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Cardioprotective Effects of an Aqueous Extract of *Solanum tuberosum* (Irish Potato Peels) on the Heart of Streptozotocin-Induced Diabetic Wistar Rats

[1,2]Kombe Mwitwa, [1,2]Sharon Kaundu, [1]Lukundo Mulambia Siame, [1]Isabel Namfukwe Luambia, [1]Ally Siabwacha and [1]Uthman Ademola Yusuf

[1]Department of Human Anatomy, School of Medicine and Health Sciences, Mulungushi University, Livingstone Campus, Zambia

[2]Department of Clinical sciences, School of Medicine, Eden University, Lusaka, Zambia

ABSTRACT

Background and Objective: Irish potato peels (*Solanum tuberosum*) are known for their antioxidant properties and have been used to treat many diseases, including diabetes. This study investigated the cardioprotective effects of *Solanum tuberosum* peel on diabetic-induced alterations in the heart of Wistar rats. **Materials and Methods:** Thirty-six male Wistar rats were divided into six groups: Normal control, Irish potato peel aqueous extract only, diabetic+Irish potato peel aqueous extract, diabetic+insulin, diabetic+metformin and diabetic only. Diabetes was induced with Streptozotocin 70 mg/kg b.wt., following 72 hrs of displayed hyperglycemia the treatment commenced with Irish potato peel aqueous extract at 100 mg/kg b.wt., insulin at 5 IU/kg b.wt. and metformin at 100 mg/kg b.wt., were administered for 4 weeks. **Results:** The diabetic+Irish potato peel extract became normoglycemic at week 3 while diabetic+insulin and diabetic+metformin were normoglycemic at week 4. The diabetic group showed the lowest body weight ($p<0.05$) and lowest relative heart weight compared to other groups. Histological studies showed disrupted heart histoarchitecture in the diabetic-only group while the treated groups were relatively similar to the control group. The diabetic-only group had the highest Lactate Dehydrogenase (LDH) and the lowest Glucose-6-Phosphate Dehydrogenase (G6PDH) activity while LDH and G6PDH activities in the treated groups were similar to the control group. The diabetic group had the lowest activities in the reduced Glutathione (GSH) and superoxide dismutase (SOD) levels compared to the treated groups. **Conclusion:** This study suggests that Irish potato peel aqueous extract has a protective effect against diabetes-induced cardiac damage.

KEYWORDS

Diabetes mellitus, streptozotocin, Wistar rats, heart, *Solanum tuberosum* peel

INTRODUCTION

Diabetes mellitus is a collection of metabolic disorders characterized by elevated blood glucose levels (hyperglycemia) brought on by deficiencies in the synthesis of insulin, its use or both[1,2]. It is presently acknowledged as one of the main global causes of morbidity and death[3-5]. Due to its persistent

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hyperglycaemic state and unusual protein, lipid and carbohydrate metabolism, it results in harmful and long-term complications[6]. Diabetes can also result in various forms of retinopathy, nephropathy, cardiomyopathy and neuropathy[7]. There are two varieties of diabetes mellitus: Types 1 and 2. The most prevalent kind of diabetes, type 2, mainly affects adults and has become more prevalent over the past three decades in all income levels of countries. It happens when the body ceases to utilize insulin. On the other hand, absolute insulin insufficiency or inadequate insulin synthesis defines type 1 diabetes, also known as juvenile diabetes or insulin-dependent diabetes[8].

According to Yusuf *et al*.[9], diabetes mellitus (DM) is one of the earliest illnesses that humans have ever encountered and it has long been believed that the strains of modern living are the cause of diabetes (DM). The growing prevalence of DM is turning into a serious public health issue. As a result, global interest in researching alternative therapies for this condition continues to grow[10]. *Solanum tuberosum* (Irish potato peel), is one such remedy that is full of nutritionally beneficial ingredients that can be used in many different ways. For instance, it contains natural antioxidants, phenolic compounds and fibers, which are just a few of the many beneficial functional elements that may be found in them and are known to have antihyperglycemic properties, guard against heart disease, lower cholesterol and lessen intestinal absorption of glucose[11]. Furthermore, its phenolic compounds are especially helpful in the prevention of cancer as well as the treatment of a few chronic illnesses[12].

Due to their ability to shield the body from free radicals and impede the progression of numerous chronic illnesses, natural antioxidants have garnered significant attention in the search for many years. Antioxidant, antiproliferative, anticancer, anti-inflammatory, analgesic, antibacterial, neuroprotective, cardioprotective and an antihyperglycemic effect are all characteristics of potato peels[13]. The study was to examined the cardioprotective effects of an aqueous extract of *solanum tuberosum* (Irish potato) peels on the heart of diabetic Wistar rats.

MATERIALS AND METHODS

Study site: This study was conducted at Mulungushi University School of Medicine and Health sciences, Department of Human Anatomy, Livingstone Town Campus, Zambia between January and October, 2024.

Plant materials: The supplier of fresh Irish potatoes was Buya Bamba farm in the Lusaka District of Lusaka Province in Zambia. Before the study began, the Irish potato peels were identified at the Department of Biological Sciences, University of Zambia School of Natural Sciences. The Irish potato peels were cleaned three times with distilled water and then allowed to air dry at room temperature. To create a uniform powder, the dry Irish potato peels (*Solanum tuberosum*) were pounded (crushed) and then sieved (500 g). This technique of extraction was adopted from[14].

Animal management: This study involved the use of thirty-six adult male Wistar rats (*Rattus norvegicus*), all of whom appeared to be in good health. The animals weighed between 170-220 g and were between 8-10 weeks old. The Department of Anatomy at Mulungushi University School of Medicine and Health Sciences hosted the animals, which were housed in six cages with six rats per cage. The Wistar rats were fed regular animal diets (Wealth-gate pelletized feeds) and given unrestricted access to clean water and food (*ad libitum*).

Induction of diabetes: The rats were subjected to an overnight fast for about 9-10 hrs before induction. Afterward, the rats were weighed and their baseline glucose level was determined. The animals were then returned to their regular feeding cycle after receiving an injection intraperitoneally of streptozotocin (STZ) at a dose of 70 mg/kg b.wt.[15,16]. Since diabetes takes around 72 hrs to develop in animals after receiving STZ, a fasting blood glucose sample was taken via a tail vein puncture 72 hrs after STZ induction to

ascertain the presence of diabetes. The blood glucose level was measured using an Accu-Chek glucometer (Mannheim, Germany) and the animals with a fasting blood glucose level of 7 mmol/L or ≥250 mg/dL were classified as diabetic in this study.

Experimental design: Thirty-six adult male Wistar rats were randomly assigned to six groups of six rats per cage. The groups included; control animals that were normoglycemic and did not receive either Irish potato peel extract, drugs or STZ; those in group B were normal and received Irish potato peel extract only; those in group C were diabetic treated with Irish potato peel extract; those in group D were diabetic treated with insulin; those in group E were diabetic treated with metformin and those in group F were diabetic only but did not receive either Irish potato peel extract, insulin or metformin.

Mode of administration: Irish potato peel aqueous extract (homogenous powder) dissolved in physiological saline at a dose of 100 mg/kg b.wt., was administered orally using an oro-gastric cannula to the Wistar rats in Groups B and C for a maximum of 4 weeks[12], Group D received 5 IU/kg b.wt., of insulin intraperitoneally for 4 weeks[17] and Group E received 100 mg/kg of metformin orally with an oro-gastric cannula for 4 weeks[7]. Group A and F rats received only 5 mL of normal saline and feeding daily for 4 weeks.

Measurement of blood glucose: The Wistar rats fasted overnight had their blood glucose levels assessed between 9:00 and 10:00 using the One Touch Ultra 2 glucometer (Accu-Chek Compact Plus) and the glucose oxidase technique. Tail clipping was used to extract blood from the tail's median caudal vein. During the 2 weeks of the acclimatization period before the onset of diabetes and the 4 weeks of treatment, the blood glucose level was checked once a week[7]

Measurement of the body weight (g): During the acclimatization period that preceded the onset of diabetes, the body weight (g) of the rats was measured for 2 weeks and then once a week during the 4 weeks of the experimental therapy. A weighing scale (Venus VT 30 SL) was used to determine body weight[15,16].

Relative organ weight (%): A sensitive weighing balance (SonyF3G brand) was used to record the relative organ weight of the heart of the rat as a percentage based on the ratio of the weight of the brain to the terminal body weight of the same rat[18].

Histological and histochemical studies: Euthanasia was used to sacrifice the animals after the investigation. On the dissection board, the Wistar rat was placed supine and had their front and rear paws pinned through. Using a scalpel coupled with a surgical blade, the animals' thorax was dissected and the heart was meticulously removed and weighed.

To assess changes in cellular morphology, tissue samples were fixed in freshly prepared formal saline for 72 hrs before processing for routine histological analysis and staining with Hematoxylin and Eosin (H&E). Specialized staining methods, such as Periodic Acid-Schiff (PAS) for detecting glycogen in cardiac muscle cells and Masson's trichrome stain for collagen fibers, were also utilized. After homogenization, tissues intended for analysis of glucose metabolism enzymes (G6PDH and LDH) and oxidative stress markers (GSH and SOD) were immediately immersed in 0.1M phosphate buffer solution (pH 7.4).

Photomicrography: The photomicrography of histological sections of the heart was taken with an Olympus Microscope (New York, United States of America) coupled with a camera at the Department of Human Anatomy, Mulungushi University School of Medicine and Health Sciences, Livingstone Campus, Zambia.

Statistical analysis: Excel was used to draw each graph and One-way ANOVA was utilized for analysis. The data was displayed as Mean±Standard Error of the mean (Mean±SEM). Less than 0.05 ($p<0.05$) was the threshold for statistical significance for p-values.

Ethical consideration: Mulungushi University School of Medicine, Health Sciences Research Ethics and the National Health Research Authority were consulted for ethical and regulatory permission.

RESULTS

Figure 1 shows the blood glucose levels of several groups of Wistar rats every week. During the acclimatization weeks (-1 and -2) the blood glucose levels of all groups were normal without a significant difference when compared to the control group ($p>0.05$). The Wistar rats in diabetes only, diabetic+potato peel extract, diabetic+insulin and diabetic+metformin groups displayed hyperglycemia after induction when compared to control and potato peel extract only, they were significant when compared ($p<0.05$). The diabetic+Irish potato peel extract showed a significant reduction in blood glucose levels and attained normoglycemia by week 3 while diabetic+insulin and diabetic+metformin attained normoglycemia at week 4 and the diabetic-only group exhibited significant ($p<0.05$) hyperglycemia compared to the control and other treated groups.

Figure 2 shows variations in average body weight among the various experimental groups of Wistar rats every week. In the weeks of acclimatization (weeks -1 and -2), the average body weights were similar in all the groups when compared to each other there was no significant ($p>0.05$). The diabetic+Irish potato peel extract and diabetic+insulin groups maintained an increase in body weight from week 2 to week 4 while the diabetic+metformin group started increasing in week 3 of the treatment period. The body weight of the control and Irish potato peel extract-only groups were similar while the diabetic-only group had the lowest body weight and when compared to the treated groups it was statistically significant ($p<0.05$).

Figure 3 shows the relative weight of the hearts of Wistar rats in the various groups. The relative heart weight in the diabetic-only group was significantly low when compared to other groups ($p<0.05$). The relative heart weight in the treated groups diabetic+potato peel extract, diabetic+insulin and

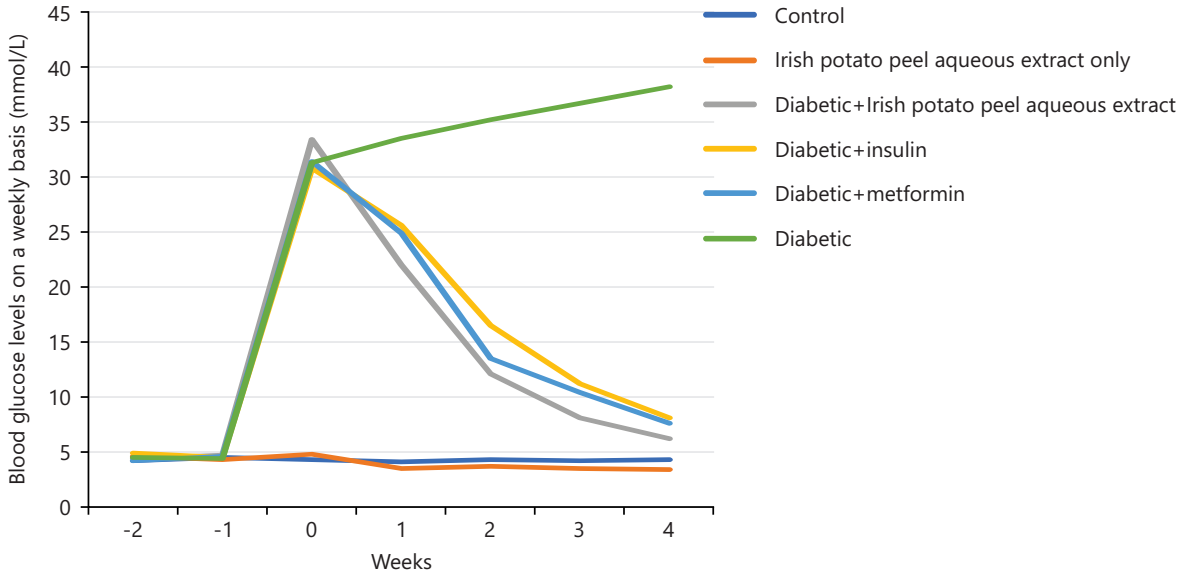

Fig. 1: Effect of an aqueous extract of Irish potato peels on the blood glucose levels on a weekly basis (mmol/L)

Data were analyzed using Mean±SEM and $p<0.05$ was considered significant

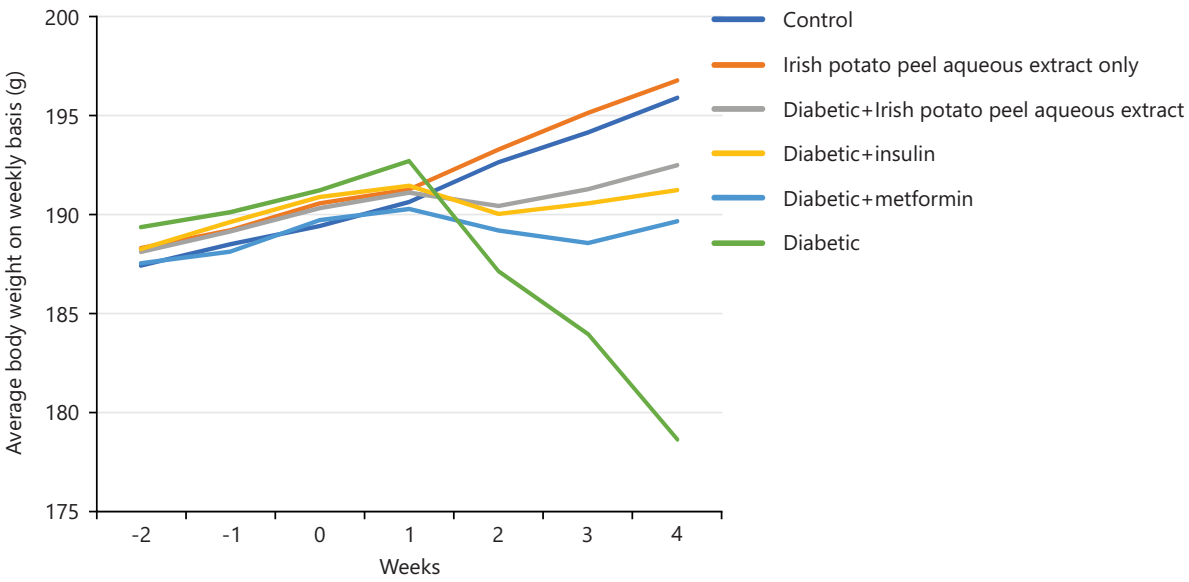

Fig. 2: Effect of an aqueous extract of Irish potato peels on the average body weight (g) every week
Data were analyzed using Mean±SEM and p<0.05 was considered significant

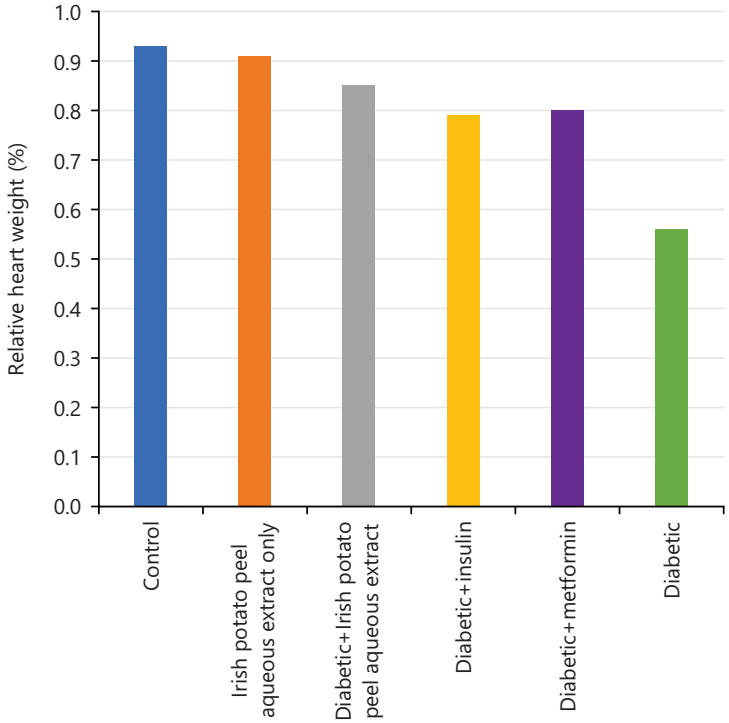

Fig. 3: Effect of an aqueous extract of Irish potato peels on the relative heart weight
Data were analyzed using Mean±SEM and p<0.05 was considered significant

diabetic+metformin were similar to the control and potato peel extract only groups with no significant difference (p>0.05).

Histology of the heart

Hematoxylin and Eosin (H&E) stain: The heart in the normal control and Irish potato peel only groups showed normal histoarchitecture with numerous healthy cardiomyocyte, (Fig. 4a-b). The diabetic+Irish potato peel, Diabetic+insulin and diabetic+metformin groups showed little disruption in their histoarchitectures and they have healthy and degenerating cardiomyocytes present (Fig. 4c-e). The diabetic group showed that the histoarchitecture was disrupted with numerous degenerating cardiomyocytes (Fig. 4f).

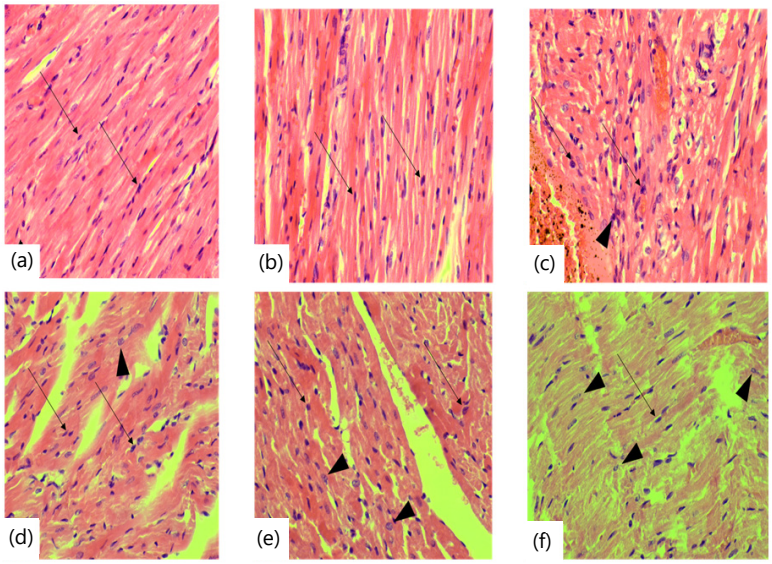

Fig. 4(a-f): Photomicrograph showing the heart at day 28, (a) Normal control, (b) Irish potato peel only, (c) Diabetic+Irish potato peel, (d) Diabetic+insulin, (e) Diabetic+metformin and (f) Diabetic
H&E stain X400, Black arrow: Cardiomyocyte and Arrowhead: Degenerating cardiomyocyte

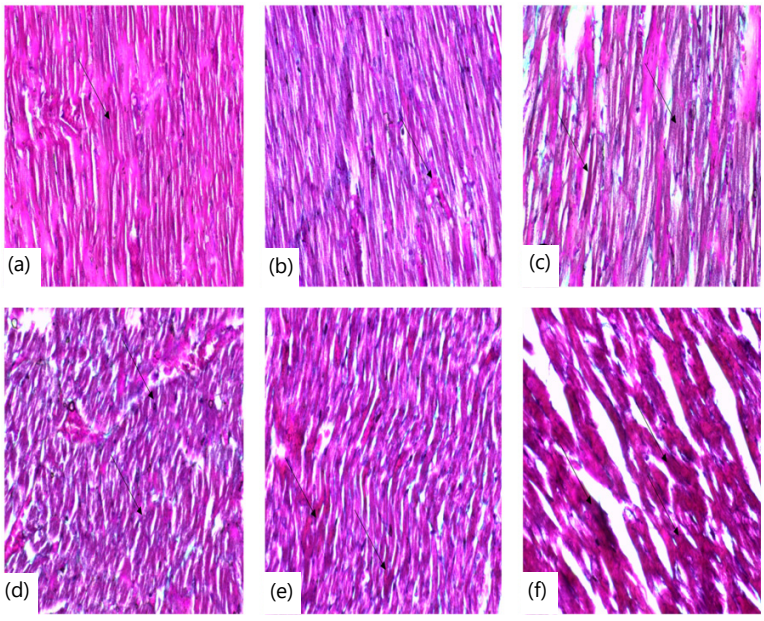

Fig. 5(a-f): Photomicrograph showing the heart at day 28, (a) Normal control, (b) Irish potato peel only, (c) Diabetic+Irish potato peel, (d) Diabetic+insulin, (e) Diabetic+metformin and (f) Diabetic
Masson X400 and Black arrow: Cardiomyocyte

Masson's Trichrome stain of the heart: In the normal control and Irish potato peel only, groups showed normal distribution of collagen (Fig. 5a-b). Diabetic+Irish potato peel, diabetic+insulin and diabetic+metformin groups showed a few deposition of collagen (Fig. 5c-e). Diabetic group showed a lot of deposition of collagen (Fig. 5f).

Periodic acid-schiff (PAS) of the heart: The normal control and Irish potato peel only groups showed normal reaction to the PAS demonstrated (Fig. 6a-b). Diabetic+Irish potato peel, diabetic+insulin and diabetic+metformin groups showed a little positive reaction to the PAS (Fig. 6c-e). Diabetic group showed positive reaction to the PAS demonstrated (Fig. 6f).

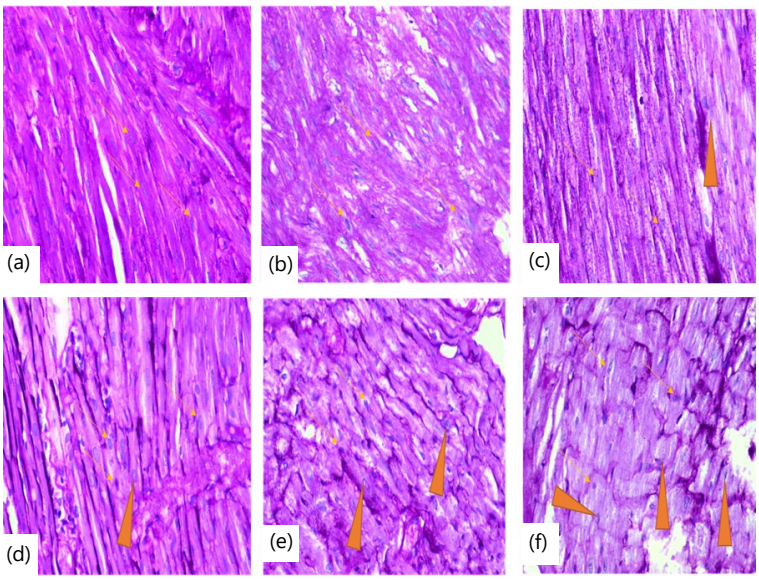

Fig. 6(a-f): Photomicrograph showing the heart at day 28, (a) Normal control, (b) Irish potato peel only, (c) Diabetic+Irish potato peel, (d) Diabetic+insulin, (e) Diabetic+metformin and (f) Diabetic
PAS stain X400 and Yellow arrow: Cardiomyocyte and Arrowhead: PAS reaction

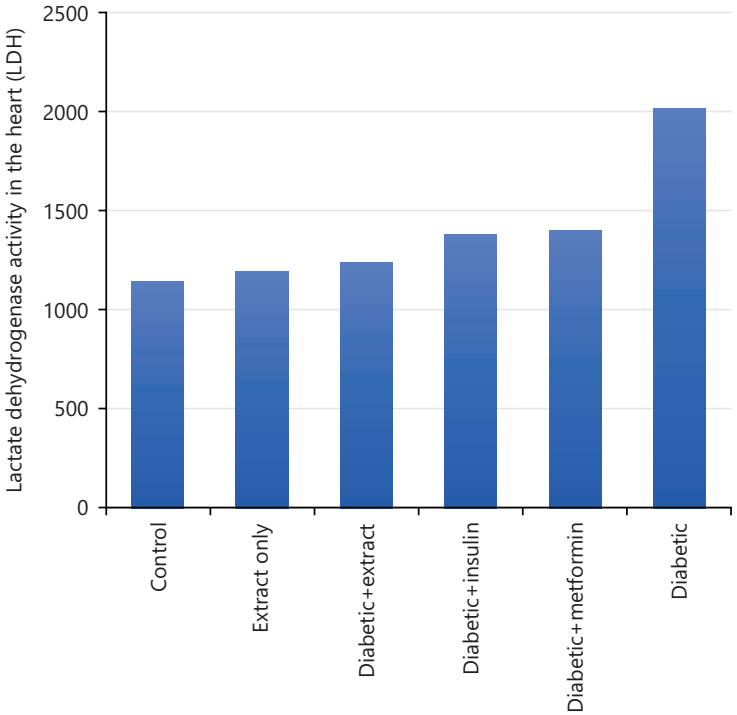

Fig. 7: Lactate dehydrogenase (LDH) activity in the heart (IU/L)
Data were analyzed using Mean±SEM and $p<0.05$ was considered significant

Histochemical studies of the heart

Lactate dehydrogenase (LDH) activity in the heart (IU/L): Figure 7 illustrates the activities of the lactate dehydrogenase enzyme (LDH) in the heart of Wistar Rats across various experimental groups. The LDH activity in the control and Irish potato peel extract-only groups was similar. The diabetic-only group had the highest LDH activity and when compared to other groups it was significant ($p<0.05$). The levels of LDH in the diabetic+extract, diabetic+insulin and diabetic+metformin groups when compared to the control was not significant ($p>0.05$).

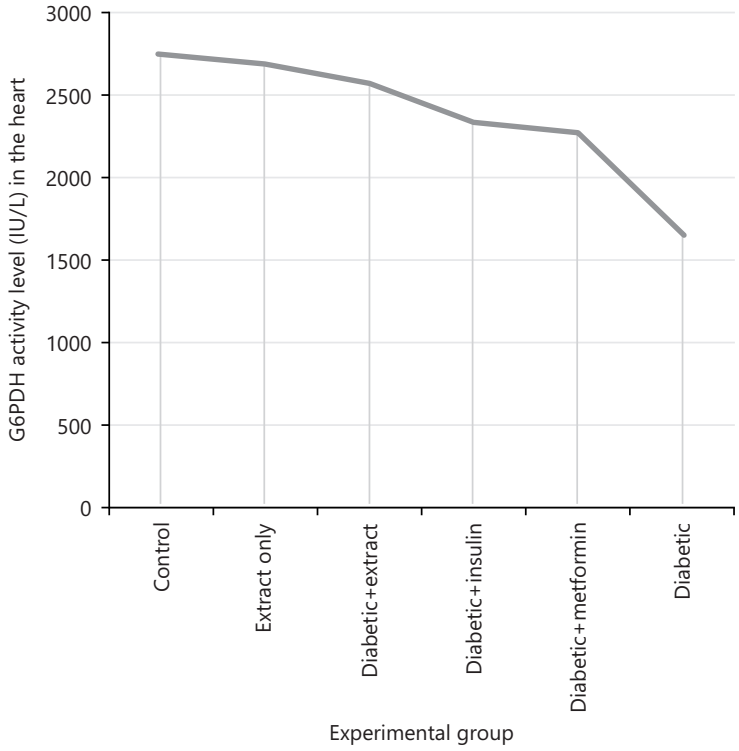

Fig. 8: Glucose-6-Phosphate Dehydrogenase (G6PDH) activity in the heart (IU/L)
Data were analyzed using Mean±SEM and p<0.05 was considered significant

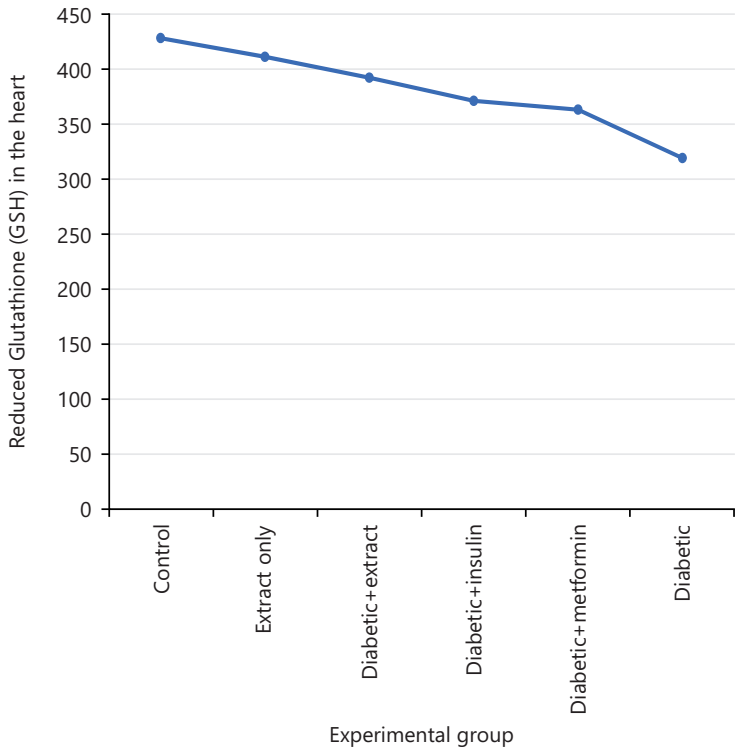

Fig. 9: Reduced Glutathione enzyme (GSH) activity in the heart (IU/L)
Data were analyzed using Mean±SEM and p<0.05 was considered significant

Glucose-6-Phosphate Dehydrogenase (G6PDH) activity in the heart (IU/L): Figure 8 shows the activities of the Glucose-6-Phosphate Dehydrogenase Enzyme (G6PDH) in the heart across different experimental groups. The control group and the Irish potato peel aqueous extract only showed significantly higher levels of G6PDH compared to the other treated groups. The diabetic-only group had

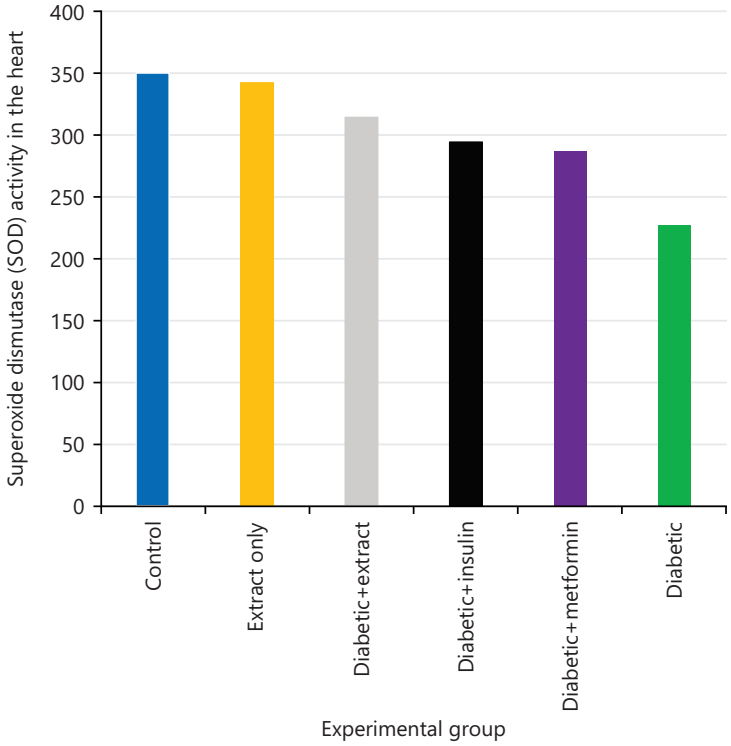

Fig. 10: Superoxide dismutase (SOD) activity in the heart (IU/L)
Data were analyzed using Mean±SEM and p<0.05 was considered significant

the lowest G6PDH activity compared to the other groups, it was significant (p<0.05). The diabetic+Irish potato peel extract, the diabetic+insulin and diabetic+metformin groups were not significant when compared to the control group (p<0.05).

Reduced glutathione (GSH) activity in the heart (IU/L): Figure 9 illustrates the variations in reduced glutathione levels among the different experimental groups. Control and Irish potato peel extract groups had higher levels of GSH compared to the other groups. The diabetic-only group had the lowest GSH level when compared to other groups it was significant (p<0.05). The GSH activity in the diabetic+Irish potato peel extract, diabetic+insulin and diabetic+metformin groups was not significant when compared to the control group (p>0.05).

Superoxide dimutase (SOD) activity in the heart (IU/L): Figure 10 shows the differences in superoxide dismutase levels among the experimental groups. The control and Irish potato peel extract-only group exhibited the highest superoxide dimutase activity compared to the other groups. The diabetic-only group exhibited the lowest SOD activity and when compared to the diabetic+Irish potato peel extract, diabetic+insulin and diabetic+metformin groups the difference was statistically significant (p<0.05). The SOD activity in the diabetic+extract, diabetic+insulin and diabetic+metformin was not statistically significant (p>0.05) when compared to control group.

DISCUSSION

Irish potato peel aqueous extract is used in the conventional treatment of hyperglycemia due to its antihyperglycemic and antidiabetic qualities[19].

This current study revealed that the diabetic-only group of Wistar rats exhibited significantly elevated blood glucose levels compared to the other groups. This could be attributed to an autoimmune response that targets and damages the pancreatic β-cells, resulting in a progressive reduction in β-cell mass and

insufficient insulin production, which ultimately leads to hyperglycemia[9,20]. Thediabetic+Irish potato peel extract group experienced a quicker reduction in blood glucose levels and attained normoglycemic levels at week 3 while the diabetic+insulin and diabetic+metformin attained normoglycemic levels at week 4. This reduction in the blood glucose levels seen in the diabetic+Irish potato peel extract is due to the presence of quercetin which encourages hepatocytes to take up glucose and reduce hyperglycemia in diabetes, as well as phenolic compoundswhich have been shown to possess strong antioxidant activity thereby lowering blood glucose[19] which is crucial for mitigating the acute complications associated with hyperglycemia[16]. The findings of this study are in agreement with Yusuf *et al*.[19] and ADAPPC *et al*.[21] who reported that the genus *Solanum* contains various steroidal saponins, steroidal alkaloids, disaccharides, flavonoids and phenolsthat have anti-inflammatory, cardioprotective, anti-atherosclerotic, immunoregulatory, anti-allergenic, antithrombolytic, antimicrobial, antitumor, anti-obesity, anticancer and anti-diabetic properties. Insulin facilitates the uptake of glucose into cells by activating glucose transporters such as GLUT4 on the cell membrane, lowering blood glucose levels and allowing glucose to be used immediately for energy or stored as glycogen in muscles and the liver. It inhibits gluconeogenesis, glycogenolysis and lipolysis, maintaining glycemic control and reducing the risk of acute and long-term complications of diabetes[22,23]. Metformin reduces blood glucose levels by improving insulin sensitivity in peripheral tissues, such as muscle and fat cells, which increases glucose uptake and utilization. It also inhibits gluconeogenesis byactivating adenosine Monophosphophosphate-Activated Protein Kinase (AMPK) in the liver. This lowers the expression of genes involved in gluconeogenesis by encouraging the translocation of glucose transporter 4 (GLUT4) to the cell surface, which facilitates the entry of glucose into cells[24,25].

The body weight of the diabetic only group of Wistar rats decreased significantlyfrom week 2-4. This was attributed to the pancreas producing insufficient insulin, which causes the body to use energy from adipose tissue due to failure to convert or breakdown glycogen to glucose, this failure causes the body to lose weight quickly in the diabetic group of Wistar rats and leads to gluconeogenesis, a common feature of untreated diabetes, where the catabolic state causes muscle wasting and fat loss due to insulin deficiency[26,27]. All the treated groups maintained their body weight. This maintenance of body weight is due to antioxidant phenolic compounds, such as quercetin, chlorogenic and caffeic acids and flavonoids, like rutin, that are present in the extract of irish potato peels, along with other chemical constituents that were able to prevent further destruction ofbeta cells in the pancreatic isletswhich can lower blood glucose levels[13]. Other reports further suggest that the chemical constituents of Irish potato peel extract promote weight recovery possibly through enhanced glucose utilisation and decreased catabolism[28]. These findings are in agreement with Xu *et al*.[29] whose study yielded that Irish potato peels are a great source of polyphenols that can increase insulin sensitivity leading to lower blood glucose levels and reduced the risk of weight gain associated with poor glycemic control and reducing fat accumulation in adipose tissues, contributing to better weight management. The diabetic+insulin group maintained weight because of the ability of insulin to inhibit gluconeogenesis, lower glucose output, increase glucose uptake and utilisation in peripheral tissues and improve energy metabolism in organs like the liver, muscle and fat[30,31] while metformin group in addition to its ability to improve glycaemic management and insulin sensitivity. It also suppresses hunger and changes the microbiota in the gut, which frequently may resultin weight reduction[32]. These findings are in agreement with Rena *et al*.[26] and Hu *et al*.[33] whose studies indicate adenosine monophosphate activated protein kinase is triggered by insulin and metformin, which inhibits gluconeogenesis, lowers glucose production, increases glucose absorption and utilisation in peripheral tissues and improves energy metabolism in organs like muscle, fat and liver.

The diabeticonly group had the lowest relative heart weight when compared to the other groups. This difference was due to an increase in oxidative stress, inflammation and cardiomyocyte apoptosis, ultimately resulting in a decrease in heart mass[18,34,35]. The relative heart weight in the diabetic+Irish

potato peel extract was relatively similar to the control group which might be explained by the antioxidant qualities of Irish potato peel, which might mitigate oxidative stress, a significant factor in diabetic heart disease thereby providing a protective effect and maintaining heart weight and possibly delaying the development of diabetes cardiomyopathy. These findings are consistent with the findings of Marwick *et al.*[35] and Jacob and Narendhirakannan[36] that irish potato peels are rich in antioxidants including flavonoids, alkaloids, phenolics and tannins, that enhance the function of pancreatic tissues by either secreting more insulin or reducing the amount of glucose absorbed through the digestive tract. The well-known diabetes medication insulin and metformin likewise displayed a similar pattern with no significant decrease in heart weight compared to the control group due to the ability of insulinto enhance the uptake and utilisation of glucose, which may lessen the cardiac muscle's metabolic load[30] while metformin has direct cardiovascular benefits, such as anti-inflammatory and antioxidative actions, which may help maintain heart weight, in addition to its effects on decreasing blood sugar[37].

The histological findings of the diabetic only group displayed a considerable histoarchitectural disruption and degeneration of cardiomyocytes, excessive collagen deposition and a strong positive response to PAS staining. These are due tothe hyperglycemic statefollowing streptozotocin induction which led to oxidative stresscaused by collagen deposition in the heart and excessive build-up of glycogen due to elevated glucose flux through pathways like polyol pathway causing thickening of the basement membrane within the heart tissueconsequently leading to heart failure[38]. This is consistent with the findings by Varma *et al.*[39] who reported that when collagen levels are too high, the cardiac tissue may stiffen, impairing the heart's capacity to contract during the systolic and diastolic phases and ultimately leading to heart failure and death. The diabetic+Irish potato peel, diabetic+insulin and diabetic+metforminphotomicrographs, revealed comparatively mild changes to the histoarchitecture showing both degenerating and healthy cardiomyocytes indicating a partial reduction of cardiomyocyte degeneration in these treatment groups. The cardioprotective effects shown in the diabetic+Irish potato peel group may be explained by the antioxidant and anti-inflammatory qualities of the irish potato peel extract which enhance balance between collagen synthesis and degradation enabling preservation of structural integrity and function allowing for normal collagen homeostasis and normal cardiac function which help mitigate the oxidative stress and inflammation exhibited in diabetes hearts[40]. These findings are in agreement with the other findings[41,42] that Irish potato peel extract contains antioxidants and polyphenols, such as chlorogenic acid and catechins, which have been demonstrated to inhibit the activation of fibroblasts responsible for collagen synthesis and reduce the expression of pro-inflammatory cytokines and reactive oxygen species (ROS). This attenuates collagen deposition, which in turn reduces cardiomyocyte degeneration and improves cardiac function in diabetic conditions. Additionally, it promotes insulin sensitivity and increases glucose metabolism, which will aid in restoring normal cardiac glycogen storage and utilisation. Insulin therapy is known to improve glucose metabolism and reduce metabolic stress on the heart[30], whereas metformin has been shown to improve insulin sensitivity and reduce hepatic glucose production and reduction in glycogen deposition which directly benefits the cardiovascular system[43].

The histochemical studies of the lactate dehydrogenase (LDH) activity revealed significantly higher in the diabeticgroup compared to other groups due to persistent hyperglycemia and poor glucose metabolism resulting in increased oxidative stress and consequent myocardial injury[44]. The LDH activity in the diabetic+Irish potato peel extract, diabetic+insulin and diabetic+metformin were relatively similar and not significantdue to theantioxidant properties of Irish potato peels that have the ability to modulate glucose metabolism and improve insulin sensitivity, leading to reduced LDH levels consequently preventing tissue damage associated with hyperglycemia[35,45,46]. This study is in agreement with Singh *et al.*[13] and Pérez-Torres *et al.*[47] that reported that the antioxidants present in Irish potato peel extract, such as chlorogenic acid, catechins and ascorbic acid, can neutralize reactive oxygen species (ROS)

and reduce oxidative stress. By mitigating oxidative damage to tissues, the extract may help lower serum LDH levels, indicating reduced cell membrane damage. Insulin reduces LDH levels by regulating glycolytic pathways and preventing anaerobic metabolism leading to reduced oxidative stress and prevention of further tissue damage thus reducing the leakage of LDH from damaged cells into the blood[48]. Metformin reduces elevated LDH levels by improving glycemic control through enhancing insulin sensitivity and reduction of hepatic glucose production, which helps maintain normoglycemic state and decreases oxidative stress, thereby protecting tissues from damage[49].

The diabetic group showed the lowest G6PDH activity compared to theother groups. This marked reduction was caused by the persistent hyperglycemia and the associated increase in reactive oxygen species (ROS) production which caused reduction in G6PDH activityleading to diminished Nicotinamide Adenine Dinucleotide Phosphate (NADPH) availability thereby reducing the heart's capacity to neutralize oxidative stress and compromised metabolic function in the heart[50]. The diabetic+Irish potato peel extract, diabetic+insulin and diabetic+metformin groups showed a relatively higher G6PDH activity due to presence of antioxidants like vitamins, flavonoids and phenolic substances in irish potato peel extractwhich lessen oxidative stress by the up-regulation of G6PDH activity, which helps to improve the antioxidant defence system and restore the cellular redox state. These findings are in agreement with Yusuf *et al.*[10] and Petersen and Shulman[32] that the antioxidants in Irish potato peel extract, such as polyphenols and flavonoids, may help to reduce oxidative stress by scavenging free radicals and enhancing the cellular redox state indirectly helping to maintain or boost G6PDH activity, which is crucial for generating NADPH and preserving the antioxidant capacity of cells. They also encourage better glycemic control which reduces the oxidative stress burden on cells, potentially preventing the inhibition or downregulation of G6PDH. A study by Sun *et al.*[30] revealed that insulin therapy is able to increase or restore G6PDH activity by promoting glycolytic flux and glucose uptake, which indirectly strengthens the pentose phosphate pathway, in which G6PDH is essential helping to fight against oxidative stress. Metformin encourages the use of glucose in processes that lead to a greater production of reducing equivalents, such as NADPH. It also protects tissues from the oxidative damage frequently associated with diabetes by increasing G6PDH activity, which contributes to the maintenance of a balanced redox status[49].

The term oxidative stress refers to an increase in reactive oxygen species (ROS), either as a result of increased production or damage to the antioxidant mechanisms. Oxidative stress is often determined by measuring the byproducts of ROS-induced cellular molecular oxidation in tissue, blood, urine, or exhaled breath[51]. Reduced Glutathione (GSH) was significantly low in the diabetic only group compared to other groups due to the hyperglycemic state that causes an excess production of reactive oxygen species (ROS), which reduces GSH stores leading to increased susceptibility to oxidative cellular damage[45]. The diabetic+Irish potato peel extract group, diabetic+insulin and diabetic+metformin groups showed higher levels of GSH levels due to the potent antioxidants present in Irish potato peels extract such as flavonoids and phenolic compounds that help to fight against oxidative damage. The findings in this study are in line with Nazir *et al.*[14] that suggests that the Irish potato peel extract possesses high antioxidant activity due to its rich content of polyphenols, flavonoids and vitamin C. These antioxidants contribute to the regeneration of GSH from its oxidized form Glutathione Disulfide (GSSG), maintaining the cellular redox balance and protecting cells from oxidative damage. Insulin through its hypoglycemic effect decreases the production of ROS, which in turn reduces the consumption of GSH for detoxification, allowing GSH levels to recover[30]. Metformin increases overall glucose metabolism by lowering blood glucose levels which facilitates the entry of glucose-6-phosphate into the pentose phosphate pathway (PPP), where G6PDH is the rate-limiting enzyme. This aids in producing NADPH, which is necessary for defending cells against oxidative stress thus maintaining cellular redox balance and promoting the regeneration of Reduced Glutathione (GSH)[49,52].

The diabetic only group revealed decreased superoxide dismutase (SOD) activity compared to other groups because the hyperglycaemic state caused excessive production of ROS, whichoverwhelmed the body's antioxidant defences. This increased oxidative stress led to modification of the enzyme's structure, reducing its activity and consequently impairing its protective function[53]. The SOD activity in the diabetic+Irish potato peel extract, diabetic+insulin and diabetic+metformin were relatively similar to that of the control group. This increase in SOD activity in the diabetic+Irish potato peel extract was because of its antioxidant compounds, such as chlorogenic acid, caffeic acid and quercetin, that help fight against ROS, thereby reducing oxidative stress and indirectly supporting the activity and expression of SOD[13]. Other reports also suggest that the phenolic compounds in the Irish potato peels can activate signaling pathways such as the nuclear factor erythroid 2-related factor 2 (Nrf2) that regulate the expression of antioxidant genes, resulting in increased levels of SOD and other antioxidant enzymes[54]. These findings are in agreement with the finding of Singh *et al*.[13] and Singh *et al*.[55] that high content of polyphenols and other antioxidant compounds in irish potato peels,help neutralize superoxide radicals, thus protecting cells from oxidative damage. The upregulation of SOD suggests that irish potato peel extracts can boost the body's natural antioxidant defense mechanisms, counteracting the oxidative stress often seen in diabetes. Insulin has been found to enhance SOD activity because it can reduce oxidative stress by lowering blood glucose levels, which decreases the production of reactive oxygen species (ROS), thus allowing SOD to function more effectively[56]. Metformin reduces the production of reactive oxygen species (ROS) by inhibiting mitochondrial complex I and causes upregulation of the expression of antioxidant enzymes, including SOD. This decrease in ROS production leads to a reduction in oxidative stress, which helps preserve SOD activity and function[49].

CONCLUSION

This study shows that an aqueous extract of Irish potato peels was able to lower the blood glucose levels, maintain the histoarchitecture of the heart and also avert the disturbance of glucose metabolism and oxidative stress.

SIGNIFICANCE STATEMENT

The study investigated the cardioprotective effects of an aqueous extract of Irish potato peels (*Solanum tuberosum*) on diabetic-induced alterations in the heart of Wistar rats. This study has shown that an aqueous extract of Irish potato peels was able to lower the blood glucose levels, maintain the histoarchitecture of the heart and also avert the disturbance of glucose metabolism and oxidative stress. According to the findings of this study, diabetic individuals may benefit from a clinical trial using an aqueous extract of *Solanum tuberosum* (Irish potato) peels.

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