Trop J Nat Prod Res, September 2025; 9(9): 4201 - 4213 **ISSN 2616-0684 (Print)**
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Coenzyme Q10 Mitigates Hepatocellular Damage in Fructose-Fed Streptozotocin-Induced Diabetic Rats via Decrease in Oxidative-stress, Inflammation, and Modulation of Key Pathways

Akinwunmi O. Adeoye[1, 2]*, Jude Akinyelu[2], Daniela J. Porta[1], John A. Falode[2], María A. Rivoira[1], Néstor H. Garcia[1]

[1]*INICSA, Enrique Barros Pabellón Biología Celular, Ciudad Universitaria, X5000, Córdoba, Argentina*
[2]*Department of Biochemistry, Federal University Oye-Ekiti, Ekiti State, Nigeria*

ARTICLE INFO

Article history:
Received 27 May 2025
Revised 03 July 2025
Accepted 04 July 2025
Published online 01 October 2025

ABSTRACT

Coenzyme Q10 (CoQ10) has been examined in several diabetic and/or insulin-resistant models; however, a thorough explanation of its precise mechanisms is still lacking. This study investigated the protective effect of CoQ10 in fructose-fed streptozotocin-induced diabetic rats via redox regulation and modulation of some key pathways. Male Wistar rats were pre-fed with 20% (w/v) fructose water for one week and thereafter injected with streptozotocin intraperitoneal. The animals were treated with CoQ10 for two weeks after confirmation of diabetes. Thereafter, they were euthanized, blood and liver samples were collected for biochemical and histopathological studies. Glycemic indices, carbohydrate metabolizing enzymes (both *in vitro* and *in vivo*), liver biomarkers, oxidative stress and inflammatory markers, and redox status were investigated. The mRNA expression level of GSK-3*β*, GLUT-2, and some inflammatory genes was also assessed. The results revealed that CoQ10 significantly modulates the glycemic indices, carbohydrate metabolizing enzymes, and mitigates the detrimental effect of the STZ-induced diabetes in the liver by lowering the concentrations of the oxidative stress markers and improving the activity of the endogenous antioxidant enzymes and the concentration of the anti-inflammatory cytokine. Administration of CoQ10 downregulated GSK-3*β*, TNF-*α,* and NF-kB mRNA expression levels, and upregulated GLUT-2 and IL-10 mRNA expression levels. CoQ10 protected the hepatic tissue from hyperglycemia and oxidative stress resulting from STZ-induced diabetes and also modulated the expression of genes implicated in the insulin signaling pathway. CoQ10 protects by alleviating the impairment of insulin signaling in diabetic rats and could be an effective therapeutic agent for the management of diabetes.

Keywords: Coenzyme Q10, Hyperglycemia, GSK-3*β*, GLUT-2, Inflammatory genes.

Introduction

Diabetes is a long-term metabolic disease that can result in serious health issues. It is characterized by hyperglycemia brought on by insufficient insulin production or insulin resistance.[1] It is worrisome to note that 462 million adults, or 6.28% of the adult population, had type 2 diabetes mellitus (T2DM) in 2020.[2] Projections show that if current trends continue, this figure may rise to 592 million by 2035, highlighting the unchecked spread of the T2DM disease.[3] An estimated 537 million adults worldwide are anticipated to have diabetes, with type 2 diabetes accounting for 90% of cases, according to the International Diabetes Federation 2021 report. It is disturbing to note that by 2045, this figure is expected to increase to 643 million.[4] Glycogen synthase kinase-3*β* **(**GSK-3*β***)** plays a significant role in insulin signaling, beta-cell function, and inflammation in the pathogenesis of diabetes.[5] GSK-3*β* activity is normally inhibited by insulin through phosphorylation, enabling the activation of glycogen synthase and the subsequent storage of glycogen.

*Corresponding author. Email: akinwunmi.adeoye@fuoye.edu.ng
Tel: +2348035597883

Citation: Adeoye AO, Akinyelu J, Porta DJ, Falode JA, Rivoira MA, Garcia NH. Coenzyme Q10 Mitigates Hepatocellular Damage in Fructose-Fed Streptozotocin-Induced Diabetic Rats via Decrease in Oxidative-stress, Inflammation, and Modulation of Key Pathways. Trop J Nat Prod Res. 2025; 9(9): 4201 – 4213 https://doi.org/10.26538/tjnpr/v9i9.16

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

This inhibitory process, however, is disrupted in diabetes, which results in elevated blood glucose and decreased glycogen synthesis. Current research highlights the possibility of using GSK-3*β* as a therapeutic target for diabetes treatment.[6] It has been demonstrated by studies that GLUT-2 is down-regulated in the liver and pancreatic *β*-cells in type 2 diabetes, which reduces insulin production and glucose uptake. Moreover, there is evidence that hyperglycemia and lipotoxicity, which are prevalent in type 2 diabetes, can lower the expression of GLUT-2, hence intensifying the condition.[7] Inflammatory signaling pathways are mainly responsible for mediating the relationship between inflammation and diabetes. TNF-*α*, interleukin-1*β* (IL-1*β*), and interleukin-6 (IL-6) are among the cytokines involved in these pathways. Activation of nuclear factor-κB (NF-κB) may prevent insulin signaling by enhancing serine phosphorylation of insulin receptor substrate-1, which can result in insulin resistance. Due to their impact on hepatic glucose production and lipid metabolism, they significantly contribute to the exacerbation of metabolic dysfunctions. Numerous genetic and environmental variables are involved in the complex etiology of diabetes.[8] While there are many medications available to treat diabetes, there are restrictions on the effectiveness, safety, and tolerance of these medications.[9, 10] As such, the search for new medications that can specifically target cutting-edge pathways implicated in the etiology of diabetes is therefore necessary. Therefore, there is an urgent need for novel strategies utilizing natural therapies.

The body contains two forms of Co-enzyme Q10 (CoQ10), a fat-soluble, vitamin-like quinone that is also known as ubiquinone: the reduced form, which functions as an endogenous antioxidant, and the oxidized form, which serves as an electron transporter during mitochondrial respiration.[11, 12] Additionally, it controls the expression of genes encoding other molecules involved in oxidative stress and

inflammation, and effectively guards against the oxidation of proteins, nucleic acids, and lipid membranes.[13, 14]

It has been reported that some dietary components are deficient in diabetes conditions, including CoQ10.[15, 16] CoQ10 depletion may be brought on by increased oxidative stress and/or decreased mitochondrial substrate metabolism, [17] which may be connected to *β*-cell dysfunction and the onset of insulin resistance.[18] Prior research has examined CoQ10 in several diabetic and/or insulin resistance (IR) models; however, a thorough explanation of its precise mechanisms is still lacking. This study investigated the protective effect of CoQ10 in fructose-fed streptozotocin-induced diabetic rats via the modulation of some key biochemical pathways.

Materials and Methods

Chemicals

Streptozotocin, CoQ10, and Metformin were purchased from Sigma-Aldrich (St. Louis, USA). All other chemicals and reagents as well as the commercially available kits used in this study were of analytical grade.

Preparation of CoQ10

CoQ10 was dissolved in dimethyl sulfoxide and 0.9% normal saline. The mixture was then swiftly mixed and kept at -40°C in a dark bottle. Every week, a fresh solution of CoQ10 was made.

Animal care and use

Wistar male rats weighing 190g±10g were procured from the Animal House, Biochemistry Department of Ekiti State University, located in Ado-Ekiti, Nigeria. For a week, the animals were acclimatized. They were housed in conventional settings with a 12-hour light/dark cycle, water, and rat feed available to them at all times. Regarding the care and use of laboratory animals, all investigations were carried out in compliance with National Institutes of Health guidelines (NIH publication 85-23, 1985). Every procedures followed the Federal University Oye-Ekiti Ethical Review guidelines and was approved by the Faculty of Science Research Ethic Committees for animal experimentation with approval number: FUOYEFSC 201122-REC2024/025. The procedures are also in compliance with the Arrive guidelines for animal research.

Ethical statement

Every procedures followed the Federal University Oye-Ekiti Ethical Review guidelines and was approved by the Faculty of Science Research Ethic Committees for animal experimentation with approval number: FUOYEFSC 201122-REC2024/025. All procedures in this study conformed to the tenets of animal research as recommended by the Declaration of Helsinki and the National Institute of Health and also in compliance with the Arrive guidelines for animal research.

Experimental design

Thirty Wistar rats were divided randomly into five groups of 6 animals per group. The streptozotocin (STZ)-induced diabetic rats were pre-fed with 20% (w/v) fructose water for one week and injected with 40 mg/kg STZ intraperitoneally. The animal grouping was as follows:

Group 1: Normal control
Group 2: Streptozotocin (STZ) (diabetic control)
Group 3: STZ + 100 mg/kg b.w. CoQ10 (STZQ10)
Group 4: 100 mg/kg b.w. CoQ10 (Q10)
Group 5: STZ + 200 mg/kg b.w. metformin (STZMet)

A pilot study was initially conducted for the use of 100 mg/kg b.w. CoQ10 (Q10). The dosage for metformin (Met) was based on a previous investigation by Quaile et al.[19] At the end of the two weeks experimental period, five (5) animals were sacrificed from each group for biochemical analysis due to cost implications.

Induction of diabetes

Before the induction of diabetes, 20% (w/v) fructose water was given *ad libitum* for one week. Diabetes was induced in overnight fasted rats intraperitoneally (i.p) with a single dose of freshly prepared Streptozotocin (STZ) (40 mg/kg b.w) as previously reported by Wilson and Islam[20] in citrate buffer (0.1M, pH 4.5). A portable glucometer (Accu-Chek, Roche, Germany) was used to confirm diabetes following a tail prick by measuring stable hyperglycemia 72 hours after STZ injection. Rats with fasting blood glucose levels greater than 250 mg/dL were considered diabetic. Treatment with CoQ10 commenced immediately and lasted for two weeks.

Sample collection and preparation

At the end of the experiment, five rats from each group were sacrificed. The rats were fasted overnight, weighed, and then anesthetized and euthanized using 200 mg/kg sodium pentobarbital intraperitoneally. After administration, the animals became unconscious and non-responsive to injurious stimuli. Blood samples were drawn from the abdominal aorta and the liver was also excised. The removal of the vital organs after the animals became unconscious led to the death of the animals. The procedures employed in this study complies with the guidelines for the care and use of laboratory animals 8th edition and the AVMA guidelines on euthanasia of animals. The serum was promptly separated through centrifugation at 1000g for 5 minutes. The liver was, quickly rinsed with ice-cold 10 mM phosphate-buffered saline (pH 7.2) to eliminate any remaining blood, and then weighed. A portion of the liver was preserved in a 10% buffered formalin for histological analysis. The rest of the tissues were immediately homogenized in five volumes of ice-cold phosphate buffer (pH 6.2) and stored frozen for subsequent biochemical tests.

Biochemical assays

Serum insulin and hepatic lipase levels were quantitatively measured using a microplate immunoenzymometric assay kit, following the manufacturer's protocol, which was based on the principles outlined by Tietz.[21] Glycogen content in the liver homogenate was measured as glucosyl units after undergoing acid hydrolysis, as described by Passoneau and Lauderdale.[22] HbA1c was assayed using the diagnostic kit (cat no BXC0670A), Glut-2 (cat no E-EL-R0354), and Glut-4 (cat no E-EL-R0430), which were assayed using ELISA assay kits. The *in vitro* *α*-amylase and *α*-glucosidase inhibitory activities of CoQ10 and *in vivo* activities were assayed in the serum according to the method of Worthington[23] and Apostolidis, [24] respectively. The method of Doumas *et al*. [25] was used to estimate serum bilirubin. Alanine and aspartate transferase activities were evaluated according to the method described by Reitman and Frankel.[26] Alkaline phosphatase activity was assessed using the method outlined by Wright et al.[27] The concentration of protein carbonyls was measured following the procedure detailed by Levine et al.[28] Malondialdehyde (MDA) was assessed as described by Nelson.[29] The total protein concentration in the serum and the liver was assayed, using Biuret reagent as described by Gornall *et al.*[30] The method of Misra and Fridovich [31] was followed for the assessment of superoxide dismutase (SOD) activity. Catalase activity was assayed using the approach outlined by Beers and Sizer.[32] The concentration of reduced glutathione (GSH) was assessed according to the method of Ellman.[33] Inflammatory biomarkers like TNF-*α* (cat. no E-EL-R2856), IL-10 (cat no E-CL-R0016), and C-reactive protein (CRP) (cat no E-CL-R0021) were also assayed using the ELISA assay kits.

Histopathological examination

The liver samples were prepared and embedded in wax after fixing. The Hematoxylin-Eosin staining method was utilized. For the histopathological evaluation and photomicrography of the slides, an Olympus light microscope with a built-in camera was used.[34]

Gene expression study

Total RNA was extracted from rat liver using the Quick-RNA MiniPrep™ Kit from Zymo Research. DNA contamination was removed through treatment with DNase I (NEB, Cat: M0303S). The RNA was then quantified and reverse transcribed into cDNA using a cDNA synthesis kit based on ProtoScript II first-strand technology from New England BioLabs. Gene amplification was performed using PCR with OneTaqR2X Master Mix (NEB) and primers provided by Inqaba Biotec (Hatfield, South Africa), as detailed in Table 1. GAPDH was employed as a reference gene for normalizing expression levels, and band intensity was analyzed using ImageJ software.[35]

Table 1: Oligonucleotide primers for mRNA expression

S/N	Gene	Sequence of Primers
1	GSK-3β	Forward: 5'-GGGACAGTGGTGTGGATCAG-3'
		Reverse: 5'-GCCGAAAGACCTTCGTCCAA-3'
2	GLUT-2	Forward: 5'TAGTCAGATTGCTGGCCTCAGCTT-3'
		Reverse: 5'-TTGCCCTGACTTCCTCTTCCAACT -3'
3	NF-kB	Forward: 5'- CTGGCAGCTCTTCTCAAAGC -3'
		Reverse: 5'- CCAGGTCATAGAGAGGCTCAA -3'
4	TNF-α	Forward: 5'-ACCACGCTCTTCTGTCTACTG-3'
		Reverse: 5'-CTTGGTGGTTTGCTACGAC-3'
5	IL-10	Forward: 5'- GAGAGAAGCTGAAGACCCTCTG-3'
		Reverse: 5'- TCATTCATGGCCTTGTAGACAC -3'
6	GAPDH	Forward: 5'-CCTCTATGCCAACACAGTGC-3'
		Reverse: 5'-CATCGTACTCCTGCTTGCTG-3'

Statistical Analysis

Results were expressed as a mean ± SEM. The data were statistically analyzed using a descriptive one-way Analysis of variance (ANOVA) with a Bonferroni post-hoc test for comparisons between groups using GraphPad Prism 9.0. Differences were considered significant at $P<0.05$ for the post-hoc test.

Results and Discussion

The progressive deterioration of lipid, protein, and carbohydrate metabolism statuses is the hallmark of diabetes mellitus (DM). According to Daniel *et al.*[36] and Bharti *et al.* [37] it is one of the major health threats facing people worldwide and affects both the wealthy and the underprivileged. From the results of the *in vitro* carbohydrate metabolizing enzymes as presented in Fig. 1, CoQ10 considerably inhibited both the *α*-amylase and *α*-glucosidase in a concentration-dependent manner. It was observed that the reference standard, acarbose had higher inhibitory percentage when compared with CoQ10. Diabetes has an intricate pathogenesis that involves several genetic and environmental factors. Even though there are several anti-diabetic drugs available for the treatment of diabetes, their effectiveness, safety, and tolerability are among their many drawbacks, and they come with a wide range of adverse effects. Therefore, there is an increasing effort for the development of new drugs from natural compounds that can target novel pathways involved in the pathogenesis of diabetes. Glucose intolerance and persistently abnormally high blood glucose levels are caused by peripheral insulin resistance, impaired *β*-cell function, and enhanced hepatic glucose production. These factors are primarily responsible for the hyperglycemia status in type 2 diabetes.

The primary basis for the application of CoQ10 as a dietary supplement and its mechanism of action in cardiovascular disease is its involvement in the bioenergetics of the mitochondria.[38, 39] CoQ10 plays a crucial role in lipid-soluble antioxidant defense against potentially harmful effects of toxic free radical species produced during regular cellular metabolism (oxidative stress) [40] and also has an anti-inflammatory impact.[41]

The disruption of cellular glucose homeostasis caused by the induction of diabetes leads to a notable decrease in insulin production. A significant decline in the weight of diabetic rats was observed when compared with the control and the treatment groups. The result of the body weight, organ weight, and organ weight to body weight ratio in STZ-induced diabetic rats and treatment group is presented in Table 2. The gluconeogenic conversion of protein and fat, which are non-carbohydrates, into glucose may be the cause of the weight loss seen in the diabetic group.[42] An observed increase (hypertrophy) in the weight of the liver could be attributed to triglyceride buildup. This may be due to hypo-insulinemia's enhanced fatty acid infusion into the liver as well as the liver's poor ability to excrete lipoproteins secretion.

The effect of CoQ10 on the glucose level is presented in Fig. 2. Administration of STZ significantly ($P<0.05$) increased the glucose level of rats after 72 hours of induction, which increased throughout the experimental period as seen in the diabetic untreated group (STZ). However, treatment with CoQ10 and the reference drug, Metformin, significantly ($P<0.05$) lowered the glucose level throughout the experimental period. The hypoglycemic effect of CoQ10 is attributed to its strong antioxidant property. The metabolism of glucose generally involves several energy-dependent activities; hence, glycemic regulation must be impacted if the body's energy supply system is hampered due to mitochondrial dysfunction or CoQ10 shortage.[43]

Fig. 3 shows the protein concentration in the serum and liver of rats following induction of diabetes with STZ and treatment with CoQ10. It was observed that the protein concentration of the STZ group (diabetic untreated) decreased significantly ($P<0.05$), both in the serum and the liver. The protein concentration of the groups treated with CoQ10 and metformin increased significantly when compared with the STZ group. The group administered CoQ10 only also had increased protein content, which compared considerably with the control.

Table 2: Effect of CoQ10 on body weight, organ weight, and organ to body ratio of fructose-fed streptozotocin-induced diabetic rat.

	Body weight (g)		Liver weight (g)	Organ/Body ratio (%)
	Initial	Final		
Control	252.50 ± 2.23^{a}	273.20 ± 6.33^{a}	5.40 ± 0.10^{a}	1.98^{a}
STZ (Diabetic control)	248.30 ± 4.35^{b}	215.50 ± 5.45^{b}	8.65 ± 0.25^{b}	4.01^{b}
STZ + 100mg/kg CoQ10	255.20 ± 5.20^{ac}	265.40 ± 4.26^{c}	6.70 ± 0.10^{c}	2.52^{c}
100mg/kg CoQ10	250.00 ± 3.30^{ab}	270.60 ± 3.27^{a}	5.70 ± 0.10^{a}	2.10^{a}
200mg/kg Metformin	249.50 ± 5.25^{b}	268.30 ± 5.35^{c}	6.60 ± 0.10^{c}	2.46^{c}

All values are expressed as mean ± SEM; n= 5 per group. Values with different alphabets differ significantly ($P<0.05$).

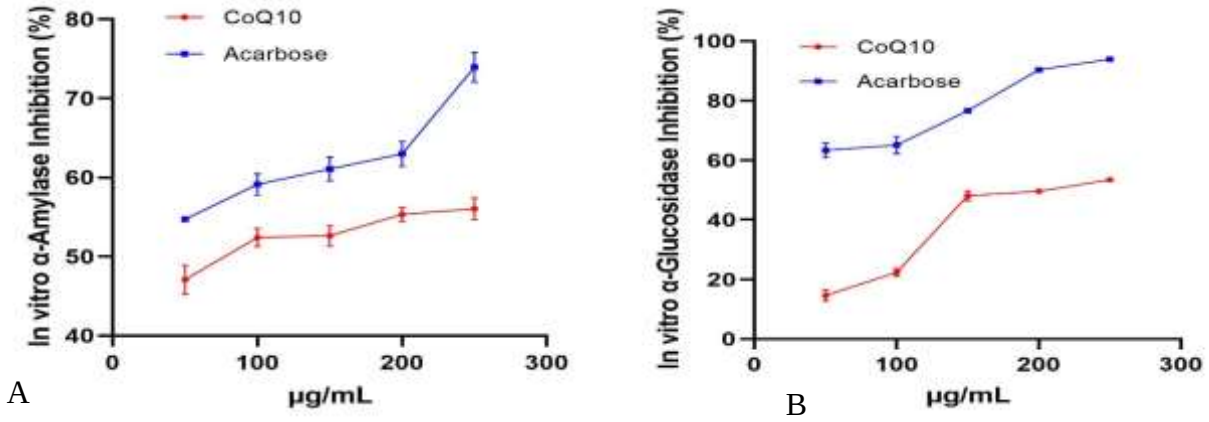


Figure 1: *In vitro* α-amylase and α-glucosidase inhibitory activities of CoQ10. All values are expressed as mean ± SEM; n= 3. A: α-amylase; B: α-glucosidase. CoQ10: Coenzyme Q10; Acarbose: Reference standard

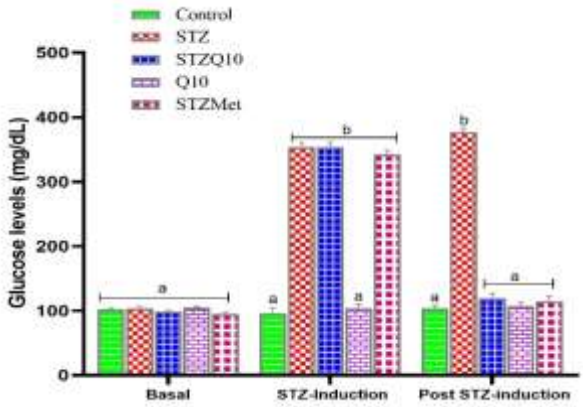


Figure 2: Effect of CoQ10 on the glucose level of fructose-fed streptozotocin-induced diabetic rats. All values are expressed as mean ± SEM; n= 5 per group. STZ: Streptozotocin (diabetic untreated); STZQ10: Streptozotocin with 100 mg/kg body weight CoQ10; Q10: CoQ10 alone; STZMet: Streptozotocin with 200 mg/kg body weight Metformin. Values with different alphabets differ significantly (P<0.05).

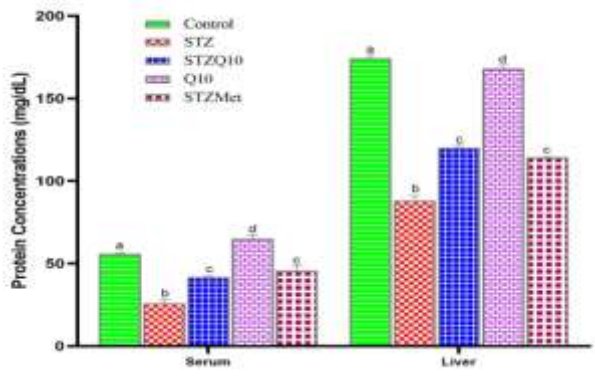


Figure 3: Effect of CoQ10 on Serum and liver protein concentrations in fructose-fed streptozotocin-induced diabetic rats. All values are expressed as mean ± SEM; n= 5 per group. STZ: Streptozotocin (diabetic untreated); STZQ10: Streptozotocin with 100 mg/kg body weight CoQ10; Q10: CoQ10 alone; STZMet: Streptozotocin with 200 mg/kg body weight Metformin. Values with different alphabets differ significantly (P<0.05).

It was observed from the results that the insulin concentration and the glycogen level reduced significantly in the diabetic group. However, treatment with CoQ10 improves both the insulin concentration and the glycogen level (Fig. 4A and C). Vascular wall proteins become glycated as blood glucose levels rise, which in turn causes dysfunction in endothelial cells. Moreover, it has been reported that advanced glycation end products may foster inflammation and oxidative stress.[44] The results showed a significant increase in the percentage of HbA1c in the diabetic group when compared to the control and the treatment groups (Fig. 4B). The hepatic lipase activity equally increased significantly in the diabetic group when compared to the control and the groups administered with CoQ10 and Met (Fig. 4D). The findings from this study align with the work of Samimi *et al.* [45] who reported a significant improvement in serum insulin and glucose homeostasis markers in patients diagnosed with metabolic syndrome or type 2 diabetes after taking 100 mg of CoQ10 daily.

CoQ10 considerably inhibited the carbohydrate metabolizing enzymes, *α*-amylase and *α*-glucosidase, in a concentration-dependent manner when compared to the reference standard, acarbose, *in vitro*. Moreover, the activities of these enzymes were significantly lowered by administration of CoQ10 *in vivo* when compared to the diabetic group, which was higher than the treatment group (Fig. 5AandB). As presented in Fig. 6, the direct and total bilirubin concentration were significantly higher in the diabetic untreated group when compared to the control and the treatment groups. Serum metabolite and enzyme levels may be significantly impacted by changes in tissue composition. Important information regarding the type and degree of pathological damage to any tissue can be obtained through measuring these enzymes. From the result of this study, a significant increase in the serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) activities (Fig. 7A-C), as well as the total bilirubin in the diabetic group, was observed. The elevated activity of these enzymes and the serum level of total bilirubin indicate a major disruption in the hepatocyte membrane, which results in the leakage of these enzymes from the liver cells. This observation is also corroborated by the histopathological results in the liver of diabetic untreated rats as presented in Plate 1. Increased activity of these enzymes has also been linked to an increased risk of type-2 diabetes in previous research, indicating a potential role for the liver in the development of the condition.[46] Significant reduction of AST, ALT, ALP, and total bilirubin levels in CoQ10-treated diabetic rats suggests the potential protective effect of CoQ10 against diabetes-mediated hepatic damage.

Chronic hyperglycemia causes elevated reactive oxygen species generation, and oxidative stress leads to diabetes.

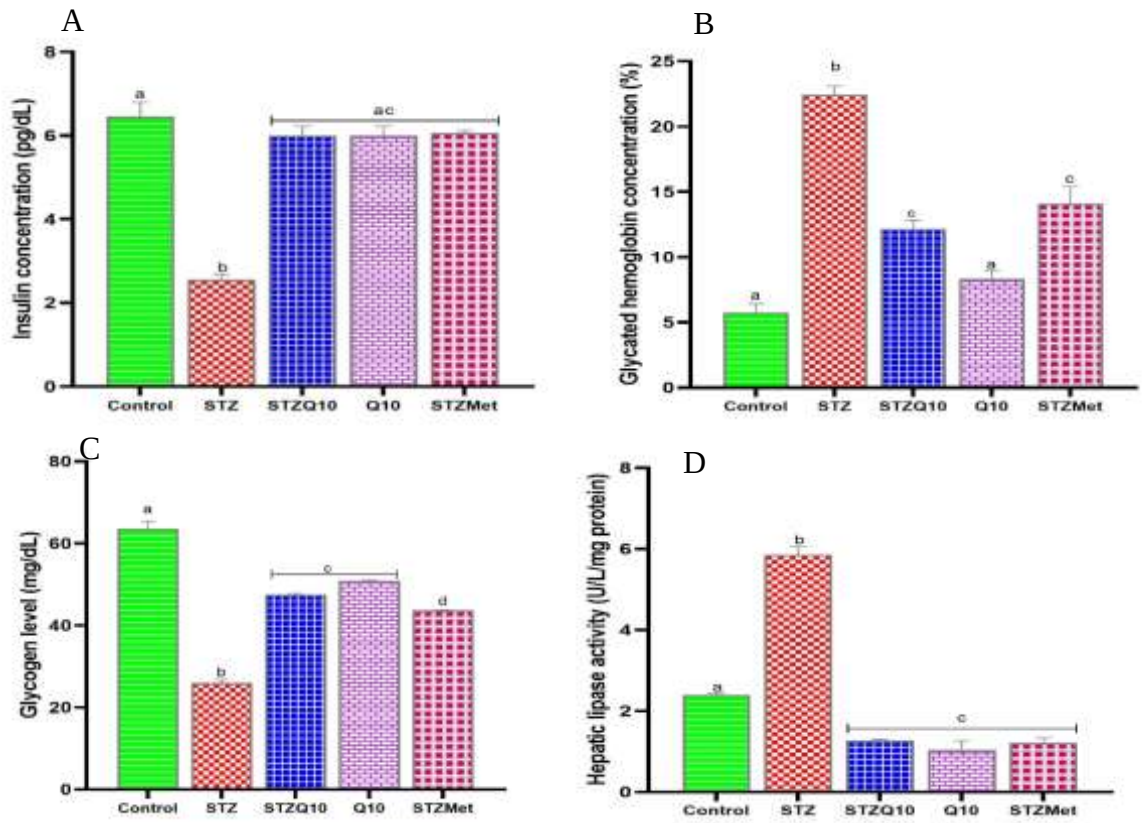


Figure 4: Effect of CoQ10 on glycemic indices and hepatic lipase activity in fructose-fed streptozotocin-induced diabetic rats. All values are expressed as mean ± SEM; n= 5 per group. A: Insulin concentration; B: Glycated hemoglobin; C: Glycogen level; D: Hepatic lipase activity. STZ: Streptozotocin (diabetic untreated); STZQ10: Streptozotocin with 100 mg/kg body weight CoQ10; Q10: CoQ10 alone; STZMet: Streptozotocin with 200 mg/kg body weight Metformin. Values with different alphabets differ significantly (P<0.05).

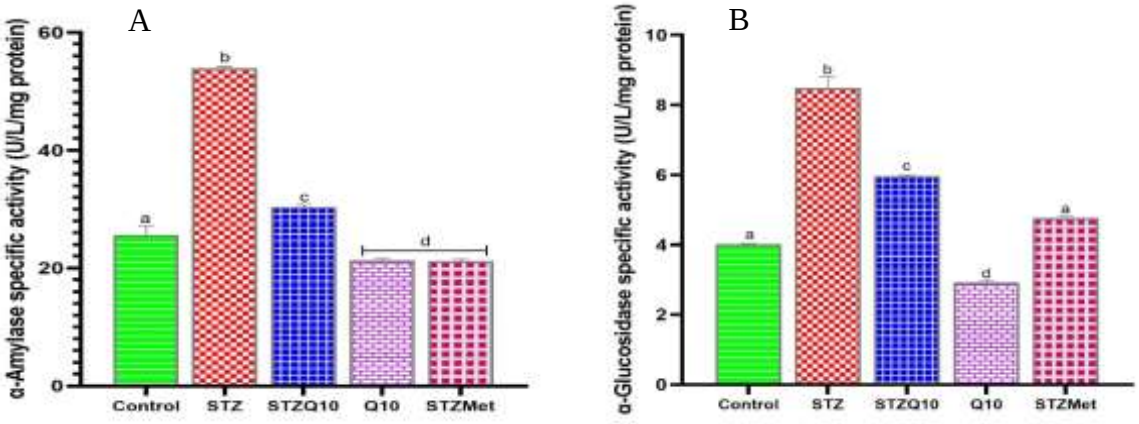


Figure 5: Effect of CoQ10 on *in vivo* α-amylase and α-glucosidase inhibitory activities in fructose-fed streptozotocin-induced diabetic rats. All values are expressed as mean ± SEM; n= 5 per group. A: α-amylase; B: α-glucosidase. STZ: Streptozotocin (diabetic untreated); STZQ10: Streptozotocin with 100 mg/kg body weight CoQ10; Q10: CoQ10 alone; STZMet: Streptozotocin with 200 mg/kg body weight Metformin. Values with different alphabets differ significantly (P<0.05).

From the result of this study, malondialdehyde (MDA) and protein carbonyl (PC) concentrations in the diabetic group increased significantly when compared to the treatment groups. The increase in protein carbonyl and MDA in the diabetic rats could be attributed to the generation of reactive oxygen species (ROS) as a result of hyperglycemia. Administration of CoQ10 significantly reduced the MDA and the protein carbonyl concentrations (Fig. 8AandB).

Observations from this study are in line with the previous report, which suggested that supplementation with CoQ10 both *in vitro* and *in vivo* could ameliorate lipid peroxidation.[47] The result is substantiated by the histopathological examinations, which revealed that there were dilated blood vessels with severe congestion and necrotic hepatocytes in the liver of the diabetic untreated rats. However, treatment with CoQ10 showed moderate congestion of the hepatocytes (Plate 1).

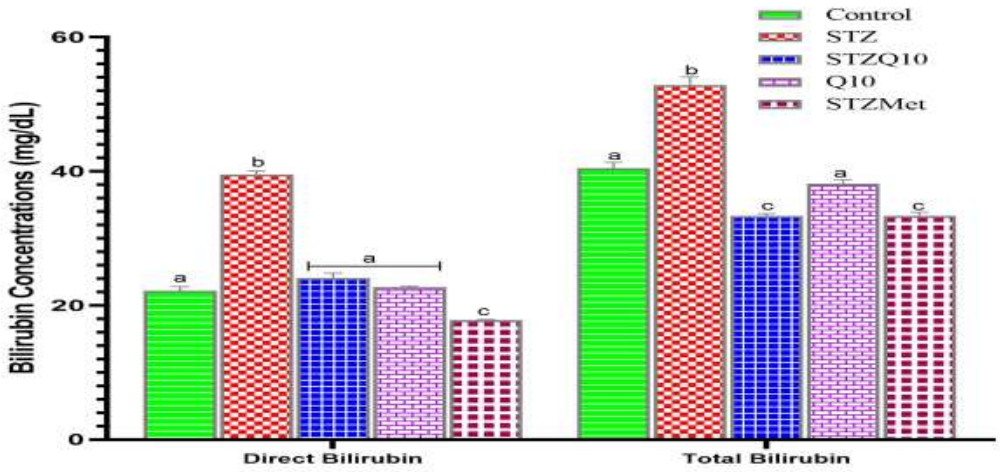


Figure 6: Effect of CoQ10 on bilirubin concentrations in fructose-fed streptozotocin-induced diabetic rat. All values are expressed as mean ± SEM; n= 5 per group. STZ: Streptozotocin (diabetic untreated); STZQ10: Streptozotocin with 100 mg/kg body weight CoQ10; Q10: CoQ10 alone; STZMet: Streptozotocin with 200 mg/kg body weight Metformin. Values with different alphabet differ significantly (P<0.05).

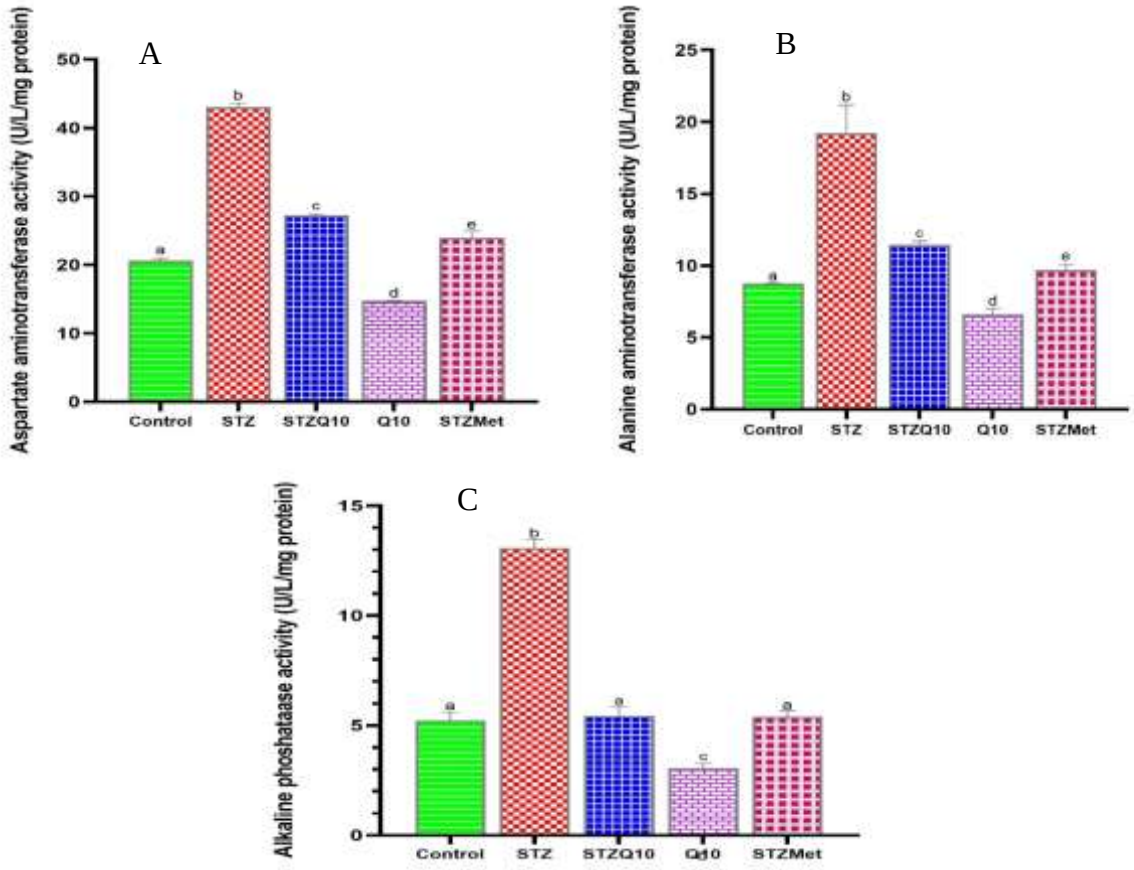


Figure 7: Effect of CoQ10 on liver enzyme biomarkers in fructose-fed streptozotocin-induced diabetic rat. All values are expressed as mean ± SEM; n= 5 per group. A: Aspartate aminotransferase activity; B: Alanine aminotransferase activity; C: Alkaline phosphatase activity; STZ: Streptozotocin (diabetic untreated); STZQ10: Streptozotocin with 100 mg/kg body weight CoQ10; Q10: CoQ10 alone; STZMet: Streptozotocin with 200 mg/kg body weight Metformin. Values with different alphabet differ significantly (P<0.05).

When cells are under oxidative stress, their antioxidant defense mechanism is suppressed by excessive oxidation products, which results in an overproduction of MDA and a decrease in antioxidant levels.[48] A significant reduction in the endogenous antioxidant enzymes, reduced glutathione (GSH), superoxide dismutase (SOD), and catalase activities was observed in the diabetic untreated group. However, treatment with CoQ10 significantly improves the concentration of GSH and activities of the SOD and catalase (Fig. 9A-C). The result is consistent with a meta-analysis study by Jorat *et al.* [49] which found that CoQ10 supplementation markedly raised antioxidant enzyme levels and lowered MDA levels in individuals with diabetes.

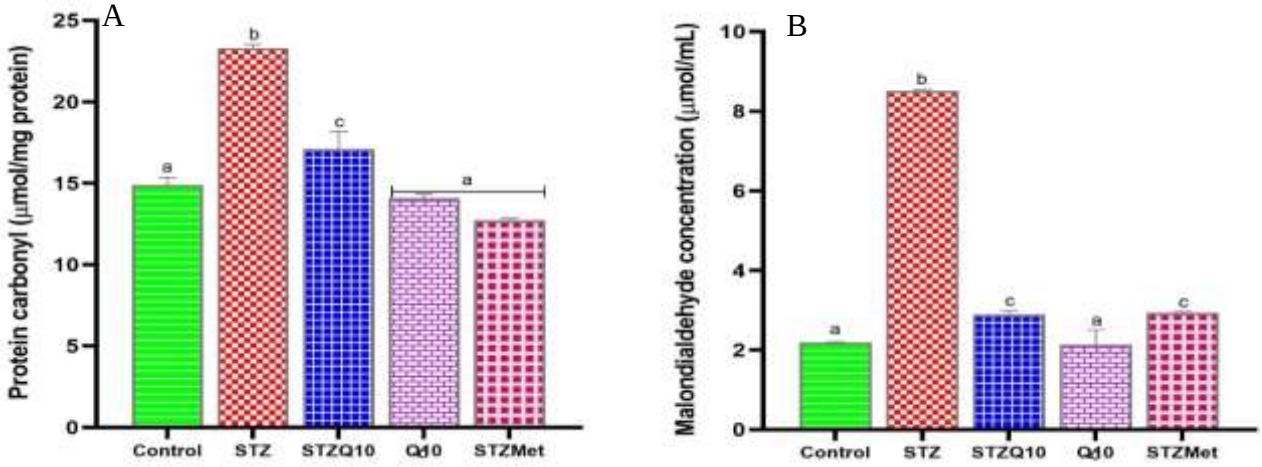


Figure 8: Effect of CoQ10 on oxidative stress markers in fructose-fed streptozotocin-induced diabetic rat. All values are expressed as mean ± SEM; n= 5 per group. A: protein carbonyl; B: Malondialdehyde concentration; STZ: Streptozotocin (diabetic untreated); STZQ10: Streptozotocin with 100 mg/kg body weight CoQ10; Q10: CoQ10 alone; STZMet: Streptozotocin with 200 mg/kg body weight Metformin. Values with different alphabet differ significantly (P<0.05).

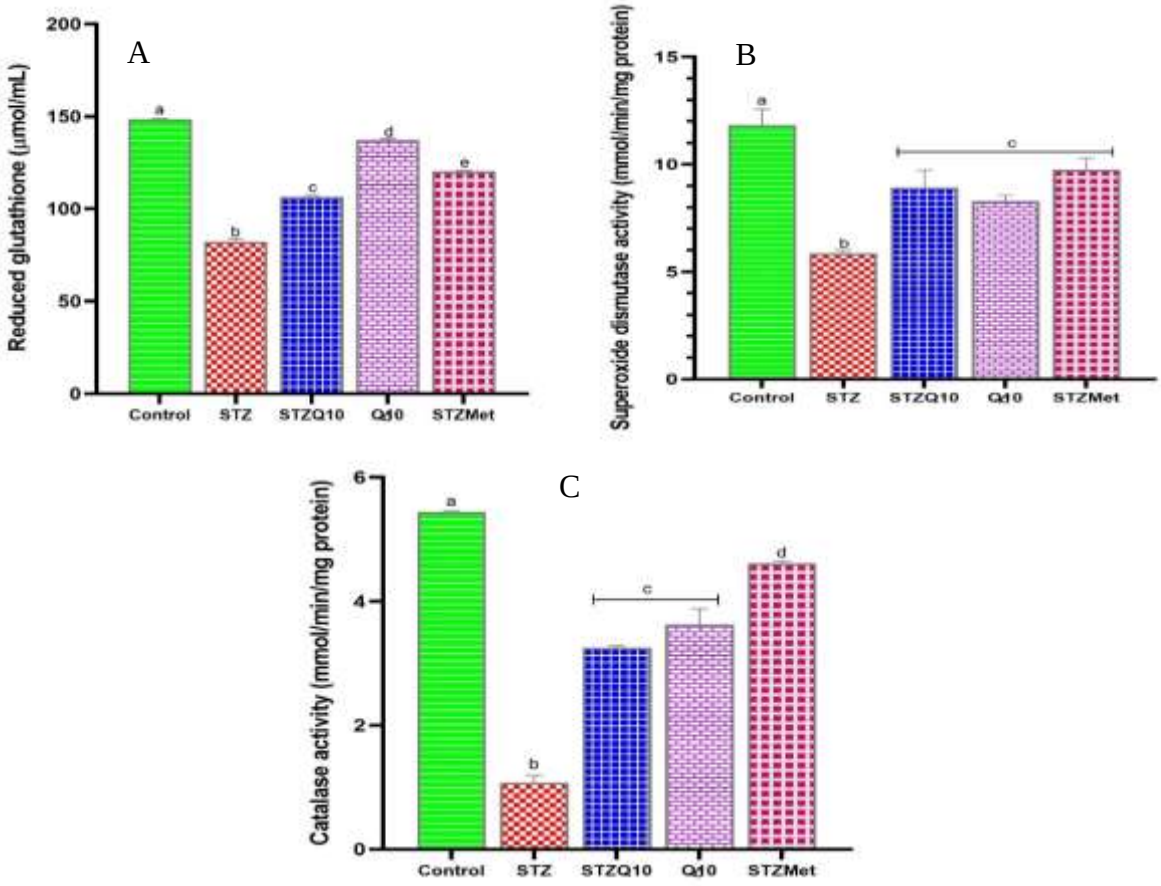


Figure 9: Effect of CoQ10 on endogenous antioxidant enzyme status in fructose-fed streptozotocin-induced diabetic rat. All values are expressed as mean ± SEM; n= 5 per group. A: Reduced glutathione level; B: Superoxide dismutase activity; C: Catalase activity; STZ: Streptozotocin (diabetic untreated); STZQ10: Streptozotocin with 100 mg/kg body weight CoQ10; Q10: CoQ10 alone; STZMet: Streptozotocin with 200 mg/kg body weight Metformin. Values with different alphabet differ significantly (P<0.05).

Activation of the nuclear factor-κB (NF-κB) pathways, interleukin-1*β* (IL-1*β*), and recruitment and activation of immune cells are thought to be the mechanisms responsible for the inflammatory state in diabetes. The inflammatory biomarkers following induction of STZ and treatment with CoQ10 is presented in Fig. 10. From the results of this study, there was a significant increase in the concentrations of the pro-inflammatory markers, tumor necrosis factor-*α* (TNF-*α)*, IL-1*β*, IL-6, as well as C-reactive protein in the diabetic group when compared to the control and the treatment groups. The observed increase in the concentration of these pro-inflammatory markers in the diabetic untreated group could be attributed to the fact that inflammation has been recognized as a key contributor to the development and progression of diabetes. Conversely, the concentration of the anti-inflammatory marker, IL-10, increased significantly in the CoQ10-treated group and the control when compared to the diabetic group. Observations from this study are in agreement with the work of Dludla *et al*. [50] who reported that supplementation of 100 mg/day CoQ10 resulted in decreased systemic levels of oxidative stress and inflammatory markers.

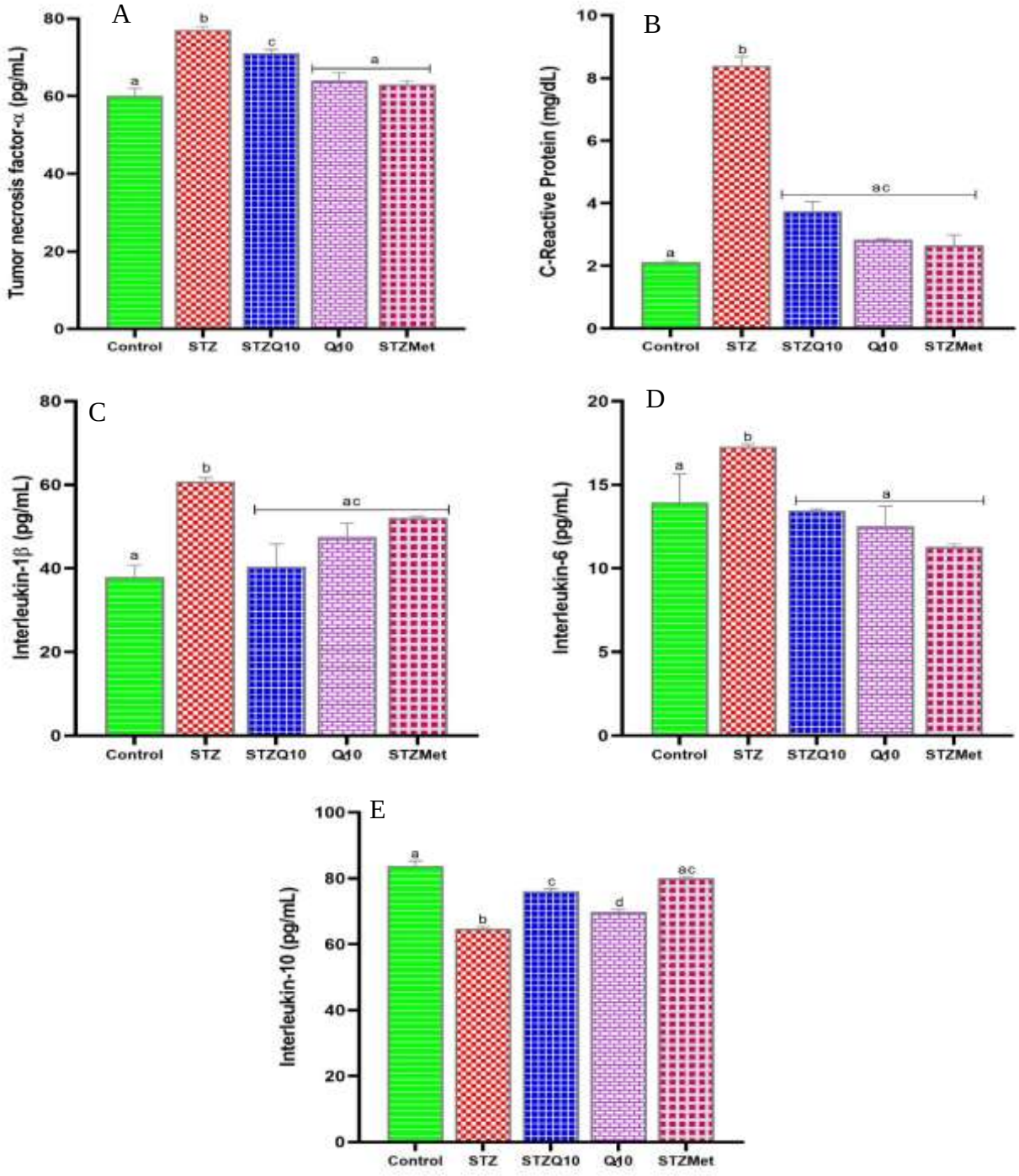
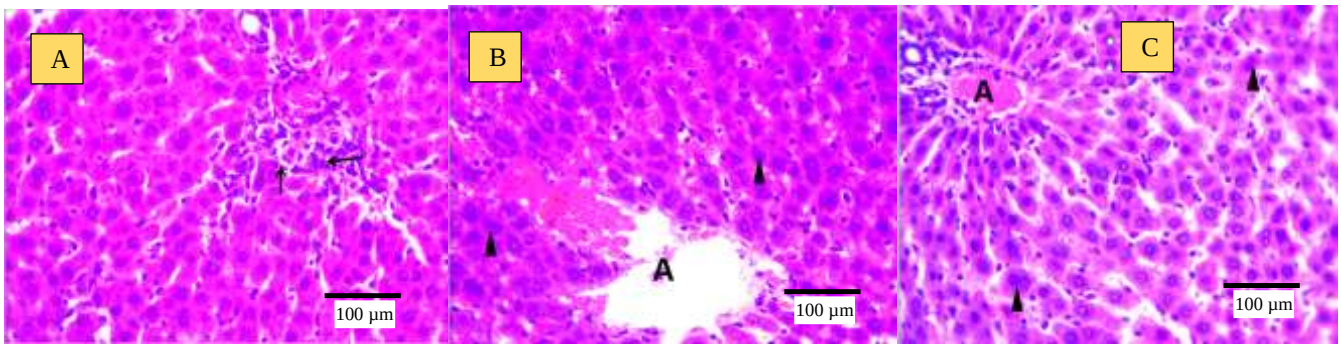
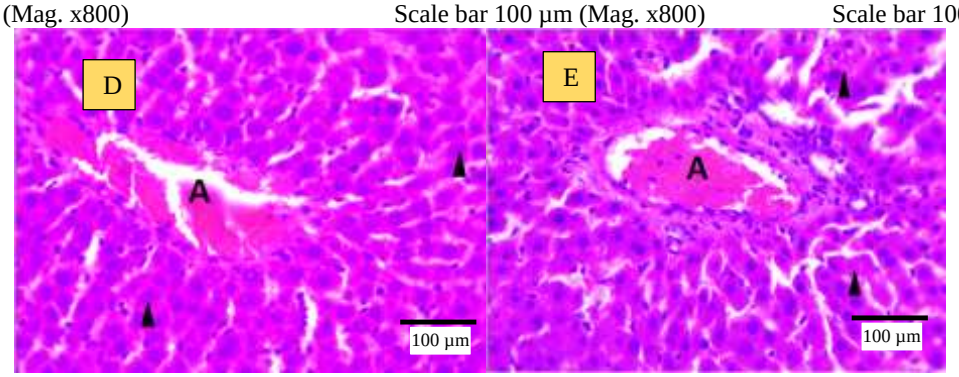


Figure 10: Effect of CoQ10 on inflammatory biomarkers in fructose-fed streptozotocin-induced diabetic rats. All values are expressed as mean ± SEM; n= 5 per group. A: Tumor necrosis factor-α; B: C-reactive protein; C: Interleukin-1β; D: Interleukin-6; E: Interleukin-10; STZ: Streptozotocin (diabetic untreated); STZQ10: Streptozotocin with 100 mg/kg body weight CoQ10; Q10: CoQ10 alone; STZMet: Streptozotocin with 200 mg/kg body weight Metformin. Values with different alphabets differ significantly (*P*<0.05).

As crucial players in insulin signaling and glucose metabolism, glucose transporters-2 (GLUT-2) and -4 (GLUT-4) are critical targets in diabetes. The activity of glucose transporter-2 was found to be significantly (P<0.05) higher in the diabetic untreated rats when compared to the control and the group treated with CoQ10 (Fig. 11A). In contrary to this, glucose transporter-4 activity increased significantly in the control and the group administered with CoQ10 and metformin (Fig. 11B). The observed increase in GLUT-2 activity could be ascribed to the inflammatory process contributing to insulin resistance. However, there was a significant reduction in the activity of the GLUT-4 in the diabetic group when compared to the control. Treatment with CoQ10 significantly increased the activity of GLUT-4. According to Garcia-Ropero *et al.* [51] *β*-cell dysfunction and insulin resistance are linked to lower GLUT-4 expression and altered GLUT-2 function.



Scale bar 100 µm (Mag. x800) Scale bar 100 µm (Mag. x800) Scale bar 100 µm (Mag. x800)



Scale bar 100 µm (Mag. x800) Scale bar 100 µm (Mag. x800)

Plate 1: Photomicrograph of liver of rats with no induction (control) showing mild swelling (arrow) with no visible lesions (A); Photomicrograph of liver of rats induced STZ (diabetic untreated) showing dilated blood vessel with severe congestion (arrowhead) and necrotic hepatocytes (denoted with A) (B); Photomicrograph of liver of rats induced with STZ and treated with 100mg/kg body weight CoQ10 showing moderate congestion (denoted with A and arrowhead) (C); Photomicrograph of liver of rats administered with only 100mg/kg body weight CoQ10 showing moderate congestion (denoted with A and arrowhead) (D); Photomicrograph of liver of rats induced with STZ and treated with 200mg/kg body weight metformin showing moderate congestion (denoted with A and arrowhead) (E). All stained with HandE (Mag. x800).

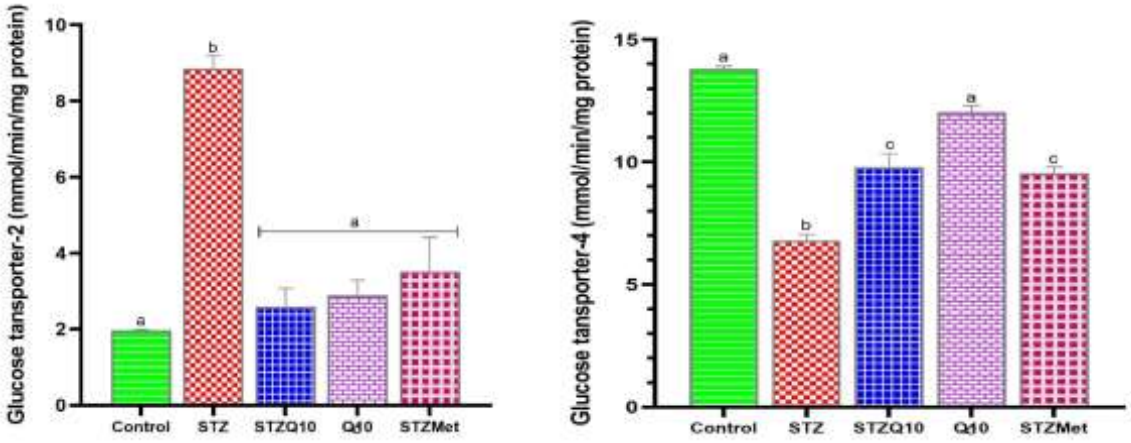


Figure 11: Effect of CoQ10 on glucose transporter activities in fructose-fed streptozotocin-induced diabetic rat. All values are expressed as mean ± SEM; n= 5 per group. A: Glucose transporter-2; B: Glucose transporter-4. STZ: Streptozotocin (diabetic untreated); STZQ10: Streptozotocin with 100 mg/kg body weight CoQ10; Q10: CoQ10 alone; STZMet: Streptozotocin with 200 mg/kg body weight Metformin. Values with different alphabet differ significantly (P<0.05).

One promising treatment approach for lowering insulin resistance and enhancing glycemic control in diabetic patients is to target novel pathways implicated in the pathophysiology of the disease. GSK-3*β* plays a critical role in insulin signaling by regulating glycogen synthesis. Inhibition or down-regulation of GSK-3*β* leads to activation of glycogen synthase and subsequent glycogen storage. In a diabetic condition, this inhibitory mechanism is disrupted, leading to decreased glycogen synthesis and high blood glucose. From the results of this study, the mRNA expression level of the GSK-3*β* gene was up-regulated in the diabetic group when compared to the control. Significant increase in the mRNA expression level of the GSK-3*β* gene in the diabetic group could be ascribed to the reduced phosphorylation of the enzyme. Treatment with CoQ10 significantly downregulates the mRNA expression level of the GSK-3*β* gene (Fig. 12D). Previous studies have reported hyperactivity of GSK-*3β* in diabetes, contributing to insulin resistance by disrupting the insulin signaling pathway. [52, 53]

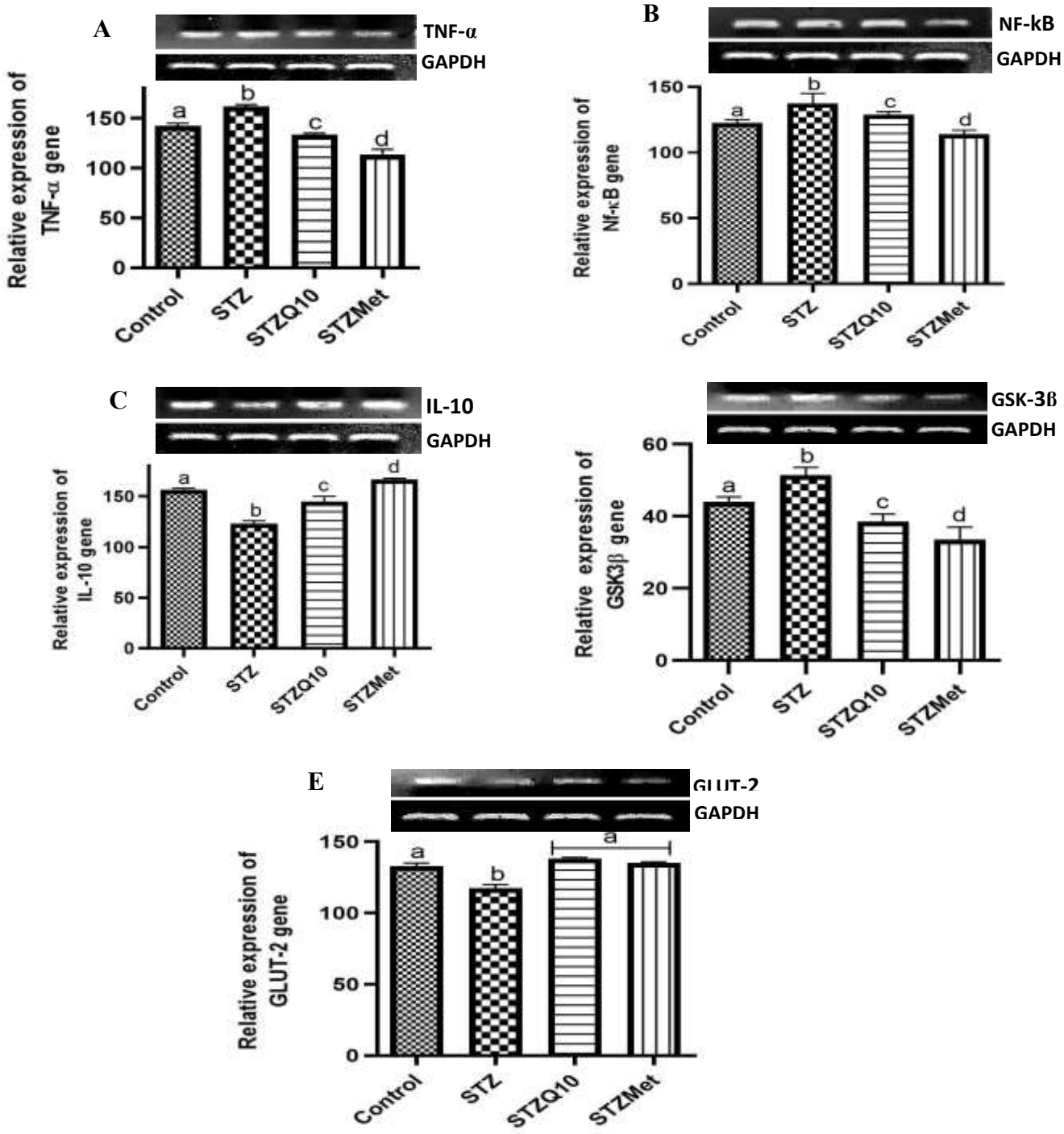


Figure 12: Effect of CoQ10 on mRNA expression level of GSK-3β, GLUT-2, and inflammatory genes in fructose-fed streptozotocin-induced diabetic rats. All values are expressed as mean ± SEM; n = 5 per group. A: Tumor necrosis factor-α (TNF-α); B: Nuclear factor kappa B (NF-kB); C: Interleukin-10 (IL-10); D: Glycogen synthase kinase-3β (GSK-3β); E: Glucose transporter-2 (GLUT-2). STZ: Streptozotocin (diabetic untreated); STZQ10: Streptozotocin with 100 mg/kg body weight CoQ10; Q10: CoQ10 alone; STZMet: Streptozotocin with 200 mg/kg body weight Metformin. Values with different alphabets differ significantly (P<0.05).

A link between overexpression of GSK-3β and elevated pro-inflammatory cytokine production in adipose tissue has been reported, which is associated with insulin resistance and metabolic syndrome in individuals with diabetes.[5] Inflammatory genes play a major role in the pathophysiology of diabetes, especially type 2 diabetes. Studies have demonstrated an increase in inflammatory cytokines in individuals with diabetes and obesity, which may lead to β-cell malfunction and insulin resistance. From the result, there was a significant increase in the mRNA expression level of TNF-α and NF-kB gene in the diabetic group when compared to the control. The observed increase in the expression of these genes in the diabetic group could be attributed to the activation of inflammatory signaling pathways. Administration of CoQ10 significantly downregulates the mRNA expression of TNF-α and NF-kB genes (Fig. 12AandB). Studies have demonstrated that the anti-inflammatory properties of CoQ10 lead to modulation of the associated inflammatory pathways by controlling the expression of CoQ10-sensitive and stress-associated genes.[54] However, the mRNA expression level of the IL-10 gene was significantly lowered in the diabetic group when compared to the control. Treatment with CoQ10 upregulates the mRNA level of the IL-10 gene (Fig. 12C).

It has been demonstrated that GLUT-2 expression and function modulation are a useful strategy for enhancing glucose regulation. Studies have shown that GLUT-2 is downregulated in the liver and pancreatic β-cells in diabetics, which reduces insulin production and glucose absorption.[55] From the result, the mRNA expression level of the GLUT-2 gene was observed to be lowered in the diabetic group when compared to the control and the treatment groups. Treatment with CoQ10 significantly upregulates the mRNA expression level of the GLUT-2 gene (Fig. 12E). The observation from this result aligns with the work of Garcia-Jacobo *et al*. [55] who demonstrated that in a mouse model of type-2 diabetes, upregulating GLUT-2 expression in pancreatic β-cells enhanced glucose-stimulated insulin production and decreased hyperglycemia.

Conclusion

Administration of CoQ10 protects the hepatic tissue from hyperglycemia and oxidative stress resulting from STZ-induced diabetes. CoQ10 also improved the glycemic indices, increased the antioxidant activities in the liver, and decreased the pro-inflammatory cytokines. Moreover, CoQ10 enhanced the anti-inflammatory cytokines and also modulated the expression of some genes implicated in the insulin signaling pathway. CoQ10 protects by alleviating the impairment of insulin signaling in diabetic rats and could be an effective therapeutic agent for the management of diabetes.

Conflict of interest

The author`s declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

Acknowledgements

The authors wish to acknowledge the Institute of Health Science Research (INICSA), National University of Cordoba, Argentina, for the collaboration.

Funding

This study was supported by Consejo Nacional de Investigaciones Cientificas y Tecnicas, CONICET.

References

1. Dowarah J, Singh VP. Anti-diabetic drugs: recent approaches and advancements. Bioorg Med Chem. 2020; 28:1152-1163. Doi:10.1016/j.bmc.2019.115263
2. Khan MA, Hashim MJ, King JK, Govender RD, Mustafa H, Al-Kaabi J. Epidemiology of type-2 diabetes: Global burden of Disease and forecasted trends. J Epidemiol Glob Health. 2020; 10(1):107-111. Doi: 10.2991/jegh.k.191028.001
3. Sun, H., Saeedi, P., Karuranga, S., Pinkepank, M., Ogurtsova, K., Duncan, BB. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022; 183: 109-119. Doi: 10.1016/j.diabres.2021.109119
4. International Diabetes Federation. IDF diabetes atlas. (2022). Accessed 23 February 2022. https://diabetesatlas.org/2022-reports.
5. Zhu Y, Wang H, Guo Y, Cao J, and Li H. Advances in the Therapeutic Potential of Inhibitors Targeting Glycogen Synthase Kinase 3 in Inflammatory Diseases. Mini Rev Med Chem. 2023; *23*(19):1893-1904. Doi: 10.2174/1389557523666230412083123
6. Wang L, Li J, and Di LJ. Glycogen synthesis and beyond: a comprehensive review of GSK3 as a key regulator of metabolic pathways and a therapeutic target for treating metabolic diseases. Med Res Rev. 2022; *42*(2):946-982. Doi: 10.1002/med.21867
7. Zhang C, Gu L, Xie H, Liu Y, Huang P, Zhang J, Luo D, and Zhang J. Glucose transport, transporters, and metabolism in diabetic retinopathy. Biochim Biophys Acta Mol Basis Dis. 2023; 1870(3):166995. Doi: 10.1016/j.bbadis.2023.166995
8. Nakhleh A, Shehadeh N. Hypoglycemia in diabetes: An update on pathophysiology, treatment, and prevention. World J. diabetes. 2021; 12(12):2036-2049. Doi: 10.4239/wjd.v12.i12.2036
9. Heurtebize MA, Faillie JL. Drug-induced hyperglycemia and diabetes. Therapie. 2024; 79(2):221-238. Doi: 10.1016/j.therap.2023.09.010
10. Gilbert MP, and Pratley RE. GLP-1 analogs and DPP-4 inhibitors in type 2 diabetes therapy: review of head-to-head clinical trials. Front endocrinol. 2020; 11:178. Doi: 10.3389/fendo.2020.00178
11. Kirkman DL, Stock JM, Shenouda N, Bohmke NJ, Kim Y, Kidd J, Townsend RR, Edwards DG. Effects of a mitochondrial-targeted ubiquinol on vascular function and exercise capacity in chronic kidney disease: a randomized controlled pilot study. Am. J. Physiol Renal Physiol. 2023; 325(4):F448-456. Doi: 10.1152/ajprenal.00067.2023
12. Adeoye AO, Olanlokun JO, Porta DJ, Akinyelu JO, Rivoira MA, and Garcia NH. Antioxidative potential and activity of potassium polyacrylate and coenzyme Q10 on rat hepatic mitochondrial permeability transition pores. Arch. Razi Inst. 2024; *79*(4):805-814. Doi: 10.32592/ARI.2024.79.4.805
13. Hargreaves I, Heaton RA, Mantle D. Disorders of human coenzyme Q10 metabolism: an overview. Int J Mol Sci. 2020; 21(18):6695. Doi: 10.3390/ijms21186695
14. Calò LA, Rigato M, Bertoldi G. ACE2/Angiotensin 1-7 protective anti-inflammatory and antioxidant role in hyperoxic lung injury: Support from studies in Bartter's and Gitelman's syndromes. QJM: An Int J. Med. 2020; 113(6):440-441. Doi: 10.1093/qjmed/hcz319
15. Keskin E, Uluışık D, Öznurlu Y, Özaydın T. Effects of coenzyme Q10 on some blood antioxidant system parameters and histological changes in the pancreas and aorta of streptozotocin-induced diabetic rats. Kocatepe Vet J. 2020; 13(2):192-202. Doi: 10.30607/kvj.702306
16. Pastor-Maldonado CJ, Suárez-Rivero JM, Povea-Cabello S, Álvarez-Córdoba M, Villalón-García I, Munuera-Cabeza M, Suárez-Carrillo A, Talaverón-Rey M, Sánchez-Alcázar JA. Coenzyme Q10: novel formulations and medical trends. Int J Mol Sci. 2020; 21(22):8432. Doi: 10.3390/ijms21228432
17. Alarcón-Vieco E, Martínez-García I, Sequí-Domínguez I, Rodríguez-Gutiérrez E, Moreno-Herráiz N, Pascual-Morena C. Effect of coenzyme Q10 on cardiac function and survival in heart failure: an overview of systematic reviews and meta-analyses. Food Funct. 2023; 14(14):6302-6311. Doi: 10.1039/d3fo01255g
18. Maruhashi T, Higashi Y. Pathophysiological association between diabetes mellitus and endothelial dysfunction. Antioxidants (Basel). 2021; 10(8):1306. Doi: 10.3390/antiox10081306

19. Quaile MP, Melich DH, Jordan HL, Nold JB, Chism JP, Polli JW, Smith GA, Rhodes MC. (2010). Toxicol. Appl Pharmacol. 2010; 243(3):340-347. Doi: 10.1016/j.taap.2009.11.026
20. Wilson RD, Islam MS. Fructose-fed streptozotocin-injected rat: an alternative model for type 2 diabetes. Pharmacol Rep. 2012; 84(1):128-139. Doi: 10.1016/s1734-1140(12)70739-9
21. Tietz NW. Clinical guide to laboratory tests. *In Clinical guide to laboratory tests*. 1995; 1096-1096.
22. Passonneau JV, and Lauderdale VR. (1974). A comparison of three methods of glycogen measurement in tissues. Anal Biochem. 1974; 60(2):405-412. Doi: 10.1016/0003-2697(74)90248-6
23. Worthington Biochemical Corp. Worthington enzyme and related biochemicals. Freehold, NJ. *Handbook of Biochemistry: 1978; Section A Proteins*, *1*.
24. Apostolidis E, Kwon YI, and Shetty K. Inhibitory potential of herb, fruit, and fungal-enriched cheese against key enzymes linked to type 2 diabetes and hypertension. Inno Food Sci Emerg. Technol. 2007; *8*(1):46-54. Doi: 10.1016/j.ifset.2006.06.001
25. Doumas BT, Perry BW, Sasse EA, and Straumfjord JV. Standardization in bilirubin assays: evaluation of selected methods and stability of bilirubin solutions. Clin Chem. 1973; *19*(9):984-993. Doi: 10.1093/clinchem/19.9.984
26. Reitman, S., and Frankel, S. A colorimetric method for the determination of serum glutamic oxalacetic and glutamic pyruvic transaminases. Am J Clin Pathol. 1957; *28*(1):56-63. Doi: 10.1093/ajcp/28.1.56
27. Wright PJ, Plummer DT, Leathwood PT. Enzyme in rat urine. Alkaline Phosphatase Enzymol. 1972; 42:317-327.
28. Levine R.L, Garland D, Oliver CN, Amici A, Climent I, Lenz AG, and Stadtman, ER. Determination of carbonyl content in oxidatively modified proteins. Methods Enzymol. 1990; 186:464-478. Doi: 10.1016/0076-6879(90)86141-h
29. Nelson WG, De Marzo AM, DeWeeSe TL, and Isaacs WB. The role of inflammation in the pathogenesis of prostate cancer. J Urol. 2004; *172*(5):S6-S12. Doi: 10.1097/01.ju.0000142058.99614.ff
30. Gornall AG, Bardawill CJ, and David MM. Determination of serum proteins by means of the biuret reaction. J. Biol. Chem. 1949; *177*(2):751-766. Doi.org/10.1016/S0021-9258(18)57021-6
31. Misra HP, and Fridovich I. The role of superoxide anion in the autoxidation of epinephrine and a simple assay for superoxide dismutase. J. Biol. Chem. 1972; *247*(10):3170-3175. Doi.org/10.1016/S0021-9258(19)45228-9
32. Beers, RF., and Sizer, IW. A spectrophotometric method for measuring the breakdown of hydrogen peroxide by catalase. J. Biol. Chem, 1952; *195*(1):133-140. Doi.org/10.1016/S0021-9258(19)50881-X
33. Ellman, GL. Tissue sulfhydryl groups. Arch. Biochem. Biophys. 1959; *82*(1):70-77. Doi: 10.1016/0003-9861(59)90090-6
34. Ortiz G, Chao C, Jamali A, Seyed-Razavi Y, Kenyon B, Harris DL, and Hamrah P. Effect of Dry Eye Disease on the Kinetics of Lacrimal Gland Dendritic Cells as Visualized by Intravital Multi-Photon Microscopy. Front Immunol. 2020; 11:1713. Doi: 10.3389/fimmu.2020.01713
35. Elekofehinti OO, Onunkun AT, Olaleye MT. *Cymbopogon citratus* (DC.) Stapf mitigates ER-stress induced by streptozotocin in rats via down-regulation of GRP78 and up-regulation of Nrf2 signaling. J. Ethnopharmacol. 2020; 262:113-130. Doi: 10.1016/j.jep.2020.113130
36. Daniel OO, Adeoye AO, Ojowu J, and Olorunsogo OO. (2018). Inhibition of liver mitochondrial membrane permeability transition pore opening by quercetin and vitamin E in streptozotocin-induced diabetic rats. Biochem Biophys Res. Commun. 2018; *504*(2):460-469. Doi: 10.1016/j.bbrc.2018.08.114
37. Bharti SK, Krishnan S, Kumar A, Kumar A. Antidiabetic phytoconstituents and their mode of action on metabolic pathways. Ther Adv Endocrinol Metab. 2018; 9:81-100. Doi: 10.1177/2042018818755019
38. Martelli A, Testai L, Colletti A, Cicero AF. Coenzyme Q10: Clinical applications in cardiovascular diseases. Antioxidants (Basel). 2020; 9(4):341. Doi: 10.3390/antiox9040341
39. Adeoye AO, Porta DJ, Rivoira MA, and Garcia NH. Pharmacoinformatics studies of coenzyme Q10 and potassium polyacrylate on angiotensin-converting enzyme associated with hypertension. J Biomol. Struct Dyn, 2024; 42(19) 9949-9960. Doi: 10.1080/07391102.2023.2254395
40. Mantle D. Coenzyme Q10 supplementation for diabetes and its complications: an overview Br J Diabetes. 2017; 17:145-148. Doi: 10.15277/bjd.2017.149
41. Gutierrez-Mariscal FM, de la Cruz-Ares S, Torres-Peña JD, Alcalá-Diaz JF, Yubero-Serrano EM, López-Miranda J. Coenzyme Q10 and cardiovascular diseases. Antioxidants (Basel). 2021; 10(6):906. Doi: 10.3390/antiox10060906
42. Tungmunnithum D, Thongboonyou A, Pholboon A, Yangsabai A. Flavonoids and other phenolic compounds from medicinal plants for pharmaceutical and medical aspects: An overview. Medicines (Basel). 2018; 5:93. Doi: 10.3390/medicines5030093
43. Xia J, Li X, Bai C, Han X. Research Progress of Coenzyme Q in Diabetes Mellitus and Its Common Complications. Diabetes Metab Syndr Obes. 2024; 3629-3641. Doi: 10.2147/DMSO.S481690
44. Sadi G, Şahin G, Bostancı A. Modulation of renal insulin signaling pathway and antioxidant enzymes with diabetes: Effects of resveratrol. Medicina (Kaunas). 2018; 55(1): E3. Doi: 10.3390/medicina55010003
45. Samimi F, Namiranian N, Sharifi-Rigi A, Siri M, Abazari O, Dastghaib S. Coenzyme Q10: A Key Antioxidant in the Management of Diabetes-Induced Cardiovascular Complications—An Overview of Mechanisms and Clinical Evidence. Int J Endocrinol. 2024; 2024(1):2247748. Doi: 10.1155/2024/2247748
46. Sarkar P, Nath K, Banu S. Modulatory effect of baicalein on gene expression and activity of antioxidant enzymes in streptozotocin-nicotinamide induced diabetic rats. Braz. J. Pharm. Sci. 2019; 55: e18201. Doi: 10.1590/s2175-97902019000118201
47. Barbato V, Talevi R, Braun S, Merolla A, Sudhakaran S, Longobardi S, Gualtieri R. Supplementation of sperm media with zinc, D-aspartate and co-enzyme Q10 protects bull sperm against exogenous oxidative stress and improves their ability to support embryo development. Zygote. 2017; 25(2):168-175. Doi: 10.1017/S0967199416000459
48. Marrocco, I., Altieri, F., Peluso, I. Measurement and Clinical Significance of Biomarkers of Oxidative Stress in Humans. Oxid Med Cell Longev. 2017; 65010-65046. Doi: 10.1155/2017/6501046
49. Jorat MV, Tabrizi R, Kolahdooz F, Akbari M, Salami M, Heydari ST, Asemi Z. The effects of coenzyme Q10 supplementation on biomarkers of inflammation and oxidative stress in among coronary artery disease: A systematic review and meta-analysis of randomized controlled trials. Inflammo Pharmacol. 2019: 27:233–248. Doi: 10.1007/s10787-019-00572-x
50. Dludla PV, Orlando P, Silvestri S, Marcheggiani F, Cirilli I, Nyambuya TM, Mxinwa V, Mokgalaboni K, Nkambule BB, Johnson R, Mazibuko-Mbeje SE. Coenzyme Q10 supplementation improves adipokine levels and alleviates inflammation and lipid peroxidation in conditions of metabolic syndrome: A meta-analysis of randomized controlled trials. Int J Mol Sci. 2020; 21(9):3247. Doi: 10.3390/ijms21093247
51. García-Ropero Á, Vargas-Delgado AP, Santos-Gallego CG, and Badimon JJ. Inhibition of sodium glucose cotransporters improves cardiac performance. Int J Mol Sci. 2019; *20*(13):3289. Doi: 10.3390/ijms20133289
52. Ramasubbu K, Devi Rajeswari V. Impairment of insulin signaling pathway PI3K/Akt/mTOR and insulin resistance induced AGEs on diabetes mellitus and neurodegenerative diseases: a perspective review. Mol Cell Biochem. 2023; 478(6):1307-1324. Doi: 10.1007/s11010-022-04587-x

53. Sharma, A., Lee-Ødegård, S., Qvigstad, E., Sommer, C., Sattar, N., Gill, J. M., and Birkeland, KI. (2022). β-cell function, hepatic insulin clearance, and insulin sensitivity in south asian and nordic women after gestational diabetes mellitus. Diabetes 2022; *71*(12):2530-2538. Doi: 10.2337/db22-0622
54. Farsi F, Ebrahimi-Daryani N, Golab F, Akbari A, Janani L, Karimi MY, Irandoost P, Alamdari NM, Agah S, Vafa M. A randomized controlled trial on the coloprotective effect of coenzyme Q10 on immune-inflammatory cytokines, oxidative status, antimicrobial peptides, and microRNA-146a expression in patients with mild-to-moderate ulcerative colitis. Eur J Nutr. 2021; 60:3397-3410. Doi: 10.1007/s00394-021-02514-2
55. Garcia-Jacobo RE, Bergamin LS, Vultaggio-Poma V, Thorstenberg ML, Tarantini M, García-Hernández MH, and Di Virgilio F. The purinergic landscape of type 2 diabetes mellitus. Molecules. 2022; *27*(6):1838. Doi: 10.3390/molecules27061838