OPEN ACCESS

MULUNGUSHI UNIVERSITY MULTIDISCIPLINARY JOURNAL (MUMJ)

Mulungushi University Multidisciplinary Journal
ISSN : 2958-3926
Vol. 4 No. 1

https://research.mu.ac.zm/research/index.php/mu

Maintenance of renal integrity of diabetic wistar rat treated with aqueous extract of psidium guajava (guava) leaves

Uthman Ademola Yusuf[1*], Mwewa Masamba[1], Betty Banda[1], Sam Beza Phiri[2] , Michelo Miyoba[3], Aminat Adejoke Yusuf[4] John Mulemena[5] , Kingsley M Kamvuma[5,] Olubukola Iyanuoluwa Ademola[6]

[1] Mulungushi University, School of Medicine and Health Sciences, Department of Human Anatomy, Livingstone, Zambia; Email: uthmanademola@yahoo.com / uademola@gmail.com
[1] Mulungushi University, School of Medicine and Health Sciences, Department of Human Anatomy, Livingstone, Zambia; Email: mawetamasamba522@gmail.com
[1] Mulungushi University, School of Medicine and Health Sciences, Department of Human Anatomy, Livingstone, Zambia; Email: bandabetty08@gmail.com
[2] Mulungushi University, School of Medicine and Health Sciences, Department of Physiological Sciences, Livingstone, Zambia; Email: sbeza@mu.ac.zm
[3] Mulungushi University, School of Medicine and Health Sciences, Department of Clinical Sciences, Livingstone, Zambia; Email: mmiyoba@mu.ac.zm
[4]Ladoke Akintola University of Technology, Faculty of Basic Medical Sciences, Department of Medical Biochemistry, Ogbomoso, Nigeria; Email: Harmejorky@gmail.com
[5] Mulungushi University, School of Medicine and Health Sciences, Department of Pathology and Microbiology, Livingstone, Zambia; Email: jmulemena@mu.ac.zm
[5] Mulungushi University, School of Medicine and Health Sciences, Department of Pathology and Microbiology, Livingstone, Zambia; Email: kkamvuma@mu.ac.zm
[6]University of Medical Sciences, Faculty of Basic Medical Sciences, Department of Medical Biochemistry, Ondo, Nigeria; Email: Osikoyaiyanuoluwa@gmail.com
*Correspondence: Uthman Ademola Yusuf, Email: uademola@gmail.com

ARTICLE HISTORY: Received 19 May 2023; Accepted 30 August 2023

ABSTRACT

Herbal medicines constitute the main component of traditional medicines, which have been used for thousands of years in the treatment of ailments, including diabetes. The aim of this study was to investigate the role of aqueous extract Psidium guajava leaves in the maintenance of renal integrity in diabetic Wistar rats. Diabetes mellitus was induced using a single intraperitoneal dose of streptozotocin of 70mg/kg bodyweight and established a persistent state of hyperglycemia after 72hours. The aqueous extract of Psidium Guajava and metformin of 200 mg/kg and 100 mg/kg bodyweight was administered daily for a period of 4 weeks. Results showed that the relative kidney weight of rats in the diabetic group was significant ($p<0.05$) compared to the other groups. The body weight and blood glucose levels in rats in the control, diabetic +guava leaves extract and diabetic +metformin groups were statistically significant ($p<0.05$) when compared to those in the diabetic group ($P<0.05$). The kidneys of rats in the control group and guava only groups showed normal histoarchitecture. Those in the diabetic group showed disorganization of macula densa and urine space was large, while those in the diabetic+guava and diabetic+metformin groups showed little disorganization in macula densa and urine space was slightly large. Those in the control and guava only groups showed normal collagen distribution while the ones in the diabetic group showed a lot of accumulation of collagen. The rats in the diabetic+guava and diabetic+metformin groups showed a little accumulation of collagen. These findings reveal that aqueous extract of Psidium guajava leaves has the ability to lower blood glucose levels and thus, prevent kidney histoarchitecture damage caused by Diabetes mellitus.

Keywords: Diabetes mellitus, Streptozotocin, Psidium guajava leaves, Metformin, Wistar rats

INTRODUCTION

The term diabetes mellitus refers to a heterogeneous collection of metabolic disorders whose main characteristic is chronic hyperglycemia[1]. The etiology is a disturbed insulin secretion, a disturbed insulin effect, or both. There are two main classifications of diabetes: Type 1 diabetes mellitus Type 2 diabetes mellitus [1]

On a global scale 415 million people live with diabetes, and an estimated 193 million people have diabetes undiagnosed [1]. 90% of patients have type 2 diabetes which often leads to microvascular and macrovascular complications that cause significant psychological and physical distress to both patients and carers: thus, putting and put a huge burden on healthcare systems.[2]

Recently, the global prevalence of diabetes has increased significantly, reaching 8.3% in 2014, which corresponds to 387 million patients [2]. Research conducted in Europe and United States of America (USA) has shown an increased incidence of Type 1 diabetes (T1DM) overtime at a rate of 3-5% per year [3]. Another concerning feature of the rapid increase of diabetes is the occurrence of Type 2 diabetes (T2DM) in children, adolescents, and young adults. In developed countries, diabetes is the leading cause of end-stage renal disease and vision loss [3]. Around 40% of T1DM and T2DM patients are started on renal replacement therapy [3]. However, the most prevalent chronic complication of diabetes is neuropathy. Distal Symmetric Polyneuropathy occurs in at least 20% of people with T1DM after 20 years and in 10-15% of newly diagnosed T2DM, increasing to 50% after 10 years [3].

Diabetes alone accounts for over 1 million deaths per year, making it the ninth leading cause of mortality [4]. There is equal gender distribution, and the incidence reaches its highest at around 55 years of age [4]. The global prevalence of Type 2 diabetes is projected to increase to 7079 individuals per 100,000 by 2030, reflecting a continued rise across all regions of the world. There are worrying trends of rising prevalence in lower-income countries. Swift public health and clinical preventive measures are therefore, warranted in developing (third world) countries.[4]

In Asia and North America, Guava (*Psidium guajava* L., Myrtaceae) leaves have been used as a folk herbal tea to treat diabetes for a long time. Over the years, the guava leaf has gone through chemical analysis and found to have alkaloids, carotenoids anthocyanins, vitamin-C and triterpenes [5]. This plant finds applications for the treatment of diarrhea, dysentery, gastroenteritis, hypertension, diabetes, caries and pain relief and improvement in locomotors coordination [5].

Currently, there is increasing interest in discovering new bioactive compounds derived from ethnomedicine. Preparations of guava (*Psidium guajava* L.,) leaves have customarily been used to control several diseases. Pharmacological studies, in-vitro as well as in-vivo have been used extensively to show the potential of the extracts from the leaves in the treatment of diverse ailments with high occurrence worldwide, upholding the long-established medicine in cases such as diabetes mellitus, cardiovascular diseases, cancer, and parasitic infections. Additionally, the biological activity has been attributed to the bioactive components of some specific phytochemical subclasses and individual compounds in the leaves. Phenolic compounds in guava leaves have been recognized in the regulation of blood-glucose levels.[6]. This study will focused on how the aqueous extract of *Psidium guajava* (guava) leaves can ameliorate the damage on the kidneys of Wistar rats caused by diabetes.

MATERIALS AND METHODS

Plant materials

The *Psidium guajava* (guava) leaves were harvested from Livingstone fruit farm, in Livingstone district, Southern province, Zambia. Before the study began, the plant materials were subjected to identification at the Department of Biology, School of Natural Sciences, University of Zambia, Lusaka district. The guava leaves were then air dried and pounded. The dry pounded leaves were thereafter sieved to obtain a homogenous powder. The extraction was done using [5] methods

Animal management

Thirty healthy adult male Wistar rats (*Rattus norvegicus*) were used for this study. The animals were between 8 to 10 weeks old with a body weight of 180-200g. The Wistar rats

were kept in groups of six in five cages and housed in the animal holdings facility of the Department of Anatomy, School of Medicine and Health Sciences (SoMHS), Mulungushi University (MU). The Wistar rats were maintained on standard animal feeds (Wealth-gate pelletized feeds) and allowed access to clean water and feeds freely (*ad libitum*).

Induction of diabetes

Streptozotocin (STZ) was used to induce diabetes in the Wistar rats. They were then weighed, and a baseline glucose level was established after an overnight fasting period. The animals were injected streptozotocin calculated at a dose of 70 mg/kg body weight and reintroduced to the normal feeding cycle[7]. It takes about 72 hours for diabetes to be established in the animals, post-administration of streptozotocin. Therefore, a fasting blood sugar was collected using a tail vein puncture, 72 hours after administration of streptozotocin to determine the induction of diabetes. A glucometer was used to determine whether or not diabetes was successfully established. A blood glucose level of above 10 mmol/l / ≥ 250 mg/dl qualified for a successful induction of diabetes.

Experimental design

Thirty adult healthy male Wistar rats were divided into five groups of six (6) Wistar rats each. Control Group A comprised normoglycemic animals that received neither STZ nor guava extract. Group B had diabetic rats that did not receive guava extract, Group C had diabetic rats treated with guava extract, Group D comprised diabetic rats treated with metformin only and Group E had rats treated with guava extract only.

Psidium guajava leaves mode of administration

The dose of the aqueous extract of *Psidium guajava* (guava) leaves used in the study was adopted from the report of [5]. Guava leaf extract was dissolved in physiological saline daily, and at 9.00-10.00 am each day, it was administered orally with an oro-gastric cannula. For Group C rats (n=6) at 200 mg/kg bodyweight was administered for a duration of four weeks, Group D (n=6) at 200 mg/kg bodyweight, Group E rats (n=6) were administered 200mg/kg bodyweight of Guava leaves extracts. Group A rats (n=6) received neither STZ nor guava leaves extract.

Measurement of blood glucose

The blood glucose was determined after rats had fasted overnight from 9:00 – 10:00 hours using Glucose oxidase method of one touch ultra 2 glucometers (Accu-Chek Compact Plus). By snipping the tip of the tail, blood was obtained from the median caudal vein of the Wistar rats. The blood glucose level was monitored weekly for two weeks (acclimatization period) before the induction of diabetes and for four weeks of treatment. [7]

Measurement of bodyweight (g)

Body weight of the rats was recorded in grams for two weeks (acclimatization period) before induction of diabetes, followed by a weekly basis during the experimental treatment for a period of four weeks. A weighing scale (Venus VT 30 SL); [7] was utilized.

The relative organ weight (%)

The relative organ weight of each rat was determined as the ratio of respective weight of the brain and the terminal body weight of the same rat. The unit was recorded as a percentage (%) using sensitive weighing balance (SonyF3G brand).

Histological process

At the end of the study, animals were sacrificed through euthanasia. They were laid supine on the dissecting board and pinned through the fore and hind paws. The skulls of the animals were dissected with bone forceps and each organ will be removed and weighed. The tissue for histological studies was fixed in freshly prepared Formol saline for 72 hours and processed for routine histological examinations stained with Hematoxylin and Eosin (H&E) to observe changes in the cellular morphology, and Masson trichome was used for collagen.

Photomicrography

Photomicrography of histological sections of the kidneys were taken with an Olympus Microscope (New York, United State of America) coupled with camera at the Department of Human Anatomy, SoMHS, MU, Livingstone Campus, Zambia.

Statistical analysis and presentation

Data was analyzed using one-way ANOVA and presented as the mean ± standard error of the mean (mean±SEM). All graphs have been drawn using Graph Pad prism. P-values less than 0.05 ($p<0.05$) were taken to be statistically significant.

Research ethics

Ethical approval was obtained from the SoMHS Research Ethics Committee, MU. The animals were subjected to standard animal care provided by the International Animal Care and Use Committee of Biotechnology Research Institute.

RESULTS

The relative weight of the rats' kidneys

Figure 1 shows a graph of the relative weight of the rats' kidneys. When compared, the weight of kidney weight of the rats from the diabetic group was the lowest. The comparison between kidneys of the rats from the diabetic and control group was statistically significant ($p<0.05$) The kidney weights of the rats in the diabetic + guava and diabetic + metformin groups when compared to the control group, were lower but was not statistically significant ($p>0.05$).

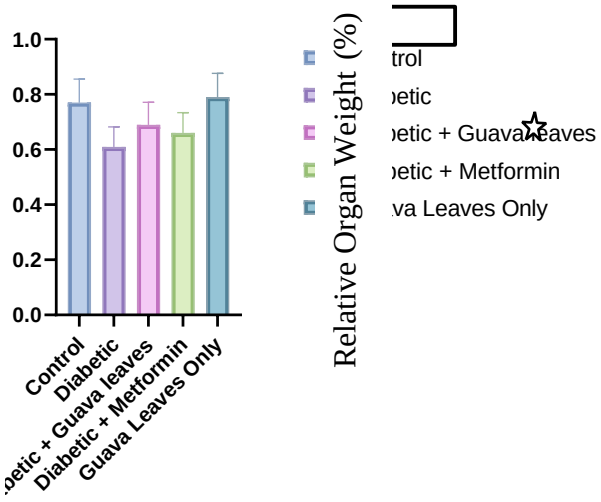

Figure 1: Relative kidney weight. Data expressed as mean±SEM ($p<0.05$). * means significance at $p<0.05$

Average body weight (g) on weekly basis

The body weight of the Wistar rats on a weekly basis is shown in figure 2. During the week of acclimatization, there was no change in the rats' body weight in all the groups. After induction of diabetes, there was still no change. In week 3, rats in the diabetic group lost significant weight when compared to those in the diabetic+guava, diabetic+metformin and control groups, and the loss was statistically significant ($p<0.05$). In week 4, those in the diabetic group lost further lost weight compared to those in other groups, and the loss was statistically significant ($p<0.05$).

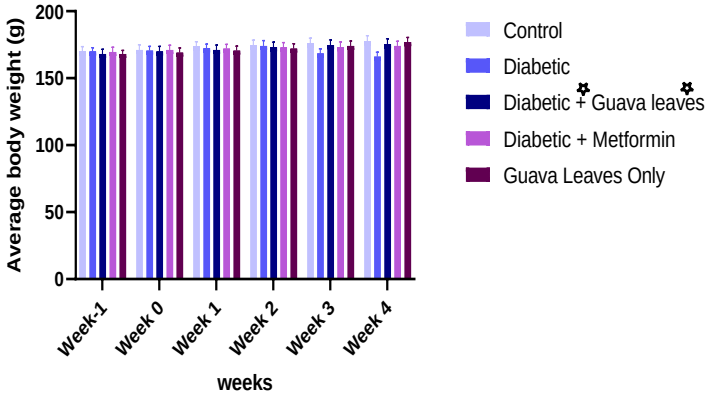

Figure 2: Average body weight (g) on weekly. Data expressed as mean±SEM ($p<0.05$). * means significance at $p<0.05$

Average Blood glucose levels on weekly basis (mg/dl)

Figure 3 shows the average blood glucose levels on a weekly basis in mg/dl. In the week of acclimatization, the rats in all the groups were normoglycemic. After induction of diabetes, there was increase in blood glucose levels of those in the diabetic, diabetic + guava leaves and diabetic + metformin groups and when compared to the control group, the difference was statistically significant ($p<0.05$). In week 1, the blood glucose level of the rats in diabetic group increased, and when compared to those in the control group, the difference was statistically significant ($p<0.05$). In contrast, the blood glucose level of rats in the diabetic +guava and diabetic + metformin groups reduced, and when compared to the control group, the difference was statistically significant ($p<0.05$). However, when compared to those in the diabetic group the difference was not statistically significant ($p>0.05$). In week 2, there was an increase in the blood glucose level of rats in the diabetic group, and when compared to those in the control group, the

difference was statistically significant ($p<0.05$). There was decrease in blood glucose level in rats in the diabetic + guava leaves and diabetic + metformin group and when compared to those in the control group, the difference was statistically significant ($p<0.05$). When compared to those in the diabetic group, the difference was also statistically significant ($p<0.05$). In week 3, there was an increase in the blood glucose level of rats in the diabetic group, and when compared to those in the control group, the difference was statistically significant ($p<0.05$). There was a decrease in blood glucose levels among the rats in the diabetic + guava leaves and diabetic + metformin groups and when compared to those in the control group, the difference was not statistically significant ($p>0.05$). However when compared to those in the diabetic group, the difference was statistically significant ($p<0.05$). In week 4, there was an increase in the blood glucose level of rats in the diabetic group and when compared to those in the control, there difference was statistically significant ($p<0.05$). There was a decrease in blood glucose level among the rats in the diabetic + guava leaves and diabetic + metformin groups, and when compared to those in the control group, the difference was not statistically significant ($p>0.05$). however, when compared to the ones in the diabetic group, the difference was statistically significant ($p<0.05$).

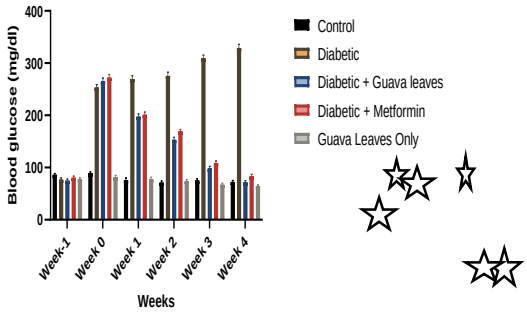

Figure 3: Changes in blood glucose (mg/dl) levels weekly. Data expressed as mean±SEM ($p<0.05$) * means significance at $p<0.05$

Histological analysis

Hematoxylin and Eosin stain (H&E)

The kidneys of the rats in the control group and guava only groups showed normal glomerulus histoarchitecture, urine space and macula densa (Figure 4: A and E). Those in diabetic group showed disorganization of macula densa and large urine space (Figure 4: B). the diabetic+guava and diabetic+metformin groups showed little disorganization in macula densa and urine space was observed a bit large (Figure 4: C and D).

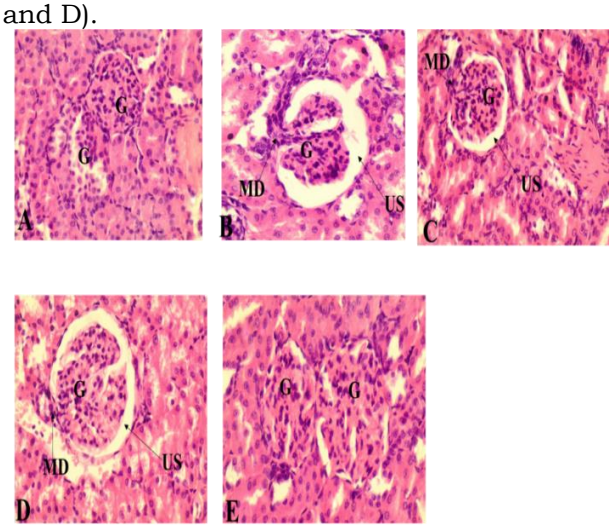

Figure 4: Photomicrograph showing the Kidneys at week 4. H&E stain X400. A-control, B – Diabetic, C – Diabetic+guava, D – Diabetic+metformin and E- Guava only. US – urine space, G - glomerulus, MD – Macula densa

Masson Trichrome stain

Rats in the control and guava only groups showed normal collagen distribution (Figure 5: A and E). those in the diabetic group showed a lot of accumulation of collagen (Figure 5: B), while those in the diabetic+guava and diabetic+metformin groups showed a little accumulation of collagen (Figure 5: C and D).

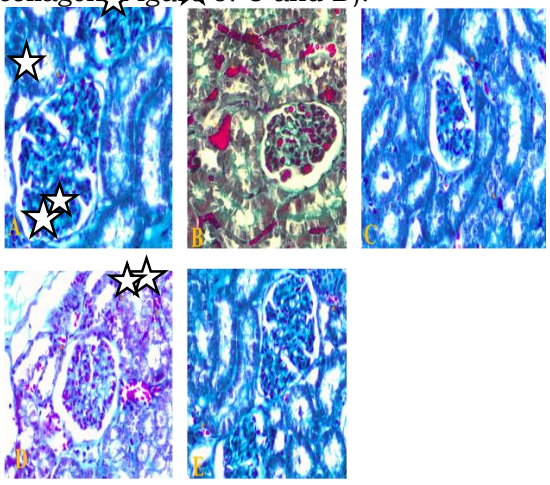

Figure 5: Photomicrograph showing the Kidneys at week 4. Masson stain X400. A-

Control, B – iabetic, C – **Diabetic+guava, D – Diabetic+metformin and E- Guava only. US – urine space, G - glomerulus, MD – Macula densa, Yellow arrow – Collagen**

DISCUSSION

Diabetes is a state of chronically elevated blood glucose precipitating symptoms of hyperglycemia such as polyuria, polydipsia and blurry vision [7]. Clinically, a blood glucose level above 100mg/dl qualifies as clinically significant diabetes in an individual provided the risk factors for the development of the disease are aligned. In this study, a blood glucose level of above 10 mmol/1 (≥ 250 mg/dl) qualified as a definition of diabetes in a Wistar rat. This was achieved by using streptozotocin calculated at a dose of 70mg/kg body weight.

The relative weight of the kidneys of the rats in the diabetic group was the lowest (Figure 1). This shows that there was significant damage to the kidneys, which could be attributed to apoptosis leading to reduction in weight [8]. Apoptosis promotes the loss of renal epithelial cells that characterizes acute and chronic kidney diseases as seen in podocytopenia and tubular cell loss leading to tubular atrophy [9]. The weight of the rats in the diabetic + guava group's kidneys were higher than the kidney weights of the diabetic + metformin group (Figure 1). This shows that there was preservation of kidney weight by the aqueous extracts of guava leaves. Guava leaves have been reported to be rich in phenolics, which help in ameliorating the kidney damage.[10]

The average body weight in grams (g) on weekly basis was recorded in the study (Figure 2). From the week of acclimatization to week 2, there was no significant change in the body weight of the rats in all the groups. In week 3 and 4, there was a statistically significant decrease in the body weight of rats in the diabetic group compared to the ones in the control group. Diabetes mellitus causes a drastic change in body weight and it may be due to excessive breakdown of the tissue proteins and lipids due to insulin insufficiency[7]. The improvement in body weight in *Psidium guajava* leaf extract-treated diabetic rats may be due to the improvement in metabolic activity of the system to maintain glucose homeostasis which can be attributed to the phenols and antioxidants in the extract [11]. Improved glycemic control inhibits gluconeogenesis through proteolysis and prevents muscle wasting, thereby preserving body weight in the diabetic + guava leaves group. [12].

The average blood glucose of the Wistar rats on a weekly basis were recorded (Figure 3). In the week of acclimatization, rats in all the groups were normoglycemic, while those of the control and guava leaves only groups were normoglycemic throughout the study. The blood glucose levels of those in the diabetic group had significant increase in blood glucose from the week of induction to week 4 of treatment. From the week of induction to the fourth week of treatment, the blood glucose level of the rat in the diabetic + metformin and diabetic + guava leaves had a significant decrease until they returned to normoglycemia. However, despite returning to normoglycemia, the blood glucose of the diabetic + metformin was higher than those in the diabetic + guava group. This could be because aqueous extract *Psidium guajava* leaves inhibits glucagon action which leads to reduction of serum glucose. This reduction in blood sugar was due to phytochemicals like beta-carotene, lycopene, vitamins C, E, and A and other substances and flavonoids like guaijaverin and avicularin which improve the function of the beta cells of the islets of Langerhans therefore improving the production of insulin [13]. Insulin is needed for the reduction of blood sugar. Rats in the diabetic + metformin group had a decrease in blood glucose because metformin increases cellular sensitivity to insulin, thereby increasing cellular uptake of glucose and reducing blood glucose levels [13].

The rats in the control and guava only groups showed normal histoarchitecture with glomerulus, urine space and macula densa (Figure 4: A and E). This shows that there was no damage to the kidney histoarchitecture. Rats in the diabetic group showed disorganization of macula densa and the urine space was large. The increase in the levels of blood glucose due to streptozotocin induction could increase the production of free radicals, especially nitric oxide radicals. Accumulation of excessive free oxygen radicals triggers oxidative stress and causes inflammation, resulting in the disruption of macula densa. [14]. Furthermore, the large urine space among rats in the diabetic group cloud have been

due to nitric oxide destruction of the Bowman's capsule which lead to increased filtration of blood across the glomerular capillary [15]. Rats in the diabetic+guava group showed little disorganization in macula densa and urine space was observed to be a bit large. The little disorganization in macula densa and urine space could have been due to antioxidant activity of polysaccharides and phenols in the aqueous extract of the guava leaves [16]. Antioxidants prevented formation of nitric oxide free radicals and subverted disorganization of macula densa and urine space [16]. Similarly, rats in the diabetic + metformin group showed little disorganization in macula densa and urine space was observed to be a bit large. This could have due to the intervention of metformin, which lowers blood glucose levels and thereby, reducing the oxidative stress and averting the kidney damage [17].

Masson's trichrome staining was performed to observe collagen deposition (Figure 5). The rats in the control and guava only groups showed normal collagen distribution. This shows that there was no damage to the kidney histoarchitecture. Rats in the diabetic group showed a lot of accumulation of collagen. Accumulation of collagen showed that there was presence of fibrosis. The hyperglycemic state in the diabetic Wistar rats could have led to upregulation of peroxiredoxin-6, which causes apoptosis of podocytes, a process culminates in fibrosis [18]. Fibrotic process leads to accumulation of collagen in kidney structures [18,22], as shown in the Figure 5 B. Rats in diabetic+guava group showed a little accumulation of collagen. The little accumulation of collagen in the diabetic + guava showed that there was little fibrosis, which points to the intervention of guava leaves extract which contains flavonoid that avert kidney damage process [19]. Similarly, the little accumulation of collagen in the diabetic + metformin group showed there was a process of reversing of fibrosis. A number of studies [20,21,22,23] report that metformin is capable of reducing blood sugar levels, causing a reduction in oxidative stress that causes damage to kidney structures.

CONCLUSION

Aqueous extract of *Psidium guajava*, through its antihyperglycemic and antioxidant properties have shown the ability to lower blood glucose levels and thus prevent kidney histoarchitecture damage caused by diabetes mellitus.

RECOMMENDATION

Based on this study, it is recommend that evaluation of the pharmacokinetics and pharmacodynamics of *Psidium guajava* aqueous extract on the control of diabetes mellitus in Wistar rats then later in human clinical trials.

ACKNOWLEDGMENTS

I want to thank Mulungushi University management for providing part of the funds used in carrying out this research.

REFERENCES

Petersmann, A., Müller-Wieland, D., Müller, U.A., Landgraf, R., Nauck, M., Freckmann, G., Heinemann, L., and Schleicher, E., (2019). Definition, Classification and Diagnosis of Diabetes Mellitus. Exp. Clin. Endocrinol. Diabetes **127,** 1–7. https://doi.org/10.1055/a-1018-9078

Chatterjee, S., Khunti, K., and Davies, M.J., (2017). Type 2 diabetes. Lancet Lond. Engl. **389**, 2239–2251. https://doi.org/10.1016/S0140-6736(17)30058-2

Maffi, P., and Secchi, A., (2017). The Burden of Diabetes: Emerging Data. Dev. Ophthalmol. **60**, 1–5. https://doi.org/10.1159/000459641

Khan, M.A.B., Hashim, M.J., King, J.K., Govender, R.D., Mustafa, H., and Al Kaabi, J., (2020). Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends. *J. Epidemiol. Glob. Health* **10**,107–111. https://doi.org/10.2991/jegh.k.191028.001

Luo, Y., Peng, B., Wei, W., Tian, X., and Wu, Z., (2019). Antioxidant and Anti-Diabetic Activities of Polysaccharides from Guava Leaves. *Mol. Basel Switz.* **24,** 1343.

https://doi.org/10.3390/molecules24071343

Díaz-de-Cerio, E., Verardo, V., Gómez-Caravaca, A.M., Fernández-Gutiérrez, A., Segura-Carretero, A., 2017. Health Effects of Psidium guajava L. Leaves: An Overview of the Last Decade. *Int. J. Mol. Sci.* **18,** E897. https://doi.org/10.3390/ijms18040897

Yusuf U.A, Kehinde AT, Adeeyo AO, A Derinola AA, Samuel MB and Segun OO (2018). Neurobehavioural study on the effects of aqueous extract of citrus medica leaf on prefrontal cortex of hyperglycemic Wistar rats. *Journal of molecular histology and medical physiology*. **3**:123

Walter, F and Addis, T., (1939). Organ work and organ weight. *J. Exp. Med.* **69,** 467–483. Sanz, A.B., Santamari, B., Ruiz-Ortega, M., Egido, J., and Ortiz, A (2008). Mechanisms of Renal Apoptosis in Health and Disease. *J. Am. Soc. Nephrol.* **19,** 1634. https://doi.org/10.1681/ASN.2007121336 Leye Jonathan Babatola and Ganiyu Oboh, (2021). Extract of varieties of guava (Psidium guajava L.) leaf modulate angiotensin-1-converting enzyme gene expression in cyclosporine-induced hypertensive rats. *Phytomedicine Plus.* **1**(4), 100045 https://doi.org/10.1016/j.phyplu.2021.100045

Abu Elez, O.M.R., Hammam, M.A and Elshony, F.M (2021). Effect of aqueous psidium guajava leaves extract as anti - hyperglycemic agent. *Menoufia J. Agric. Biotechnol.* **6**, 83–93. https://doi.org/10.21608/mjab.2021.207622

Lazzaroni, E., Ben Nasr, M., Loretelli, C., Pastore, I., Plebani, L., Lunati, M.E., Vallone, L., Bolla, A.M., Rossi, A., Montefusco, L., Ippolito, E., Berra, C., D'Addio, F., Zuccotti, G.V., Fiorina, P (2021). Anti-diabetic drugs and weight loss in patients with type 2 diabetes. *Pharmacol. Res.* **171,** 105782. https://doi.org/10.1016/j.phrs.2021.105782

Jayachandran, M., Vinayagam, R., Ambati, R.R., Xu, B and Chung, S.S.M (2018). Guava Leaf Extract Diminishes Hyperglycemia and Oxidative Stress, Prevents β-Cell Death, Inhibits Inflammation, and Regulates NF-kB Signaling Pathway in STZ Induced Diabetic Rats. *BioMed Res. Int.* e4601649. https://doi.org/10.1155/2018/4601649

Liu, R., Garvin, J.L., Ren, Y., Pagano, P.J and Carretero, O.A (2007). Depolarization of the macula densa induces superoxide production via NAD(P)H oxidase. *Am. J. Physiol.-Ren. Physiol.* **292,** 1867–1872. https://doi.org/10.1152/ajprenal.00515.2006

Falkson, S.R., Bordoni, B., 2023. Anatomy, Abdomen and Pelvis: Bowman Capsule, in: StatPearls. StatPearls Publishing, Treasure Island (FL).

Zhao, Y.-J., Li, J.-K., Zhang, X., and Gao, J.P (2018). Study on antioxidant activity of flavonoids from leaves of Psidium guajava. *Chin. Mater. Medica* **43,** 760–765. https://doi.org/10.19540/j.cnki.cjcmm.20180104.013

Qu, S., Zhang, C., Liu, D., Wu, J., Tian, H., Lu, L., Xu, G.-T., Liu, F and Zhang, J (2020). Metformin Protects ARPE-19 Cells from Glyoxal-Induced Oxidative Stress. *Oxid. Med. Cell. Longev.* 1740943. https://doi.org/10.1155/2020/1740943

Zhang, Q., Hu, Y., Hu, J.-E., Ding, Y., Shen, Y., Xu, H., Chen, H., and Wu, N., (2021). Sp1-mediated upregulation of Prdx6 expression prevents podocyte injury in diabetic nephropathy via mitigation of oxidative stress and ferroptosis. *Life Sci.* **278,** 119529. https://doi.org/10.1016/j.lfs.2021.119529

Hartati, R., Nadifan, H.I and Fidrianny, I., (2020). Crystal Guava (Psidium guajava L. "Crystal"): Evaluation of In Vitro Antioxidant Capacities and Phytochemical Content. *Scientific World Journal.* 9413727. https://doi.org/10.1155/2020/9413727

Luo, Y., Peng, B., Wei, W., Tian, X., and Wu, Z., (2019). Antioxidant and Anti-Diabetic Activities of Polysaccharides from Guava Leaves. *Mol. Basel Switz.* **24,** 1343. https://doi.org/10.3390/molecules24071343

Cheng, K.-Y., Lin, Z.-H., Cheng, Y.-P., Chiu, H.-Y., Yeh, N.-L., Wu, T.-K., and Wu, J.-S.,

(2018). Wound Healing in Streptozotocin-Induced Diabetic Rats Using Atmospheric-Pressure Argon Plasma Jet. Sci. Rep. **8,** 12214. https://doi.org/10.1038/s41598-018-30597

Yusuf Uthman Ademola , Kalande Kaimba, Francine Kafula, Kalipenta, Kabwe Hellen, Kalipenta Wandi, Mesole B Samuel, Kingsley Kamvuma, Warren Chanda, Michelo Miyoba, and Sam Bezza Phiri, (2022)Some of the effects of Aqueous extract of Cactus on the Histology of Cerebellar Cortex of Streptozotocin induced Diabetic Wistar Rats. ACTA Scientific Anatomy. 1(5):2-9

Yusuf Uthman Ademola, Kalipenta Wandi, Kalande Kaimba, Francine Kafula, Kalipenta, Kabwe Hellen, Warren Chanda, Michelo Miyoba, Sam Bezza Phiri, Christopher Newton Phiri, Aminat Adejoke Yusuf and John Amos Mulemena (2022) Cactus Extract and Anti-diabetic: hepatoprotective effect in Diabetic Wistar Rats. WJPPS. 11(7):16-2