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Anti-hyperglycaemic Effects of Rutin on Blood Glucose, Oxidative Stress Biomarkers and Lipid Peroxidation in Alloxan-induced Hyperglycaemic Wistar Rats

*** [1]Y. Tanko, [2]A. I. Salisu, [3] K. A. Mohammed, [4]S. A. Musa, [1]A. Jimoh, [5]R. Yusuf**

[1]Department of Human Physiology, Ahmadu Bello University, Zaria, Nigeria [2]Department of Human Physiology, Bayero University, Kano, Nigeria [3]Department of Human Physiology, Kaduna State University, Nigeria [4]Department of Human Anatomy, Ahmadu Bello University, Zaria, Nigeria [5]Department of Chemical Pathology, Ahmadu Bello University, Zaria, Nigeria

Summary: The present study investigated the anti-hyperglycaemic effect of rutin on blood glucose, oxidative stress biomarkers and lipid peroxidation in alloxan induced hyperglycaemic wistar rats. Diabetes was induced in rats by an intraperitoneal *(i.p)* injection of alloxan monohydrate 150 mg/kg body weight. Twenty five wistar rats were divided as follows; Group1 served as diabetic control received distilled water 2 mg/kg, Group served as positive control received 2 mg/kg glibenclamide, 3, 4 and 5 received rutin at 50, 100 and 200 mg/kg body weight for 28 days respectively. At the end of the treatment, rats were sacrificed and the blood and serum were used for the analysis of blood glucose and oxidative stress biomarkers respectively. The determinations of blood glucose levels were carried out at intervals of 7, 14, 21 and 28 days respectively Serum oxidative stress biomarkers lipid peroxidation, were done on the 28 days. Administrations of rutin at the three different doses 50,100 and 200 mg/kg to diabetic rats significantly ($p<0.05$) decreased the blood glucose levels as compared to diabetic control. The dose of 200 mg/kg exhibited a maximum glucose lowering effect with blood glucose of 102.8± 0.06 as compared to diabetic control 346.2±0.16. Furthermore, in relation to the oxidative stress biomarkers there was a significant ($p<0.05$) increased in the levels of gluthathione peroxidase, superoxide dismutase and catalase as compared to control. However, there was also a significant decreased in the malondialdehyde levels as compared to control. It may be concluded that oral administration of Rutin for 28 days decreases blood glucose levels and prevented oxidative stress and antioxidant status in hyperglycaemic rats.

Keywords*:* Rutin, Blood Glucose, Oxidative Stress Biomarkers, Lipid Peroxidation

**Address for correspondence*: yusuftanko@abu.edu.ng ; yusuftanko@yahoo.com

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INTRODUCTION

Diabetes mellitus (DM), one of the most challenging health pandemics of the 21st century currently affects about 347 million people worldwide (Eleazu et al., 2013). This number is rapidly increasing and is expected to double by the year 2030, making diabetes the 7th leading cause of death in the world. DM is a complex metabolic disorder, characterized by high blood glucose levels (hyperglycaemia) and impaired lipid, carbohydrate and protein metabolism as a result of defects in insulin secretion, insulin action or both (Noriega-Cisneros *et al.,* 2012, Ramachandran *et al.,* 2012). Hyperglycaemia plays a vital role in the development and progression of diabetic complications by numerous mechanisms, including increased oxidative stress, decreased nitric oxide bioavailability, glucose autoxidation and non-enzymatic protein glycation (Rahimi *et al.*, 2005). It is also well known that oxidative stress develops when reactive oxygen-derived free radical production exceeds the antioxidant defense mechanism of the cell (Rahimi *et al.*, 2005, Huang *et al.*, 2007). DM has been shown to be associated with increased free radical formation and decreased antioxidant capacity, leading to oxidative damage to lipid, carbohydrate, protein and nucleic acids (Rahimi *et al.,* 2005). Antioxidants decrease diabetic complications by attenuation of free radical associated damage (Huang *et al.*, 2007). Rutin is abundantly present in onions, apples, tea and red wine (Hertog *et al.*, 1993). Rutin exhibits multiple pharmacological activities including antibacterial, anti-tumour, anti-inflammatory, anti-diarrhoeal, antiulcer, anti-mutagenic, myocardial protecting, vasodilator, immunomodulator and hepatoprotective activities (Janbaz *et al.*, 2002). Much interest has gathered in the role and usage of natural antioxidants as a means to prevent oxidative damage in diabetes with high oxidative stress. Flavonoids represent the most common and widely distributed group of plant phenolics (Harborne 1986) and are abundant in foods.

Quercetin (3,3o,4o,5,7-pentahydroxy flavone) is one of the most common native flavonoids occurring mainly in glycosidic forms such as rutin (5,7,3o,4o-OH, 3-rutinose) (fig. 2) (Havsteen 1983). Quercetin and rutin are the flavonoids most abundantly consumed in foods (Nakamura *et al.* 2000). Rutin is a citrus flavonoid glycoside found in buck wheat (Kreft *et al*., 1999). It is also found in the fruit of the favadanta tree, fruit and flowers of the pagoda tree, fruit and fruit rinds (especially the citrus fruits, orange, grapefruit, lemon and lime) and apple; berries such as mulberry, ash tree fruits and cranberries. Rutin is one of the primary flavonoids which are ingredients of numerous multivitamin preparations and herbal remedies. It has some established pharmacological effects due to its antioxidant and anti-inflammatory properties, and cytoprotective actions connected with anti-ageing and anti-cancer properties (La Casa *et al*., 2000). The aim of this study is to determine the anti-hyperglycaemic effects of Rutin on blood glucose and oxidative stress biomarkers in alloxan induced hyperglycaemic Wistar rats.

MATERIALS AND METHODS

Chemical/drug used

Alloxan monohydrate was purchased from Sigma Chemicals (St Louis, U.S.A.), glibenclamide and Rutin were purchased from Sigma Aldrich. All chemicals used were of analytical grade.

Experimental animals

Twenty-five (25) Wistar rats of both sexes weighing between 150-200 g were obtained from the Animal House of the Department of Human Physiology, Ahmadu Bello University, Zaria, Nigeria. The Rats were maintained on standard laboratory animal feed and water *ad libitum*, and housed in polypropylene cages at room temperature throughout the study. These studies were carried out in Ahmadu Bello University in accordance with the rules governing the use of laboratory animals as accepted internationally.

Induction of Diabetes Mellitus

The Wistar rats were fasted for about 16-18 h, after which diabetes was induced by a single intraperitoneal injection of Alloxan monohydrate dissolved in 0.9% cold normal saline solution at a dose of 150mg/kg body weight (Katsumata *et al*., 1999). The rats were also treated with 20% glucose solution orally for 6 hours. After which they were placed on 5% glucose solution for 24 hours (Dhandapani *et al*., 2002). Blood was collected from the tail artery of the rats after 72 hours of Alloxan injection. The rats having fasting blood glucose level greater than 200mg/dl were selected for the study.

Determination of blood glucose levels

Fasting blood glucose levels were determined by using the glucose oxidase method (Beach and Turner, 1958) with ONE TOUCH BASIC® Glucometer (LIFESCAN, Inc 2001 Milpitas, CA 95035, USA) Results were reported as mg/dl. Blood glucose level was determined at 7, 14, 21 and 28 days respectively by collection of blood sample from the tail artery. Rat with blood glucose levels 200 mg/dl were considered for the study.

Experimental design

The animals were randomly divided into five groups of five rats each as follows:

Group 1: Diabetic control and administered (0.5 ml/kg body weight) distilled water

Group 2: Diabetic received glibenclamide 2 mg/kg b w for 28 days orally

Group 3: Diabetic and treated with 50 mg/kg *bwt* Rutin for 28 days orally.

Group 4: Diabetic and treated with 100 mg/kg *bwt* Rutin for 28 days orally.

Group 5: Diabetic and treated with 200 mg/kg *b w* Rutin for 28 days orally

Blood Sample Collection and Serum Preparation

After the treatment all animals were sacrificed using light chloroform and 5 mL of blood sample were collected by cardiac puncture into specimen bottles and allowed to clot and separated by centrifugation at 3,000 *g* for 10 minutes using Centrifuge Hitachi (Universal 32, Made in Germany). The supernatant obtained were used for the determination of lipid profile and liver enzymes.

Determination of oxidative stress Biomarkers

Glutathione Peroxidase

The NWLSS^{TM} Glutathion peroxidase Assay kit was used which is an adaptation of the method of Paglia and Valentine (1967). Glutathione peroxidase catalyses the reduction of hydrogen peroxide (H_2O_2), oxidizing reduced glutathione (GSH) to form oxidized glutathione (GSSG). GSSG was then reduced by glutathione reductase (GR) and β-nicotinamide adenine dinucleotide phosphate (NADPH) forming $NADP^+$ (resulting in decrease absorbance at 340 nm) and recycling the GSH. Since GPx is limiting, the decrease in absorbance at 340nm is directly proportional to the GPx concentration. The absorbance was read at 1,2 and 3 minutes against reagent blank. The absorbance for blank was subtracted from the sample reading to give the corrected value. Thus, GPx activity was calculated using 8.412 as the extinction coefficient:

GPx(U/L) = 8.412 x Δ A 340/min

U/L = unit activity per liter

Δ A 340/min = change in absorbance at 340 per minute.

Superoxide dismutase activity

Superoxide dismutase (SOD) activities were measured by the method of Misra and Fridovich (1972). Serum (0.5 mL) was diluted to 1.0 mL with distilled water, and 250 µl of chilled ethanol and 150 µl of chilled chloroform were added. The mixture were shaken and centrifuged. The supernatant were used for the assay of enzyme activity. To 1.2 mL of the supernatant were added 1.5 mL of 0.1 mol/L carbonate-bicarbonate buffer, pH 10.2, containing0.2 mmol/L EDTA. The contents were mixed, and the reaction as initiated by adding 200 µl of epinephrine (pH 3.0, 3 mmol/L) to the buffered reaction mixture. The changes in optical density per minute were measured at 470 nm.

Catalase activity

Catalase (CAT) activities were assayed by the method of Sinha (1972). 0.1 mL of Plasma and 1.5 mL of phosphate buffer were added. To this, 0.4 mL of hydrogen peroxide was added and the reactions were arrested after 30 and 60 second by the addition of 2.0 mL dichromate acetic acid reagent. A control was also carried out simultaneously. All the tubes were heated in a boiling water bath for exactly 10 min, cooled and absorbance read at 620 nm. Standards in the range of 2-10 Mmoles were taken and processed as the test. The activities of catalase were expressed as µmoles of hydrogen peroxide consumed/min/mg of protein (unit per milligram of protein).

Lipid peroxidation biomarker (MDA)

Lipid peroxidation can be evaluated by the thiobarbituric acid reactive substances method (Gallou *et al*., 1993). Plasma malondialdehyde (MDA) levels were measured by the double heating method of Draper and Hadley (1990) using Malondialdehyde Assay kits from Northwest Life Sciences Specialties (NWLSS^{TM}, product NWK-MDA01). Butylated hydroxytoluene (BHT) in methanol reagent was used as the control.

The method is based on the spectrophotometric measurement of the purple color generated by the reaction of thiobarbituric acid (TBA) with MDA at 532 nm. The MDA formed will therefore be quantified using an extinction coefficient of 1.56 x 10^5/mole/cm (Yagi, 1987). The amount of MDA formed in the control samples is subtracted from the amount in the experimental samples to obtain the amount of MDA in each sample. Since absorbance is directly proportional to the concentration, thus; concentration of MDA in each sample = Absorbance in sample – Absorbance in control x 10^5 nmol/ml ÷ 1.56 x 10^5 $M^{-1}CM^1$

Statistical Analysis

Data obtained from each group were expressed as mean ± SEM. The data were statistically analyzed using (ANOVA) with Tukey's *post-hoc test* to compare the levels of significant between the control and experimental groups. All statistical analysis was evaluated using SPSS version 17.0 software and Microsoft Excel (2007). The values of $p \leq 0.05$ were considered as significant.

RESULTS

Effect on blood glucose levels

Table 1 showed administration of rutin at the doses of 50, 100 and 200 mg/kg respectively significantly ($p<0.05$) decreased the blood glucose levels as compared to control. Also in relation to the positive control, glibenclamide as compared to control, there was a significant ($p<0.05$) decreased in the blood glucose levels. However, the dose of 200 mg/kg had the maximum glucose lowering effect as compared with the control.

Effect on lipid peroxidation and oxidative stress biomarkers

Table 2 showed administration of rutin significantly ($p<0.05$) decreased the malondialdehyde levels as compared to control. Furthermore, it significantly ($p<0.05$) as regards to oxidative stress biomarkers (GPx, SOD and CAT), there was a significant increased as compared to control.

Table 1: Effect of rutin on blood glucose levels (mg/dl) in alloxan-induced hyperglycaemicwistar rats

Group/Treatment	Week 0	Day 7	Day 14	Day 21	Day 28
Group I (Diabetic untreated)	409.1 ±0.09	409.6 ± 2.09	382.5 ± 1.22	380.2 ± 0.53	348.20 ± 0.15
GroupII (2mg/kg Glibenclamide)	411.6 ± 0.07	382.3 ± 1.09 ^{ns}	228.2 ± 0.10^{a}	186.40 ± 0.14^{a}	166.3 ± 0.13^{a}
Group III (Rutin 50 mg/kg)	411.4 ± 0.04	293.4 ± 1.02^{a}	142.10 ± 103 ^{a}	129.7 ± 0.21^{a}	119.5 ± 0.08^{a}
Group IV (Rutin 100 mg/kg)	408.3 ± 0.09	211.2 ± 0.09 ^{a}	129.20 ± 0.08 ^{a}	140.2 ± 1.21^{a}	126.4 ± 1.11^{a}
Group V (Rutin 200 mg/kg)	418.2 ± 0.04	194.3 ± 0.08 ^{a}	142.1 ± 0.07 ^{a}	120.50 ± 1.14^{a}	102.5 ± 0.08^{a}

Values are mean ± SEM; n=5. Values are statistically significant compared to control at: $^{a}P<0.05$ ns= not significant.

Table 1, showed the effect of the three doses of rutin (50,100 and 200 mg/kg) and glibenclamide (2 mg/kg) on blood glucose levels, there was a significant ($p<0.05$) decreased in the blood glucose levels as compared to control. The highest activity resides at 28 days of administration when compared to control

Table 2: Effects of rutin on lipid peroxidation and oxidative stress biomarkers in alloxan Induced hyperglycaemic wistar rats

Group/Treatment	GPx U/mg protein	SOD U/mg protein	CAT U/mg protein	MDA(nmol/mg protein)
Group I (Diabetic untreated	32.2 ± 1.22	3.52 ± 0.12	30.5 ± 1.02	3.34 ± 0.23
Group II (2mg/kg Glibenclamide)	60.4 ± 1.11[a]	1.50 ± 0.04[a]	46.0 ± 0.14 [a]	1.32 ± 0.17[a]
Group III (Rutin 50 mg/kg)	66.6 ± 0.24[a]	1.60 ± 0.09[a]	48.2 ± 0.16 [a]	1.26. ± 0.15[a]
Group IV (Rutin 100 mg/kg)	58.8 ± 0.12[a]	1.74 ± 0.08[a]	44.2 ± 0.20 [a]	1.49 ± 0.10[a]
Group V (Rutin 200 mg/kg)	61.2 ± 1.14 [a]	1.46 ± 0.05[a]	49.6 ± 0.14 [a]	1.23 ± 0.14[a]

Values are mean ± SEM; n=5. Values are statistically significant compared to control at: [a]P<0.05 ns= not significant.

Table 2 showed the effect of the three doses of rutin (50,100 and 200 mg/kg) and glibenclamide (2 mg/kg) on serum glutathione peroxidase(GPx) superoxide dismutase (SOD) catalase(CAT) and malondialdehyde (MDA) on hyperglycaemic Wistar rats after 28 days of treatment. However there was a significant increase in the levels of GPx, SOD and CAT in all the doses administered as compared to the control. Also there a significant decreased in the levels of malondialdehyde as compared to control.

DISCUSSION

Oxidative stress is suggested to be a potential contributor to the development of complications in diabetes (Baynes 1991). Increased free radical production or reduced antioxidant defense responses, both of which occur in the diabetic state may give rise to increased oxidative stress (Halliwell & Gutteridge 1990). Consequences of oxidative stress are adaptation or cell injury, i.e. damage to DNA, proteins and lipids, disruption in cellular homeostasis and accumulation of damaged molecules (Jakus 2000). Reduced oxidative stress in the diabetic condition has been observed in experimental animals after the administration of certain polyphenols (Sanders *et al.* 2001). From our findings as regards to the blood glucose levels administration of rutin at the three different doses tested, significant decrease the blood glucose levels as compared to control. Furthermore at 14 days of treatment there was a significant decrease when compared with the control. Also 21 and 28 days of treatments with the three doses of rutin, there was a significant decrease in the blood glucose level when compared with the control. The possibly mechanism of action of rutin could be by enhancing peripheral glucose utilization either direct stimulation of glucose uptake or via the mediation of enhanced insulin secretion and inhibiting the glucose transporter activity. Vessal *et al.* (2003) reported that quercetin, the aglycone of rutin decreased blood glucose concentration and increased insulin release in streptozotocin -induced diabetic rats. The rise in serum MDA indicated that oxidative stress incurred sufficiently could cause free radical mediated peroxidation of lipid component in cell membrane, thus MDA is a good indicator for evaluating oxidative stress in degenerative disease such as diabetes mellitus (Padalkar *et al.*, 2012). The present investigation showed that administration of Rutin significantly decreases serum MDA levels when compared with the diabetic control. This observed effect of Rutin may probably be due to its various antioxidant defense strategies, most especially the scavenging of two of the ROS: singlet molecular oxygen and peroxyl radicals (Atessahin *et al.*, 2005). Antioxidant enzymes such as SOD, CAT, GPx and GR are primary enzymes that are involved in the direct elimination of free radicals (Oguntibeju *et al.*, 2010). Also, in the present study, there were an increased activities of serum SOD, CAT, and GPx following oral administration of Rutin for 28 days to diabetic rats. The MDA is a reactive aldehyde the major electrophilic species known to elicit stress of toxic nature in cells and know to form covalent protein adducts (Farmer and Davoire 2007). SOD catalysis anions which are important reactive oxygen species in cells and involved in cell membrane damage. The elevation of GPx and SOD activities may be endogenous compensatory mechanism for prolonged over production of free radical and oxidative stress (Aksoy *et al.*, 2003). Catalase is also an antioxidant enzyme located in peroxisomes and decomposes H_2O_2 to H_2O and O_2 (Rausder *et al.*, 2001). The ability of Rutin treatment of diabetic animals to restore the depleted serum antioxidants enzymes in the current investigation may be attributed to its antioxidant property. Serum antioxidant enzymes (SOD, CAT and GPx) activities were significantly decrease in diabetic rats when compared with normal control animals. Hyperglycemia is a main cause for elevated free radical levels, followed by production of ROS, which can lead to increased lipid peroxidation and altered antioxidant defense and further impair glucose metabolism in biological system (Balasubashini *et al.*, 2004). An imbalance between oxidation and antioxidant status has been shown to play an important role in mediating oxidative stress (Ramesh and Saralakumari, 2012). Rutin scavenges free radicals and inhibits superoxide radical production as well as enhance the activity of antioxidant enzymes, glutathione peroxidase and reductase to maintain the levels of the reduced glutathione, which is a biological antioxidant (Kamalakkannan *et al.*, 2006).Overwhelming free radicals generated due to oxidative stress may develop several adverse effects commonly seen in diabetes such as neuropathy, nephropathy, retinopathy, and vascular disorders (Al-Azzawie and Alhamdani, 2006). The major antioxidant enzymes, including SOD, CAT, and GPx,

are regarded as the first line of the antioxidant defense system against ROS generated *in vivo* during oxidative stress and act cooperatively at different sites in the metabolic pathway of free radicals (Cheng and Kong 2011). In conclusion oral administration of rutin for 28 days decreases blood glucose levels and prevented oxidative stress and antioxidant status in hyperglycaemic rats.

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