehydes such as malondialdehydethat will damage cell membranes[47].In this study thereis a significant increase in the mean of serum Malondialdehyde level in alloxan diabetic rabbitswhen compared to the control group, and no significant differences demonstrated in Malondialdehyde level in alloxan diabetic rabbitstreated with lycopene extract when compared to group 2.These results agreement with [49]that indicate the significantly higher levels of lipid peroxidation ratein diabetes when compared with control, and no significant improvement in the lipid peroxidation rate in diabetic patients of tomato supplementation (200g/day), and also several studies have reported have significant increase in lipid peroxides in diabetes mellitus [45, 47, 48].Generally, the effect of the treatment with lycopene extract compared with the effect of glibenclamide, is known as standard drug for diabetes.

We concluded from this study that administration of tomato product produced significant decrease in serum glucose, Malondialdehyde and Glycosylated Hemoglobin [HbA1c] level, and significant increase in serum catalase level in alloxan diabetic rabbits.

REFERENCES

[1] R. Glic, S. Wild, A. Green, R.Sicree, H.King., ***Global prevalence of diabetes***: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004; 27:1047–53.

[2] G.W. Davison, L. George, S.K. Jackso, et al.Exercise, ***free radicals, and lipid peroxidation in type 1 diabetes mellitus***. Free RadicBiol Med.,2002; 33:1543–1551

[3] D.E. Laaksonen, Atalay M, Niskanen L, Uusitupa M, Hänninen O, Sen CK.Increased ***resting and exercise-induced oxidative stress in young IDDM men***. Diabetes Care 1996;19:569–574 .

[4] A. Ceriello, D. Giugliano, A. Quatraro, P.Dello Russo, P.J. Lefebvre., ***Metabolic control may influence the increased superoxide generation in diabetic serum***. Diab. Med , 1991; 8:540–542

[5] D. E. Laaksonen,C.K. Sen., ***Exercise and oxidative stress in diabetes mellitus***. In: Sen CK, Packer L, Hanninen O (eds) Handbook of oxidants and antioxidants in exercise. Elsevier, Amsterdam, 2000;1105–1136

[6] H.P. Rang, M.M. Dale.,***The Endocrine System Pharmacology***. 2nd ed. Longman Group Ltd.; Harlow, UK: 1991:504–508.

[7] A.J.Krentz, C.J. Bailey., ***Oral antidiabetic agents***: current role in type 2 diabetes mellitus. Drugs. 2005;65:385–411.

[8] H.Sies and W. Stah.,Vitamin E, C, ***beta – carotene and othercarotenoids as antioxidants.*** Am. J. Clin.Nutr., 1995; 62: 1315-1321.

[9] S.Agrawal and A.V.Rao.,***Tomato lycopene and low densitylipoprotein oxidation a human dietary intervention study***.Lipids, 1998; 33: 981-4.

[10] S.Agrawal and A. V.Rao,... ***Role of lycopene as antioxidantcarotenoids in the prevention of chronic diseases***, a review:Nutr. Res.1999; 19: 305-23.

[11] K. Frederic, C. Lorena, P. S. Bernstein, J.Farth.,Chemistry, ***distribution and metabolism of tomatocarotenoids and their impact on human health***. Experiment.Biol. Med., 2002; 227: 845-51.

[12] E. Jane, W. H. Upritchard, J. I. Sutherland., ***Effectof supplementation with tomato juice,*** vitamin E and C onLDL oxidation and products of inflammatory activity in type-II diabetes. Diabetes Care 2000; 23: 733-8.

[13] E. S. Ford, J.C. Will, B. A. Bowman, K.M. Narayan., ***Diabetes Mellitus and serum carotenoids findings from the thirdnational and nutritional examination survey***. Am.J. Epidemiol., 1999; 149: 168-76.

[14] K. Anurag, S.Richa,C.Dethikanwaljit.; ***Lycopene attenuates diabetes associated cognitive decline in rats.*** Life sciences, 2008; 83:128-34.

[15] T.Haribabu,D.Kalyani,G.Divakar. ***Evaluation of anti-diabetic activity of Lycopene and its synergistic effect with Metformin hydrochloride and Glipizide in Alloxan induced diabetes in rats. Sch***. Acad. J. Pharm., 2013; 2(2):119-124.

[16] S. Tahira, A.Mahmood and M. Muhammad.***Antihyperglycemic and hypolipidimic effects of methanolic extract of METHANOLIC EXTRACT OF Euphorbia prostrata on Alloxan induced diabetic rabibts***. European Scientific Journal : 2014: 1857 – 7881.

[17]. K.Subhash, C. Bose, B. K.Agrawal**.,** ***Effect of short term supplementation of tomatoes on antioxidant enzymes and lipid peroxidation type-II diabetes***. Indian J. Clin. Biochem. 2007; 22:95–98.

[18] J. Bancroft, and C. Stevens,***Theory and practice of histological techniques***. Churchill Livingstone. London, Melbourne, New York, 1982; 32-33: 275, 372-374.

[19] P. Trinder, ***Determination of glucose in blood using glucose oxidase with an alternative oxygen receptor***, Ann. Clin. Biochem. 1969 6, 24-27.

[20] H. Ohkawa, Na. Ohishi and K. Yagi, ***Assay of lipid peroxides in animal tissue by TBA reaction***, Anal Biochem. 1979;95:351-358.

[21] G.P. Senthilkumar, and S. Evaluation of antioxidant potential of Terminaliachebula fruits studiedin streptozotocin-induced diabetic rats. Pharm. Biol. 2007. 45 (6): 511-518.

[22] L. Koman, K. Kamos, J. Flores, et al. ***Experimental study of the hypoglycemic effect of some antidiabetic plants***. Arch. Inverst. Med . Mex. 1991, 22:87-93.

[23] G.S.Viana,A.C. Medeiros, A.M.Lacerda, L.K. Leal, T.G. Vale, F.J.Matos.,***Hypoglycemic and anti-lipemic effects of the aqueous extract from Cissussicyoides***. BMC Pharmacol, 2004;8: 4-9.

[24] N.Ahmed, and N. Zahra, ***Neurochemical Correlates of Alloxan Diabetes: Glucose and Related Brain Metabolism in the Rat***. Neurochem Res. 2011; 36(3): 494-505.

[25] A. Rohilla, and S. Shahjad., ***Alloxan Induced Diabetes***: ***Mechanisms and Effects Internat J Res Pharmaceut Biomed Sci***. 2012; 3 (2): 819-823.

[26] A. Jörns, R.Munday, M.Tiedge, S. Lenzen.,:***Comparative toxicity of alloxan, N-alkylalloxans and ninhydrin to isolated pancreatic islets in vitro***. J Endocrinol. 1997;155:283–293

[27] E.Peschke, H.Ebelt, H.J.Brömme, D. Peschke.,'***Classical' and 'new' diabetogens comparison of their effects on isolated rat pancreatic islets in vitro***. Cell Mol Life Sci. 2000; 57:158–164.

[28] S. S. Alam, A.H. Khan, G. A.Siehindi, S. Khan, ***Alloxan induced diabetes in rabbits.*** Pakistan Journal of Pharmacology. 2005; 22 (2):41-45.

[29] M. K. Nouri, and A. K. Rezapour, ***Effect of Tomato Supplementation on The Level of Serum Lipids and Lipoproteins in Rats Fed With High Cholesterol***. Advances in Environmental Biology, 2011; 5(9): 3036-3041.

[30] H.S. Ibrahim, L.A. Ahmed, MM. El-din; ***The functional role of some tomato products on lipid profile and liver function in adult rats***. J Med Food.2008; 11(3): 551-9.

[31] M. M. Ali, F.G. Agha,***Amelioration of streptozotocin-induced diabetes mellitus, oxidative stress and dyslipidemia in rats by tomato extract lycopene***. Scand J Clin Lab Invest., 2009;69(3): 371-9.

[32] V.P. Upadhyay, K. Pandey. ***Ayurvedic approach to diabetes mellitus and its management by indigenous resources. In: Bajaj JS ed. Diabetes mellitus in developing countries***. All India Med Sci, 1984:375-7.

[33] G.P.Dubey, A. Aruna, S.Alok. ***Evaluation of D-400, an indigenous Herbal preparation, in diabetes mellitus***. Indian J Int Med 1993:3: 183-6.

[34] S. A.Otoom, S. A. Al-Safi, Z.K.Kerem, A.Alkofahi.***The use ofmedicinal herbs by diabetic Jordanian patients***. J Herb Pharmacother. 2006;6(2):31-41.

[35] J.K.Jadhav, V.J.Masirkar, V. N.Deshmuck. ***Antihyperglycemic effect of diaspyrosmeloxylon bark against alloxan induced diabetic rats***, International Journal of Pharmtech Research, 2009; 1:196-200.

[36] A. J. Krentz, C.J. Bailey. ***Oral antidiabetic agents: current role in type 2 diabetes mellitus.*** Drugs. 2005;65(3):385–411.

[37] M. S. Akhtar, U. M. khan, L. Khalifa , ***The effect of Euphorbia prostrate in normoglycemic and alloxa treated hyperglycaemic rabbits***, Plant. Med. 1984, 50:138-142.

[38] T.Rissanen, S.Voutilainen, K.Nyyssönen, J. T. Salonen.,Lycopene, ***atherosclerosis and coronary heart disease***. Exp. Biol. Med. 2002; 227(10): 900-907.

[39] R. Klein.,***Hyperglycemia and microvascular and macrovascular disease in diabetes***. Diabetes Care, 1995, 18, 258–268.

[40] A.Upadhayay, K.Girhepunje, R. Pal, N. Thirumoorthy, ***Antidiabetic and in vivo antioxidant activity of ethanolic extract of Geniosporumprostratum aerial parts on STZ induced diabetic rats***. Der Pharmacia Lettre, 2011, 3(2):187-193

[41] S.Ozmutlu, S.Dede, E. Ceylan;***The effect of lycopene treatment on ACE activity in rats with experimental diabetes***. Journal of the Renin-Angiotensin-Aldosterone System 2012, (0) 1–6

[42] C. Sunil,P.G.Latha, S.R.Suja,V.J. Shine, G.I.Shayamal;***Effect of Ethanolic Extract of Pisonia alba Span. Leaves on Blood Glucose levels and Histological Changes in Tissues of Alloxan-Induced Diabetic Rats***. International Journal of Applied Research in Natural Products, 2009;2 (2):pp. 4-11.

[43] S.K. Jain, M. Robert, D. John, J.H. John: ***Erythrocyte membrane lipid peroxidation and glycosylated hemoglobin in diabetes***. Diabetes, 1989;38: 1539–1543.

[44] K.S. Bose, BK. Agrawal.: ***Effect of long term supplementation of tomatoes (cooked) on levels of antioxidant enzymes, lipid peroxidation rate, lipid profile and glycated haemoglobin in Type 2 diabetes mellitus***. West Indian Med J 2006;55:274-8.

[45] P.Di Mascio, S.Kaiser, H. Sies; ***Lycopene as the most efficient biological carotenoid singlet oxygen quencher***. Arch BiochemBiophys 1989;274:532

[46] S.K. Clinton;Lycopene: ***chemistry, biology and implications for human health anddisease.*** Nutr Rev 1998;56:35

[47] P. Martin-Gallan, A.Carrascosa, M.Gussinye, C. Dominguez; ***Biomarkers of diabetes-associated oxidative stress and antioxidant status in young diabetic patients with or without subclinical complications.*** Free RadicBiol Med 2003; 34:1563-1574

Kirkuk University Journal /Scientific Studies (KUJSS)
Volume 10, Issue 3, September 2015 , p.p(140-154)
ISSN 1992 – 0849

[48] B. Halliwell,J.M. Gutteridge;***Role of free radicals and catalytic metal ions in human disease:*** An overview. Meth Enzymol 1990; 186:1–85.

AUTHOR

Entedhar Rifaat Sarhat: received B.Sc.degrees in veterinary medicinefrom Baghdad University / Baghdad -Iraq, and M.S.andPh.D degrees in in Biochemistry department from College of Medicine Tikrit University / Tikrit - Iraq,. During 2006-2010,she worked as a Asst. lecturer in College of medicine and dentistry . At 2010 till now as a lecture . in College of Dentistry Tikrit University.