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Research Article

Fermented Cabbage Mitigates Tumour Necrosis Factor Alpha and Pancreatic Tissue Oxidative Stress in Streptozotocin-Nicotinamide Induced Type 2 Diabetic Wistar Rats

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Abstract

Diabetes mellitus is predicted to affect 552 million people by 2030, up from 366 million in 2011. This research examined the efficacy of fermented cabbage (FC) on pancreatic oxidative stress and tumour necrosis factor-α. After type 2 diabetes induction, rats with blood glucose levels ≥ 150 mg/dL were grouped into six sets of five at random. Group 1 received 1 mL/kg of distilled water as the normal control. Group 2 received 1 mL/kg of distilled water in addition to serving as the negative control group (the diabetic untreated group). As the positive control, group 3 received metformin (500 mg/kg). Fermented cabbage was administered to groups 4, 5, and 6 at 12.5%, 25%, and 50%, respectively. In comparison to the diabetic untreated group, treatment with FC significantly ($p< 0.05$) reduced lipid peroxidation. When compared to the diabetic untreated group, all of the FC-treated groups showed a significant ($p< 0.05$) increase in pancreatic tissue superoxide dismutase and catalase. In addition, in comparison to the diabetic untreated group, treatment with FC significantly ($p< 0.05$) enhanced the reduced glutathione level. In the diabetic, untreated group, compared to the normal control, TNF-α levels were considerably higher. However, when compared to the diabetic untreated group, there was a significant decrease ($p< 0.05$) in all FC-treated groups. Thus, fermented cabbage decreases oxidative stress markers and TNF-α with improved glycaemic control. Fermented cabbage was shown to cause a steady decrease ($P < 0.05$) in blood glucose levels in a dose dependent manner.

Key Words: Type 2 diabetes, tumour necrosis factor-alpha, and pancreatic oxidative stress.

INTRODUCTION

The occurrence of type 2 diabetes mellitus (DM) has been steadily increasing globally (Olokoba *et al*., 2012). It is safe to state that DM is one of the most ancient non-communicable diseases that affect people. It was originally referenced in an Egyptian text some 3,000 years ago (Ahmed, 2002). People who have type 2 diabetes mellitus (T2DM) are more vulnerable to numerous complications, many of which result in early death (Galicia-Garcia, 2020). T2DM patients are likely to experience higher morbidity and mortality attributable to the slow progression and late diagnosis, especially in resource-poor developing countries like Africa (Azevedo and Alla, 2008). By 2030, there will be 552 million more people with DM than the 366 million who were anticipated to have it in 2011. T2DM is becoming more common, with low and middle-income nations accounting for 80% of incidents (IDF, 2011). T2DM is predicted to affect around 590 million people by 2035, which is concerning considering its increased prevalence (Ozougwu *et al*., 2013; Guariguata *et al*., 2014). Management of T2DM typically includes dietary changes, lifestyle adjustments, increased physical activity, and the use of a variety of anti-diabetic drugs (Thompson and Kanamarlapudi, 2013).

Metformin has several beneficial effects on patients with diabetes, including reducing insulin resistance in peripheral tissues, enhancing the release of glucagon-like peptide 1 (GLP-1) after meals, slowing down digestion, and decreasing glycogenolysis in the liver (Raz, 2013). However, orthodox anti-diabetic drugs like metformin, thiazolidinediones, and sulfonylureas can still have negative effects on patients (Susilawati *et al*., 2023). To address this, researchers have turned their attention to plant extracts with anti-diabetic properties, which have the potential to be effective treatments for type 2 diabetes mellitus (T2DM) with fewer adverse effects (Lee *et al*., 2021). Laboratory studies have shown that these plant extracts can affect key pathways involved in glucose transport and utilization, antioxidant activity, anti-inflammation, and lipid metabolism, providing evidence for their effectiveness in managing T2DM (Amraee and Bahramikia, 2019). One family of plants that stands out is the Brassicaceae family, which includes around 3709 species and 360 genera. Among these, B. oleracea is a prime example, encompassing varieties like broccoli, cauliflower, kale,

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kohlrabi, and cabbage, which can be identified by the shape of their fruits (Samec *et al*., 2017). Cabbage, in particular, is known for its high nutritional value, containing significant amounts of fiber, minerals, and vitamin (such as C, K, A, and folate) contents (Korus*et al*., 2021). Additionally, cabbage is rich in secondary metabolites like s-methyl cysteine sulfoxide, sulphur-containing glucosinolates, and phenolic compounds (Nawaz *et al*., 2018). Given these properties, the aim of this study was to investigate the impact of fermented cabbage on specific indicators of T2DM.

MATERIALS AND METHODS

Chemicals: The chemicals and pharmaceuticals (Streptozotocin, nicotinamide, and metformin) used for the research were of analytical grade and obtained from Sigma Chemical Company in St. Louis, USA.

Plant identification: Fresh cabbage was obtained from Kubani Farm in July 2022 in Zaria, Kaduna State, Nigeria. The plant identification was carried out at the Herbarium unit, Department of Botany, Ahmadu Bello University's Zaria. For reference purposes, a voucher number of 43382 was given.

Preparation of fermented cabbage supplement: After washing with clean water, the outer, unclean leaves of fresh cabbage were removed and trimmed. A clean towel was placed on top, the cabbage was compressed with a weight, and fermentation was allowed to take place for 5 to 7 days. 30 g of salt was then spread in layers for every kg of cabbage. The addition of salt during fermentation restricts the growth of gram-negative bacteria and enhances the growth of lactic acid bacteria (LAB). The LAB tolerates high salt concentrations, which give them an advantage over other less salt-tolerant species and allows the LAB to produce acid that inhibits the growth of undesirable microorganisms and for this reason, initiates the majority of lactic acid fermentations (Mike and Sue, 1998). Following fermentation, the cabbage was shade-dried, weighed, and moulded with the animal feed (grower's mash) to create mixtures in 12.5%, 25%, and 50% proportions (Muhammad *et al*., 2021).

Animal care: Thirty (30) male adult Wistar rats weighing 150 to 250 g were used for the study. The experimental animals utilised in the study were obtained from the Department of Human Physiology, Ahmadu Bello University and were housed in cages under laboratory condition having access to feed and water ad libitum. They were fed with grower's mash (Vital Feeds® Company Plc., Jos). The Animal Use and Care Committee at Ahmadu Bello University Zaria provided ethical approval for the study (ABUCAUC/ 2018/ 068).

Induction of Diabetes: After an overnight fast, the rat's blood glucose levels were assessed before diabetes induction. Diabetes was induced by a single intraperitoneal dosage (65 mg/kg) of streptozotocin (STZ), freshly prepared in a cold sodium citrate buffer solution (50 mM, pH 4.5), for 15 minutes. This was followed by the intraperitoneal administration (120 mg/kg) of nicotinamide (Balaji *et al*., 2020). To prevent hypoglycaemia, the animals received a 10% glucose solution for 6 hours after induction for 24 hours. (Furman, 2015). A one-touch digital glucometer (Boche Diagnostic Company) was used to determine the blood glucose level on the 7th day post-diabetes induction. Experimental animals with fasting blood glucose readings of ≥ 150 mg/dL were employed for this study (Donovan and Brown, 2006; Furman, 2015).

Experimental design: The experimental animals were grouped into six (6) groups, with each group having five animals (n = 5). Group 1: Normal control (NC): rats that received distilled water (1 ml/kg). Group 2: Diabetic control (negative): untreated diabetic rats that received distilled water 1 mL/kg (DCUT). Group 3: Positive control: diabetic rats that received 500 mg/kg of metformin (MET) as standard drug. Group 4: Experimental group: diabetic rats that were fed with 12.5% FC supplementation (added to feed). Group 5: Experimental group: diabetic rats that were fed with 25% FC supplementation (added to feed). Group 6: Experimental group: diabetic rats that were fed with 50% FC supplementation (added to feed). Daily administration was done orally and lasted for four (4) weeks (Muhammad *et al*., 2021).

Blood sample and tissue collection: At the completion of the experiment, the experimental animals were sedated using chloroform inhalation. Cotton wool was soaked in chloroform and placed in a desiccator for five minutes before exposure to ensure circulation. After 30-35 seconds, the chloroform-exposed experimental animals became completely comatose (Aguwa *et al*., 2020). The experimental animals were subsequently euthanized by cervical dislocation (Cheng, 2021). Blood samples were collected through cardiac puncture (Parasuraman *et al*., 2010). The pancreatic tissues were carefully harvested from the surrounding tissues and then homogenised using phosphate buffer solution (PBS pH 7.4).

Determination of blood glucose level: Determination of blood glucose levels was carried out at weeks 0, 1, 2, 3 and 4. The experimental animals were fasted for six to eight hours before having their blood glucose levels measured using a digital glucometer (Accu-Check Advantage, Roche Diagnostic®, Germany) using the glucose oxidase method (Beach and Turner, 1958). The findings were presented in mg/dL (Rheney and Kirk, 2000).

Pancreatic tissue oxidative stress assay: The method of Mockett *et al* (2002) was used to estimate the superoxide dismutase activities; glutathione peroxidase activity was determined using the method described by Flohe and Gunzler (1984) and catalase activity was determined using the method described by Aebi (1984) The lipid peroxidation was determined by measuring MDA level using the technique described by Miller and Aust (1989).

Tumour necrosis factor-α assay: Tumour necrosis factor-alpha (TNF-α) was assayed using the rat tumour necrosis factor ELISA kit (Shanghai Coon Koon Co., Ltd.) with Cat No. CK-bio-15469.

Statistical analysis: Data obtained were expressed as mean + Standard Error of Mean (SEM) and analyzed using one way analysis of variance (ANOVA) using SPSS version 22. Tukey’s post-hoc test was used to compare the level of significant differences between control and test groups. Values of $p < 0.05$ were considered significant.

RESULTS

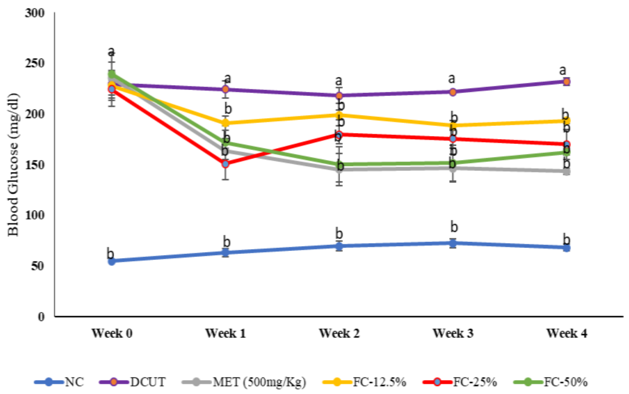

Figure 1:
Effect of FC on blood glucose level
[a, b, c, d]$p < 0.05$ NC vs DCUT, MET, and FC 12.5%, respectively.

Figure 1 demonstrates the impact of fermented cabbage supplement over a four-week treatment period in STZ/NA-induced diabetic male Wistar. When compared to the diabetic untreated control group, treatment of diabetic rats with graded doses of fermented cabbage (12.5%, 25%, and 50%) and metformin (500 mg/kg) caused a significant ($p<0.05$) decrease in blood glucose level.

The effect of fermented cabbage supplement (FC) on pancreatic tissue lipid peroxidation (MDA) and superoxide dismutase (SOD) activity is presented in Fig. 2. The MDA level of diabetic untreated rats was significantly higher than the MDA of normal control rats ($p < 0.05$). Metformin treatment significantly ($p < 0.05$) decreased MDA level (Fig. 2A). Treatment with FC moderately reduced MDA levels in the FC treated rats. Furthermore, the effect of FC on pancreatic superoxide dismutase activity (SOD) is on fig. 2B, In the diabetic untreated group SOD was significantly ($p<0.05$) lower than that of the normal control group. Metformin treatment significantly boosted SOD activity when compared to the diabetic untreated group (Fig. 2B). Treatment with FC significantly increased SOD activity in dose dependent manner ($p < 0.05$).

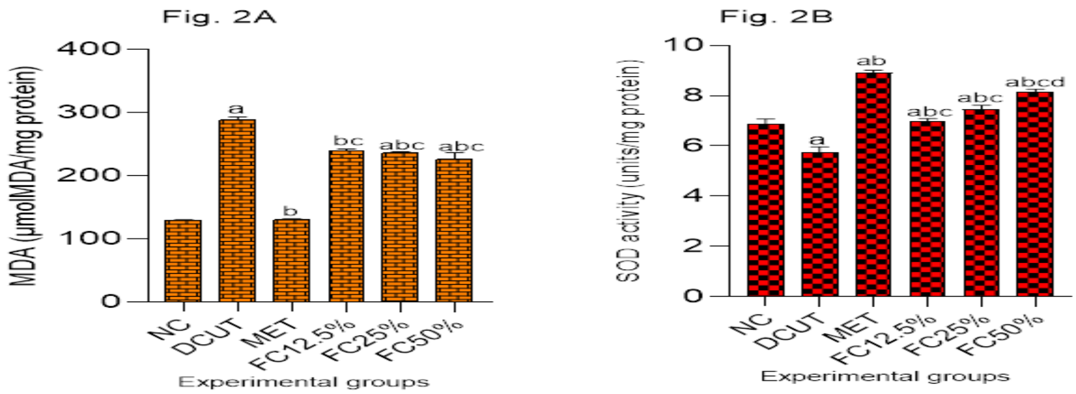

Figure 2:
Effect of FC on pancreatic lipid peroxidation and superoxide dismutase activity superscripts a, b, c, and d denote a statistically significant difference ($p < 0.05$) compared to NC= normal control, DCUT= diabetic control untreated, MET= metformin, FC= fermented cabbage

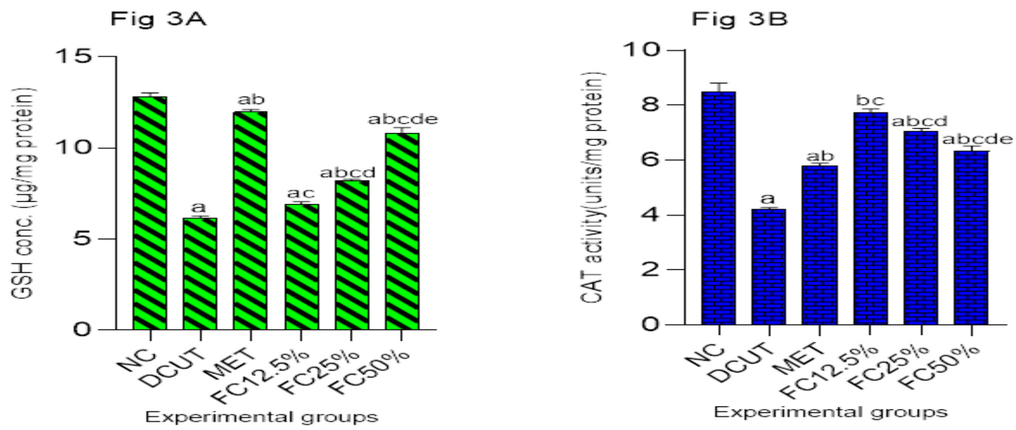

Figure 3:
Effect of FC on pancreatic reduced glutathione and catalase activity superscripts a, b, c, and d denote a statistically significant difference ($p < 0.05$) compared to NC= normal control, DCUT= diabetic control untreated, MET= metformin, FC= fermented cabbage

The concentration of GSH in the diabetic untreated group was significantly lower ($p < 0.05$) than that in the normal control group (fig. 3A). Compared to the diabetic untreated group, metformin treatment significantly ($p < 0.05$) raised GSH concentration. In addition, when compared to the untreated diabetic group, treatment with 50% FC produced the most significant ($p < 0.05$) increased GSH activity (Fig. 3). Furthermore, metformin treatment significantly ($p < 0.05$) increased CAT activity compared to the untreated diabetic and the normal control groups. In addition, there was a significant ($p < 0.05$) increase in CAT activity with FC treatment when compared to the untreated diabetes group.

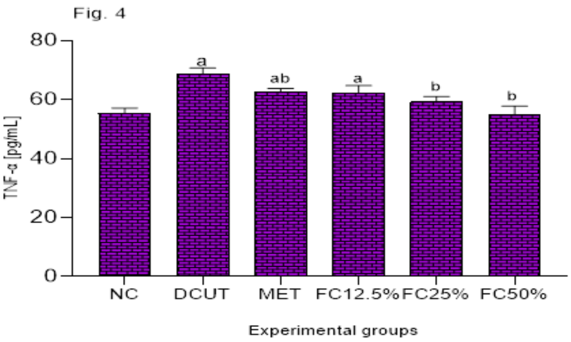

Figure 4:
Effect of fermented cabbage supplement on Tumour necrosis factor alfa (TNF-α). Superscripts a and b denote statistically significant differences ($p < 0.05$) compared to the NC and DCUT respectively.

The effect of fermented cabbage supplement on the levels of Tumour necrosis factor-alpha (TNF-α), a pro-inflammatory mediator in experimental groups is presented in Fig. 4. TNF-α was significantly elevated in the diabetic untreated group. However, treatment with metformin and FC decreased the level of TNF-α, with 50% FC producing the highest effect.

DISCUSSION

Fermentation is a technology that employs the development and metabolism of microorganisms to preserve food (Nuraida, 2015; Wilburn and Ryan, 2017; Terefe, 2022). It is among the most widespread and economical methods of meal preparation. Fermented foods have been shown to improve immunity, reduce the signs of lactose intolerance, lower blood cholesterol levels and prevent infections (Tamang and Kailasapathy, 2010).

The present study investigated the effect of fermented cabbage supplement on blood glucose level, TNF-α and pancreatic oxidative stress markers in STZ/NA-induced diabetic male Wistar rats. In this study, the elevated blood glucose levels observed in the diabetic untreated control group may be primarily explained by insulin resistance, which reduces the responsiveness of peripheral tissues (muscle and fat cells) to insulin; elevated glycogen breakdown; increased gluconeogenesis; increased hepatic glucose production and insulin deficiency. These occur because of pancreatic β-cell destruction following diabetic induction with streptozotocin. Tumour necrosis factor-alpha (TNF-α) may also interfere with endothelium, lipolytic and insulin signalling, among other processes (Tangvarasittichai, 2015). The impact of pro-inflammatory cytokines such as TNF-α has been documented in insulin signalling pathways, leading to the development of insulin resistance in pancreatic β-cells and increasing the risk of type 2 diabetes (Bashir *et al*., 2020).

Long-term addition of fermented cabbage (FC) to feeds of diabetic animals protected against deleterious effects of streptozotocin (STZ), thus demonstrating the antihyperglycemic and antidiabetic properties of FC. Biomolecules like flavonoids and saponins present in FC might facilitate the regeneration of pancreatic beta cells and restores insulin sensitivity. Thus, fermented cabbage improved glucose metabolism by lowering blood glucose levels (Ansari *et al*., 2023). This effect can also be attributed to the presence of lactic acid bacteria in fermented cabbage supplement as a result of the fermentation process. This is another potential mechanism by which FC might be able to lower blood glucose levels. Lactic acid bacteria could promote glycaemic control by acting on the gut bacteria to produce insulin-tropic polypeptides, glucagon like peptide-1 and glucose-dependent insulinotropic polypeptide (Yao etal., 2017). Lipids can interact with and be modified by reactive oxygen species (Augustine *et al*., 2021). Evidence of lipid peroxidation was substantiated by current investigation with significant increase in pancreatic MDA levels in the untreated diabetes group. These results corroborate Takasu's research which showed that DNA fragmentation is mediated by rising MDA levels (Takasu *et al* 1991).

Prolonged hyperglycaemia in systemic circulation enhances the production of ROS from protein glycosylation and glucose autoxidation (Giri *et al*., 2010). This explains why the untreated diabetic group in the current study exhibited lower levels of antioxidant enzymes. However, in the current investigation, FC treatment led to a considerable rise in pancreatic antioxidant enzymes. The release of bioactive substances from conjugated phytochemicals may be responsible for the mechanisms behind the differences in antioxidant activity. It has been demonstrated that fermenting cabbage with lactic acid increases its antioxidant capacity (Kusznierewicz *et al*., 2008; Sun *et al*., 2009 and Kim *et al*., 2011). Microbial enzymes can improve the nutritional value and organoleptic quality of foods by converting phenolic compounds from bound form to free form during fermentation (Zhao *et al*., 2021).

Additionally, the structural disintegration of cabbage brought about by fermentation may cause the release of antioxidant molecules or the synthesis of entirely new antioxidant substances. Another explanation for the increase in antioxidant activity in foods fermented with lactic acid bacteria is the fact that it has both enzymatic and non-enzymatic antioxidant pathways (Hur *et al*., 2014).

TNF-α was the first pro-inflammatory cytokine whose role in the development of insulin resistance and type 2 diabetes has been reported (Alzamil, 2020). The insulin-regulated transporter type 4 (GLUT 4), which is mostly present in adipocytes, skeletal and cardiac muscles, has been demonstrated to be down regulated by TNF-α (Akash *et al*., 2018). In the current study, it was observed that the TNF-α level was elevated in the untreated diabetic group than the normal control. However, FC treatment at 25% and 50% significantly reduced TNF-α in comparison to the diabetic untreated group. There is evidence that plant-based fermented foods have anti-inflammatory and immunoregulatory properties (Zulkawi *et al*., 2017; Birhanu *et al*., 2018 and Zhao *et al*., 2020). Some studies have reported bioactive chemicals such as phenolic compounds, antioxidants and GABA as being responsible for the antidiabetic effects of fermented foods (Sivamaruthi *et al*., 2018). In conclusion, fermented cabbage mitigates pancreatic tissue oxidative stress and TNF-α in Streptozotocin-Nicotinamide-induced Type 2 diabetes in Wistar Rats.

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REFERENCES

Aebi, H. (1984). Catalase in vitro. Meth. Enzymol. 105: 121-126.

Aguwa, U.S., Eze, C.E., Obinwa, B.N., Okeke, S.N., Onwuelingo, S.F., Okonkwo, D.I., Ogbuokiri, D.K., Agulanna, A.E., Obiesie, I. J. and Umezulike, A. J. (2020). Comparing the Effect of Methods of Rat Euthanasia on the Brain of Wistar Rats: Cervical Dislocation, Chloroform Inhalation, Diethyl Ether Inhalation and Formalin Inhalation. *J Adv Med Med Res*.32(17): 8-1.

Ahmed, A. M. (2002). History of diabetes mellitus. *Saudi Med J*. 23(4): 373-378.

Akash, M.S.H., Rehman, K. and Liaqat, A. (2018). Tumor necrosis factor-alpha: role in the development of insulin resistance and pathogenesis of type 2 diabetes mellitus. *J. Cell. Biochem.* 119(1): 105–110.

Alzamil, H (2020). Elevated Serum TNF-α is Related to Obesity in Type 2 Diabetes Mellitus and is Associated with Glycemic Control and Insulin Resistance. .*J Obes*. doi: 10.1155/2020/5076858

Amraee, S. and Bahramikia, S. (2019). Inhibitory effect of effective fraction of salvia officinalis on aldose reductase activity: Strategy to reduce complications of type 2 diabetes. *Orient Pharm Exp Med*. 19: 211–216.

Ansari, P., Samia, J.F., Khan, J.T., Rafi, M.R., Rahman, Md.S., Rahman, A.B., Abdel-Wahab, Y.H.A. and Seidel, V. (2023). Protective Effects of Medicinal Plant-Based Foods against Diabetes: A Review on Pharmacology, Phytochemistry, and Molecular Mechanisms. *Nutrients*. 15(14): 3266.

Augustine, J., Troendle, E. P., Barabas, P., McAleese, C. A., Friedel, T., Stitt, A. W. and Curtis, T. M. (2021). The Role of Lipoxidation in the Pathogenesis of Diabetic Retinopathy. *Front Endocrinol*. 11: doi: 10.3389/fendo.2020.621938

Azevedo, M. and Alla, S. (2008). Diabetes in Sub-Saharan Africa: Kenya, Mali, Mozambique, Nigeria, South Africa and Zambia International. *Int. J. Diabetes Dev*. Ctries. 28(4): 101-108.

Balaji, P., Madhanraja, R., Rameshkumar, K., Veeramanikandan, V., Eyini, M/, Arun, A., Thulasinathane, B., Al Farraj, D.A., Elshikh, M.S., Alokda, A.M., Mahmoud, A.H., Tack, J.C. and Kimi, H.J. (2020). Evaluation of the antidiabetic activity of Pleurotus pulmonarius streptozotocin-nicotinamide induced diabetic Wistar albino rats. *Saudi J Biol Sci*. 27 (3): 913-924.

Bashir, H., Bhat, S, A., Majid, S., Hamid, R., Koul, R.K., Rehman, M.U., Din, I., Bhat, J.A., Qadir, J. and Masood, A. (2020). Role of inflammatory mediators (TNF-α, IL-6, CRP), biochemical and hematological parameters in type 2 diabetes mellitus patients of Kashmir, India. *Med J Islam Repub Iran.* 34: 5.

Beach, E.F. and Turner, J.J. (1958). An enzymatic method for glucose determination in body fluids. *Clin. Chem*. 4(6): 462-75.

Birhanu, B. T., Kim, J. Y., Hossain, M. A., Choi, J. W., Lee, S. P. and Park, S. C. (2018). An in vivo immunomodulatory and anti-inflammatory study of fermented DendropanaxmorbiferaLéveille leaf extract. *BMC Complement. Altern Med*. 18(1): 222.

Cheng, Z. (2021). Modified Cervical Dislocation, A Better Way in Laboratory Rat Euthanasia. *Mod. J. Med. Biol*. (1):1-3.

Donovan, J. and Brown, P. (2006). Blood Collection. Curr Protoc Immunol. DOI: 10.1002/0471142735.im0107s73

Flohe, L. and Gunzler, W.A. (1984). Assays of Glutathione peroxidase. *Meth. Enzymol*. 105(1):114-21.

Furman, B.L. (2015). Streptozotocin-Induced Diabetic Models in Mice and Rats. *Curr ProtocPharmacol*. 70(1): 1-21.

Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K.B., Ostolaza, H. and Martín, C (2020). Pathophysiology of Type 2 Diabetes Mellitus. *Int J Mol Sci.* 21(17): 6275.

Giri, B., Dey, S., Das, T., Sarkar, M., Banerjee, J. and Dash, S.K (2010). Chronic hyperglycaemia mediated physiological alteration and metabolic distortion leads to organ dysfunction, infection, cancer progression and other pathophysiological consequences: An update on glucose toxicity.Biomed. *Pharmacother*. 107: 306-328.

Guariguata, L., Whiting, D.R., Hambleton, I., Beagley, J., Linnenkamp, U. and Shaw, J. E. (2014). Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract*.103(2):137–149.

Hur, S. J., Lee, S. Y., Kim, Y. C., Choi, I. and Kim, G. B. (2014). Effect of fermentation on the antioxidant activity in plant-based foods. *Food Chem*. 160: 346-356.

International Diabetes Federation. (2011). Global burden of diabetes. Diabetic Atlas fifth edition, Brussels. Available at http://www.idf.org/diabetesatlas (Accessed 18th December 2022).

Kim, S., Song, Y. H., Lee, J. Y., Choi, S. R., Dhandapani, V., Jang, C. S. and Han, T. (2011). Identification of the BrRHP1 locus that confers resistance to downy mildew in Chinese cabbage (Brassica rapa ssp. pekinensis) and development of linked molecular markers. *Theor. Appl. Genet*. 123 (7): 1183-1192.

Korus, A., Bernaś, E. and Korus, J. (2021). Health-Promoting Constituents and Selected Quality Parameters of Different Types of Kimchi: Fermented Plant Products. *Int J Food Sci*. doi: 10.1155/2021/9925344

Kusznierewicz, B., Śmiechowska, A., Bartoszek, A., Namieśnik, J. (2008). The effect of heating and fermenting on antioxidant properties of white cabbage. *Food Chem*. 108(3): 853-861.

Lee, J., Noh, S., Lim, S. and Kim, B. (2021). Plant Extracts for Type 2 Diabetes: From Traditional Medicine to Modern Drug Discovery. *Antioxidants* (Basel). 10(1):81 doi: 10.3390/antiox10010081

Miller, D.M. and Aust, S.D. (1989). Studies of ascorbate-dependent, iron-catalyzed lipid peroxidation. *Arch. Biochem. Biophys*. 271 (1): 113-119.

Mockett, R.J., Bayne, A-C.V., Sohal, B.H. and Sohal, R.S. (2002). Biochemical assay of superoxide dismutase activity in Drosophila. *Meth. Enzymol*. 349: 287-292.

Muhammad, A., Mohammed, A., Kawu, M.U. and Tanko, Y. (2021). Effect of Fermented Cabbage (Brassica Olaeracae) Supplementation on Liver Enzymes Level in Streptozotocin-Nicotinamide Induced Type 2 Diabetic Male Wistar Rats. *JMBSR*. 2(1):55-63.

Nawaz, H., Shad, M. A. and Muzaffar, S. (2018). Phytochemical composition and antioxidant potential of Brassica. InTech. DOI: 10.5772/intechopen.76120

Nuraida, L. (2015). A review: Health-promoting lactic acid bacteria in traditional Indonesian fermented foods. Food Sci. Hum. *Wellness*. 4 (2):47–55.

Olokoba, A. B., Obateru, O. A. and Olokoba, L. B. (2012). Type 2 diabetes mellitus: a review of current trends. *Oman Med*. J. 27(4), 269–273.

Ozougwu, J. C., Obimba, K. C., Belonwu, C. D. and Unakalamba, C.B. (2013). The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. *J. Physiol. Pathophysiol*. 4:46–57.

Parasuraman, S., Raveendran, R. and Kesavan, R. (2010). Blood sample collection in small laboratory animals. *J PharmacolPharmacother.* 1(2): 87–93.

Raz, I. (2013). Guideline approach to therapy in patients with newly diagnosed type 2 diabetes. *Diabetes Care*. 36(2): 139–144.

Rheney, C.C. and Kirk, J.K. (2000). Performance of three blood glucose meters. Ann. Pharmacother. 34(3): 317-21.

Samec, D., Urlić, B. and Salopek-Sondi, B. (2019). Kale (Brassica oleracea var. acephala) as a superfood: Review of the scientific evidence behind the statement. *Crit Rev Food Sci Nutr*.59(15): 2411–2422.

Sivamaruthi, B. S., Kesika, P., Prasanth, M. I. and Chaiyasut, C. A. (2018). Mini Review on Antidiabetic Properties of Fermented Foods. *Nutrients.* 10(12): 1973.

Sun, Y. P., Chou, C. C. and Yu R., C. (2009). Antioxidant activity of lactic-fermented Chinese cabbage. *Food Chem.* 115(3): 912 917.

Susilawati, E., Levita, J., Susilawati, Y. and Sumiwi, S. A. (2023). Review of the Case Reports on Metformin, Sulfonylurea, and Thiazolidinedione Therapies in Type 2 Diabetes Mellitus Patients. *Med Sci*. 11(3): 50.

Takasu, N., Komiya I., Asawa, T., Nagasawa, Y. and Yamada, T. (1991). Streptozocin and alloxan-induced H2O2 generation and DNA fragmentation in pancreatic islets. *Diabetes*. 40: 1141-1145.

Tamang, J. P., and Kailasapathy, K. (2010). Fermented foods and beverages of the world. *Food Sci*. Available: https://doi.org/10.1201/EBK1420094954

Tangvarasittichai, S. ((2015). Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus. *World J Diabetes*. 6(3): 456–480.

Terefe, N. S. (2022). Recent developments in fermentation technology: toward the next revolution in food production. Available: https://www.researchgate.net/publication/356890271

Thompson, A. and Kanamarlapudi, V. (2013). Type 2 Diabetes mellitus and glucagon-like peptide-1 receptor signaling. *Clin. Exp. Pharmacol*. 1: 3. DOI: 10.4172/2161-1459.1000138

Wilburn, J. R. and Ryan, E. P. (2017). Fermented foods in health promotion and disease prevention: An overview A2 – Frias, Juana. In Fermented foods in health and disease prevention, eds. C. Martinez-Villaluenga and E. Penas, 3-19. Boston: Academic Press.

Yao, W., Goualié, B.G., Ouattara, H.G. and Niamké, S. (2017). Growth Capacity of Bacillus Potential Starter Strains Isolated from Cocoa Beans Fermentation Under Culture Stress Conditions. *Sci. Stud. Res*. 18(2): 201-211.

Zhao, J., Gong, L., Wu, L., She, S., Liao, Y., Zheng, H., Zhao, Z., Liu, G. and Yan, S. (2020). Immunomodulatory effects of fermented fig (Ficus carica L.) fruit extracts on cyclophosphamide-treated mice. *J. Funct. Foods.* 75: https://doi.org/10.1016/j.jff.2020.104219

Zhao, Y. S., Eweys, A. S., Zhang, J. Y., Zhu, Y., Bai, J., Darwesh, O. M. and Xiao, X. (2021). Fermentation affects the antioxidant activity of plant-based food material through the release and production of bioactive components. *Antioxidants.* 10(12): 320-332.

Zulkawi, N., Ng, K. H., Zamberi, R., Yeap, S. K., Satharasinghe, D., Jaganath, I. B., Jamaluddin, A. B., Tan, S. W., Ho, W. Y. and Alitheen, N. B. (2017). In vitro characterization and in vivo toxicity, antioxidant and immunomodulatory effect of fermented foods; Xeniji. *BMC Complement Altern. Med*. 17: 344. https://doi.org/10.1186/s12906-017-1845-6.