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EXPLORING THE POTENTIAL OF 1-DEOXYNOJIRIMYCIN IN MANAGING PROTEIN METABOLISM AND MARKER ENZYMES IN DIABETIC TILAPIA

Raja Latha and Dr. Gani Sharmila Banu*

PG & Research Department of Zoology, NKR Government Arts College for Women, Namakkal- 637 001, Tamilnadu, India.

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***Corresponding Author**
Dr. Gani Sharmila Banu
PG & Research Department of Zoology, NKR Government Arts College for Women, Namakkal- 637 001, Tamilnadu, India.

ABSTRACT

Diabetes is a chronic metabolic disorder characterized by high blood glucose levels, which can lead to various complications, including liver and kidney damage. 1-Deoxynojirimycin (DNJ) is a naturally occurring compound found in certain plants and has been shown to have antihyperglycemic properties. The present study investigated the possible protective effect of DNJ on certain biochemical markers in diabetic Tilapia. To induce a transdermal hyperglycemic state in the tilapia, the fish were exposed to water containing 50g/lit of glucose for 14 days. This hyperglycemic state mimics the conditions observed in diabetic individuals and leads to physiological and biochemical alterations. In diabetic tilapia, alterations in blood levels of glucose, urea, uric acid, and creatinine, as well as plasma levels of albumin and albumin/globulin ratio, have been reported. Additionally, the activities of diagnostic marker enzymes, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (g-GT), in plasma, liver, and kidney can be affected in diabetic conditions. The administration of DNJ at doses of 10 and 20 mg/kg body weight for 14 days was used to assess its potential protective effect. The study aimed to evaluate whether DNJ could restore the altered biochemical parameters to near-normal levels in diabetic tilapia. The restoration of these parameters would indicate a potential antihyperglycemic effect of DNJ and its ability to alleviate liver and renal damage associated with diabetes in tilapia. In conclusion, the present study aimed to explore the effects of DNJ on biochemical markers in diabetic tilapia. Understanding the protective

effects of DNJ could have implications for the development of therapeutic interventions for diabetes-related complications in both aquatic species and humans. Further research is needed to elucidate the underlying mechanisms and validate the safety and efficacy of DNJ in the treatment of diabetes-related conditions.

KEYWORDS: 1-Deoxynojirimycin (DNJ), diagnostic marker enzymes, liver and renal damage, diabetic Tilapia model, therapeutic interventions.

INTRODUCTION

Hyperglycemia, a chronic metabolic disease associated with diabetes mellitus, can result in various complications, including impaired protein metabolism. Recently, there has been growing interest in studying natural substances with antidiabetic properties as a means of managing diabetes and its consequences. One such natural compound is 1-deoxynojirimycin (DNJ), which is present in several plants and has demonstrated hypoglycemic and anti-diabetic effects.[1] Protein metabolism, encompassing protein synthesis (anabolism) and breakdown (catabolism), is a crucial aspect affected by hyperglycemia, a chronic metabolic disorder often linked to diabetes mellitus. These processes are tightly regulated to maintain protein homeostasis and ensure optimal cellular and tissue functioning.[2] It is crucial to further investigate the potential of natural compounds, like DNJ, in the management of diabetes and its associated complications. Understanding their impact on protein metabolism could provide valuable insights for developing effective therapeutic strategies in the future.[3]

Protein metabolism is a complex and tightly regulated process that plays a crucial role in maintaining cellular homeostasis, supporting growth, and facilitating tissue repair. The balance between protein synthesis and breakdown is essential for ensuring adequate protein levels and overall protein turnover within the body.[4] Disruptions in protein metabolism can have significant implications for cellular function and contribute to the development of various metabolic diseases, including diabetes, obesity, and conditions associated with muscle wasting.[5] In the context of diabetes, alterations in protein metabolism have been observed. Chronic hyperglycemia, a characteristic feature of diabetes, can disrupt protein balance by reducing protein production and increasing protein breakdown. Factors such as dysregulation of insulin signaling pathways, changes in amino acid availability, and upregulation of the ubiquitin-proteasome system may contribute to these effects.[6] Understanding the underlying processes that regulate protein metabolism in diabetes is

crucial for developing treatment approaches that aim to maintain protein homeostasis and prevent complications associated with altered protein metabolism.

On the other hand, marker enzymes are specific enzymes that serve as biomarkers or indicators for specific biological processes or conditions. These enzymes are often associated with specific cellular compartments or metabolic pathways, and their activities or levels can provide valuable information about cellular status or the presence of specific diseases or disorders.[7,8] Marker enzymes are frequently utilized in clinical diagnosis, research, and experimental studies to evaluate and monitor various physiological and pathological processes. The activity, expression levels, or subcellular localization of these enzymes can be quantified or subjectively assessed to evaluate changes in cellular function or disease progression.[9,10] Different marker enzymes are employed to assess specific processes or conditions. For example, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are measures of liver function, while troponin and creatine kinase are indicators of cardiac injury.[11,12]

Marker enzymes play a crucial role in diagnosing, prognosing, and monitoring illnesses, as well as assessing cellular and organ health. By monitoring their activities or levels, healthcare professionals and researchers can gather essential information about tissue damage, inflammation, metabolic abnormalities, and other physiological or pathological processes.[13] High glucose-induced hyperglycemia is a condition characterized by elevated blood glucose levels resulting from exposure to high glucose levels. It often occurs in conjunction with diabetes mellitus, a metabolic condition marked by decreased insulin sensitivity or insulin resistance. Hyperglycemia can arise from persistently high blood glucose levels, such as in untreated diabetes, due to inadequate insulin synthesis, poor insulin action, or both.[14] High glucose-induced hyperglycemia has been found to impact protein metabolism by promoting protein breakdown and inhibiting protein synthesis. Enzymes involved in glucose metabolism, such as hexokinase, glucokinase, and glucose-6-phosphatase, are examples of marker enzymes that may be affected by increased glucose levels. Therefore, it is important to evaluate the potential of DNJ to modify these characteristics in the context of diabetes.[15]

Studying the effects of DNJ on protein synthesis and marker enzymes in diabetic tilapia can provide valuable insights into its potential as a treatment for diabetes-related issues. By investigating the mechanisms through which DNJ affects protein metabolism and marker

enzyme activities, new therapeutic approaches for managing diabetes can be developed. This study aims to assess the impact of DNJ on protein synthesis and marker enzymes in an experimental model of diabetic tilapia induced by high glucose levels. Tilapia (Oreochromis spp.) is commonly used as an experimental model for studying diabetes due to its physiological and genetic similarities to mammals. By examining the effects of DNJ on protein synthesis and marker enzyme activities in this model, we can gain a better understanding of DNJ's potential as a diabetes treatment. This study has the potential to contribute to the development of novel therapeutic strategies for managing diabetes and its associated complications.

MATERIALS AND METHODS

Drugs and chemicals

The drugs and biochemicals utilized in this investigation were supplied by The Sigma Chemical Company Inc., located in St. Louis, Missouri, USA. All substances employed in this study were of analytical quality.

Fish

Samples of apparently healthy and deceased tilapia fish (Oreochromis niloticus) were chosen at random from farms located in Namakkal district in Tamil Nadu. Juvenile fish of both sexes, weighing 60.6g ± 4.8g, were acclimatized in the test chamber for a minimum of 14 days. The fish were housed in 5-L thermostated tanks, with continuous chemical, biological, and mechanical water filtration and aeration (7.20 mg O2/L), in groups of ten. They were fed commercial flakes containing 48% protein, 8% fat, and 2% fiber three times a day and maintained on a 14 h/10 h day/night photoperiod cycle. All fish used in the tests were randomly selected from various clusters.

Induction of hyperglycemia in tilapia

Ten fish were divided into six groups and exposed to water containing 50g/lit of glucose for 14 days to induce transdermal diabetes, using the approach described by Capiotti et al.[16] to achieve the highest survival rate and a blood glucose profile consistent with published data. The feeding schedule and general maintenance measures were the same as described in the previous section. To prevent opportunistic microbial infection, the glucose solutions were changed three times per week. The fish were monitored for signs of stress, such as difficulty swimming or excessive gill movement, after being placed in each solution.[17]

Blood samples were then collected before placing the fish in clean freshwater. Fish that received glucose were treated with either glibenclamide or DNJ.

Experimental design

A total of 60 fish were enrolled in the study, with 40 surviving fish in the diabetic group and 20 fish in the control group. The fish were divided into six groups, with each group consisting of 10 fish (n = 10). After undergoing high glucose induction therapy for 14 days, the diabetic fish were given oral treatments with DNJ and glibenclamide. On the fifteenth day, different doses of DNJ and glibenclamide were diluted in water and orally administered to the fish. Before obtaining blood samples, all fish received the appropriate pharmacological treatment.

- Group I: Non-diabetic, control
- Group II: Non-diabetic treated with DJN (20 mg/kg b.w)
- Group III: Diabetic control
- Group IV: Diabetic treated with DJN (10 mg/kg b.w)
- Group V: Diabetic treated with DJN (20 mg/kg b.w)
- Group VII: Diabetic treated with glibenclamide (0.6 mg/kg b.w)

At the end of the experiment, the fish were euthanized. Blood samples of 150 to 200 µl were extracted from the caudal vein of each fish and placed in test tubes containing a mixture of potassium oxalate and sodium fluoride (in a ratio of 3:1). The test tubes were then centrifuged at 3000 rpm for five minutes to obtain serum. The liver, pancreas, and kidney were promptly dissected, cleaned in ice-cold saline to remove any blood, and subsequently stored at -80°C for future utilization.

Biochemical and enzymatic estimations

Glucose levels were determined using commercially available glucose kits that utilize the glucose oxidase technique (Quimefa®, Cuba) for the assessment of biochemical parameters. The serum levels of urea, uric acid, and creatinine were measured using an Autoanalyzer with a reagent kit obtained from Boehringer (Mannheim, Germany). The protein levels of plasma, liver, and kidney were quantified by earlier literature.[12,18,20] The albumin and globulin content of the plasma and AST, ALT, ALP and γ-GT were measured using the technique described by earlier literature.[12,18-20]

Statistical Analysis

The mean ± standard deviation was utilized to express the findings of the different studies, with a sample size of 10 (n = 10). Statistical significance was determined by performing one-way analysis of variance (ANOVA) using SPSS Version 22 (SPSS, Cary, NC, USA). Duncan's multiple range test (DMRT) was used for individual comparisons. A p-value less than 0.05 was deemed statistically significant.

RESULTS AND DISCUSSION

In non-diabetic individuals, when blood sugar levels rise, insulin is produced by the pancreas to aid in the absorption of glucose into cells, particularly in muscle and adipose tissue. Additionally, insulin promotes the storage of excess glucose as glycogen in the liver. However, this mechanism becomes problematic in individuals with diabetes or insulin resistance, leading to high glucose levels.[21,22] Prolonged hyperglycemia caused by elevated glucose levels can have various harmful effects on the body, including advanced glycation end products, oxidative stress, and activation of inflammatory pathways, which contribute to the development of diabetes-related cardiovascular, retinopathy, nephropathy, and other complications.[18,23]

Common treatments for high glucose-induced hyperglycemia include oral hypoglycemic medications, insulin administration, and lifestyle modifications such as adopting a balanced diet and engaging in regular exercise. Close monitoring of blood glucose levels is crucial to minimize the risk of complications and promote overall health.[24] In research settings, high glucose-induced hyperglycemia can be experimentally induced to study the pathophysiology of diabetes, evaluate new treatment strategies, and investigate mechanisms related to hyperglycemia-associated complications.

High glucose-induced hyperglycemia is characterized by elevated blood sugar levels due to inadequate insulin synthesis or action. If left uncontrolled, it can have detrimental effects on the body and is directly linked to diabetes.[25] Previous research has demonstrated the hypoglycemic effects of DNJ in diabetic animal models, along with its potential to improve insulin sensitivity and glucose tolerance.[5] However, limited research has been conducted on the specific effects of DNJ on protein metabolism and diabetes marker enzymes.

DNJ on liver, kidney, and pancreas weight

The study examined the impact of DNJ on liver, kidney, and pancreas weight in control and high glucose-induced experimental tilapia. Liver weights were measured for different treatment groups, with the normal control group having an average weight of 5.60 ± 0.31 g. The DNJ-20 group showed a slightly higher average liver weight of 5.68 ± 0.71 g. In contrast, the diabetic control group had a lower average liver weight of 4.28 ± 0.54 g. However, the diabetic groups treated with DNJ at both 10 mg/kg (5.70 ± 0.91 g) and 20 mg/kg (5.93 ± 0.45 g) exhibited increased liver weights compared to the diabetic control group. Notably, the diabetic group treated with glibenclamide (0.6 mg/kg) showed the highest liver weight of 6.13 ± 0.97 g. Similarly, kidney weights were analyzed for the different treatment groups. The normal control group had an average kidney weight of 1.06 ± 0.03 g, while the DNJ-20 group had a slightly higher average weight of 1.11 ± 0.03 g. In contrast, the diabetic control group had a significantly higher average kidney weight of 1.50 ± 0.07 g. The diabetic groups treated with DNJ at 10 mg/kg (1.28 ± 0.05 g) and 20 mg/kg (1.08 ± 0.05 g) demonstrated reduced kidney weights compared to the diabetic control group. The diabetic group treated with glibenclamide (0.6 mg/kg) had a kidney weight similar to that of the DNJ-20 group, with an average of 1.12 ± 0.07 g (**Table 1**). In a related study by Latha et al,[26] the effects of DNJ on insulin resistance and skeletal muscle in db/db mice, a model of type 2 diabetes, were investigated. Although the primary focus of the study was on skeletal muscle, the impact of DNJ on liver and kidney weight was also examined as indicators of metabolic changes in the context of insulin resistance.

The study analyzed the pancreas weights of different treatment groups. The normal control group had an average pancreas weight of 0.43 ± 0.02 g, while the DNJ-20 group showed a slightly higher average weight of 0.44 ± 0.06 g. In contrast, the diabetic control group had a significantly lower average pancreas weight of 0.21 ± 0.01 g. However, the diabetic groups treated with DNJ at 10 mg/kg (0.32 ± 0.02 g) and 20 mg/kg (0.39 ± 0.03 g) exhibited increased pancreas weights compared to the diabetic control group. The diabetic group treated with glibenclamide (0.6 mg/kg) had a pancreas weight similar to that of the normal control and DNJ-20 groups, with an average of 0.41 ± 0.01 g **(Table 1)**. In a study by Madheswaran et al.[27] the preventive effects of DNJ against obesity and metabolic syndrome in mice were examined. The study aimed to investigate how DNJ influences hepatic lipogenesis and endoplasmic reticulum stress in the development of metabolic diseases, with liver weight being one of the metabolic markers measured. Additionally,

Kumar et al.[28] investigated the effects of DNJ on rat food intake and gastrointestinal motility. While the study did not specifically focus on organ weight, it explored the impact of DNJ on various physiological indicators, including liver and kidney weight, as part of the assessment of DNJ's effects on the gastrointestinal system.

Table 1: Effect of DNJ on liver, kidney, and pancreas weight in control and high glucose-induced experimental tilapia.

Treatment Group (mg/kg)	Liver wt (g)	Kidney wt (g)	Pancreas wt (g)
Normal control	5.60 ± 0.31^{a}	1.06 ± 0.03^{a}	0.43 ± 0.02^{a}
DJN- 20	5.68 ± 0.71^{a}	1.11 ± 0.03^{a}	0.44 ± 0.06^{a}
Diabetic control	4.28 ± 0.54^{b}	1.50 ± 0.07^{b}	0.21 ± 0.01^{b}
Diabetic + DJN 10	5.70 ± 0.91^{c}	1.28 ± 0.05^{c}	0.32 ± 0.02^{c}
Diabetic + DJN 20	5.93 ± 0.45^{d}	1.08 ± 0.05^{d}	0.39 ± 0.03^{d}
Diabetic + glibenclamide 0.6	6.13 ± 0.97^{d}	1.12 ± 0.07^{d}	0.41 ± 0.01^{d}

Values are given as mean ± S.D. for groups of ten fish each. Values not sharing a common superscript (a–d) differ significantly at $p<0.05$, Duncan's multiple range test (DMRT).

DNJ on blood levels of urea, uric acid, and creatinine

Research has examined the impact of DNJ on blood urea levels, a marker of protein metabolism and renal function. However, there is limited information available on the effects of DNJ specifically on blood urea levels, and interpretations may vary depending on the experimental design and research methodology. In a study on control and high glucose-induced experimental tilapia, the effects of DNJ on blood urea levels, uric acid, and creatinine were investigated. The results showed that the normal control group had an average blood urea level of 23.22 ± 4.64 mg/dl. The DNJ-20 group had a slightly higher average urea level of 24.18 ± 4.13 mg/dl. In contrast, the diabetic control group had a significantly higher average blood urea level of 37.76 ± 5.76 mg/dl. However, the diabetic groups treated with DNJ at both 10 mg/kg (29.04 ± 4.87 mg/dl) and 20 mg/kg (25.03 ± 4.92 mg/dl) demonstrated reduced blood urea levels compared to the diabetic control group **(Table 2)**. The diabetic group treated with glibenclamide (0.6 mg/kg) had a blood urea level similar to that of the normal control group, with an average of 22.78 ± 3.90 mg/dl.

Table 2: Effect of DNJ on blood levels of urea, uric acid, and creatinine in control and high glucose-induced experimental tilapia.

Treatment Groups (mg/kg)	Urea (mg/dl)	Uric acid (mg/dl)	Creatinine (mg/dl)
Normal control	23.22 ± 4.64^{a}	1.12 ± 0.12^{a}	0.97 ± 0.14^{a}
DJN- 20	24.18 ± 4.13^{a}	1.10 ± 0.14^{a}	1.03 ± 0.19^{a}
Diabetic control	37.76 ± 5.76^{b}	1.99 ± 0.16^{b}	2.46 ± 0.24^{b}
Diabetic + DJN 10	29.04 ± 4.87^{c}	1.62 ± 0.07^{c}	1.77 ± 0.15^{c}
Diabetic + DJN 20	25.03 ± 4.92^{a}	1.53 ± 0.07^{c}	1.36 ± 0.17^{d}
Diabetic + glibenclamide 0.6	22.78 ± 3.90^{a}	1.19 ± 0.05^{a}	1.27 ± 0.18^{d}

Values are given as mean ± S.D. for groups of ten fish each. Values not sharing a common superscript (a–d) differ significantly at $p<0.05$, Duncan's multiple range test (DMRT).

Overall, the available research suggests that DNJ may have potential therapeutic benefits for metabolic disorders such as diabetes and obesity. However, further studies are necessary to gain a comprehensive understanding of the effects of DNJ on various metabolic markers, including blood urea levels, and to determine its potential as a therapeutic agent.

Indeed, elevated levels of uric acid in the blood, known as hyperuricemia, are often associated with conditions such as gout and metabolic syndrome. Uric acid is a waste product of metabolism that can build up in the body when its production exceeds its excretion.[29,30] Research has shown that DNJ may have beneficial effects in regulating uric acid levels. Although the specific effects of DNJ on blood uric acid levels have not been mentioned in the previous context, it is important to note that DNJ has been studied for its potential protective effects on kidney function. In a study conducted by Ganesan et al.[31] using a mouse model of STZ-induced diabetes, DNJ was found to have protective effects on the kidneys. This suggests that DNJ may help preserve kidney function, which could potentially contribute to maintaining normal blood uric acid levels. Further research is necessary to fully understand the effects of DNJ on blood uric acid levels and its potential therapeutic applications for conditions associated with hyperuricemia. However, the existing evidence suggests that DNJ shows promise as a potential intervention for managing uric acid-related diseases such as gout and metabolic syndrome.

In the study conducted by Pandian et al.[32] the impact of DNJ extracted from mulberry on the renal transport of urate and glucose in hyperuricemic mice was investigated, and the effects of DNJ on uric acid levels were also examined. The results showed that DNJ had an effect on uric acid metabolism and renal function, indicating its potential therapeutic uses.

The blood uric acid levels analyzed in the study were as follows: normal control group (1.12 ± 0.12 mg/dl), DJN-20 group (1.10 ± 0.14 mg/dl), diabetic control group (1.99 ± 0.16 mg/dl), diabetic + DNJ-10 group (1.62 ± 0.07 mg/dl), diabetic + DNJ-20 group (1.53 ± 0.07 mg/dl), and diabetic + glibenclamide 0.6 group (1.19 ± 0.05 mg/dl) **(Table 2)**. Similarly, the study conducted by Vijayapriya et al.[33] examined the effects of DNJ produced from mulberry leaves on rats with normal blood sugar levels and diabetic rats treated with streptozotocin. As part of the overall assessment of DNJ's effects on glucose and lipid metabolism, the study also assessed the influence of DNJ on various metabolic indicators, including blood levels of urea, uric acid, and creatinine.

The study conducted by Kumar et al[34] analyzed the blood creatinine levels in various groups, including the normal control group (0.97 ± 0.14 mg/dl), DJN-20 group (1.03 ± 0.19 mg/dl), diabetic control group (2.46 ± 0.24 mg/dl), diabetic + DNJ-10 group (1.77 ± 0.15 mg/dl), diabetic + DNJ-20 group (1.36 ± 0.17 mg/dl), and diabetic + glibenclamide 0.6 group (1.27 ± 0.18 mg/dl) **(Table 2)**. These findings provide valuable insights into the effects of DNJ on uric acid and creatinine levels, indicating its potential therapeutic uses in managing conditions related to these metabolic markers and renal function.

DNJ on serum protein, albumin and A/G ratio

Albumin, a protein produced by the liver, is the most abundant protein subtype in serum protein and accounts for approximately 60% of total serum protein. Albumin is essential for maintaining blood volume and transporting various substances such as hormones, drugs, and fatty acids throughout the body. A decrease in albumin levels (hypoalbuminemia) may indicate liver disease, malnutrition, inflammation, or kidney disease.[35,36] The albumin-to-globulin (A/G) ratio is a measure of the relative amounts of albumin and globulins in the blood and can provide information on liver function and immune system activity. Low A/G ratios may indicate liver disease, while high A/G ratios may indicate autoimmune disorders. Monitoring serum protein, albumin, and A/G ratios is essential in diagnosing and managing liver and protein-related disorders.[37,38]

On the other hand, certain inflammatory diseases or monoclonal gammopathies can lead to high blood protein levels (hyperproteinemia). The impact of DNJ on serum protein, albumin, and A/G ratio was examined in control and high glucose-induced experimental tilapia. The protein levels were measured as follows: Normal control - 8.67 ± 1.81 g/dl, DNJ-20 - 8.58 ± 1.67 g/dl, Diabetic control - 6.02 ± 1.81 g/dl, Diabetic + DNJ 10 - 7.56 ±

1.55 g/dl, Diabetic + DNJ 20 - 8.51 ± 1.59 g/dl, and Diabetic + glibenclamide 0.6 - 8.04 ± 1.53 g/dl **(Table 3)**. Serum protein levels are commonly assessed through standard blood tests in clinical practice. Changes in blood protein levels can provide valuable insights into a patient's nutritional status, liver function, kidney health, and other disease states. Low levels of albumin in the blood, known as hypoalbuminemia, are indicative of various illnesses, including liver disease, malnutrition, inflammation, renal disease, and conditions that cause protein loss.[39,40] Patients with severe malnutrition, nephrotic syndrome, chronic liver disease, or inflammatory diseases are particularly susceptible to hypoalbuminemia.[41] Albumin, the most abundant protein in the blood, plays a vital role in maintaining fluid balance, transporting substances, and regulating osmotic pressure. The liver is primarily responsible for its production. Fluctuations in albumin levels can serve as indicators of renal disease, nutritional status, or liver disease.[42,43]

Hypoalbuminemia, which refers to low serum albumin levels, can be associated with renal disease, malnutrition, inflammation, or liver disease. It is commonly observed in severe cases of protein-energy malnutrition, nephrotic syndrome, and cirrhosis. Although less common, high blood albumin levels can be caused by dehydration or certain rare diseases.[24, 28, 44, 45] In the study, the albumin levels were measured as follows: Normal control - 4.64 ± 0.47 g/dl, DNJ-20 - 4.76 ± 0.89 g/dl, Diabetic control - 2.72 ± 0.77 g/dl, Diabetic + DNJ 10 - 3.86 ± 0.39 g/dl, Diabetic + DNJ 20 - 4.27 ± 0.47 g/dl, and Diabetic + glibenclamide 0.6 - 4.38 ± 0.89 g/dl **(Table 3)**.

Table 3: Effect of DNJ on serum protein, albumin, A/G ratio in control, and high glucose-induced experimental tilapia.

Treatment Groups (mg/kg)	Protein (g/dl)	Albumin (g/dl)	A/G ratio
Normal control	8.67 ± 1.81^{a}	4.64 ± 0.47^{a}	1.24 ± 0.43^{a}
DJN- 20	8.58 ± 1.67^{a}	4.76 ± 0.89^{a}	1.33 ± 0.22^{a}
Diabetic control	6.02 ± 1.81^{b}	2.72 ± 0.77^{b}	0.68 ± 0.25^{b}
Diabetic + DJN 10	7.56 ± 1.55^{c}	3.86 ± 0.39^{c}	0.97 ± 0.72^{c}
Diabetic + DJN 20	8.51 ± 1.59^{d}	4.27 ± 0.47^{a}	1.12 ± 0.82^{d}
Diabetic + glibenclamide 0.6	$8.04 \pm 1.53^{a, d}$	4.38 ± 0.89^{a}	$1.13 \pm 0.75^{a, d}$

Values are given as mean ± S.D. for groups of ten fish each. Values not sharing a common superscript (a–d) differ significantly at $p<0.05$, Duncan's multiple range test (DMRT).

The albumin-to-globulin ratio, also known as the A/G ratio, provides additional information about the distribution of different protein fractions in the blood. It is calculated by dividing

the albumin level by the globulin level. In certain conditions such as chronic inflammation, autoimmune disorders, specific infections, or multiple myeloma, a lower A/G ratio may indicate an increase in globulin levels.[24,46] Conversely, an elevated A/G ratio may suggest relatively higher albumin levels and can be observed in cases of dehydration or certain liver diseases. In the study, the A/G ratio was measured as follows: Normal control - 1.24 ± 0.43, DNJ-20 - 1.33 ± 0.22, Diabetic control - 0.68 ± 0.25, Diabetic + DNJ 10 - 0.97 ± 0.72, Diabetic + DNJ 20 - 1.12 ± 0.82, and Diabetic + glibenclamide 0.6 - 1.13 ± 0.75 **(Table 3)**.

DNJ on serum diagnostic marker enzymes

Serum diagnostic marker enzymes are specific enzymes that are assessed in the blood to evaluate the health of various organs and tissues in the body. When organs or tissues suffer injury or malfunction, these enzymes are released into the bloodstream. The impact of DNJ on blood diagnostic marker enzymes was investigated in experimental tilapia exposed to high glucose levels, as well as in control groups. AST, also known as SGOT, is present in various tissues, including the liver, heart, skeletal muscle, kidneys, and brain.[39,40] AST plays a crucial role in amino acid metabolism by catalyzing the reversible transfer of an amino group from aspartate to alpha-ketoglutarate, resulting in the production of oxaloacetate and glutamate. Increased AST levels can indicate liver injury, heart disease, or muscle damage.[47] In the study, the AST levels were measured as follows: Normal control - 86.33 ± 8.53 IU/L, DNJ-20 - 85.41 ± 7.27 IU/L, Diabetic control - 120.46 ± 10.55 IU/L, Diabetic + DNJ 10 - 104.35 ± 9.75 IU/L, Diabetic + DNJ 20 - 94.22 ± 8.73 IU/L, and Diabetic + glibenclamide 0.6 - 94.57 ± 7.56 IU/L **(Table 4)**.

AST is particularly useful as an indicator of liver disease due to its high production by hepatocytes. Increased AST levels can be associated with viral hepatitis, alcoholic liver disease, NAFLD, drug-induced liver injury, and liver cirrhosis.[48] However, non-hepatic diseases such as myocardial infarction, muscle damage, pancreatitis, and renal disease can also cause elevated AST levels. AST plays a critical role in amino acid metabolism by catalyzing the reversible transfer of an amino group from aspartate to alpha-ketoglutarate, resulting in the production of oxaloacetate and glutamate.[18, 20, 49] ALP is found in various tissues including the liver, bones, kidneys, and intestines. Increased blood levels of ALP have been associated with conditions affecting the liver or bones, such as liver disease or bone metastases. ALP is an enzyme that plays a role in removing phosphate groups from molecules and is involved in various biological functions, including liver function and bone

mineralization.[50] In the study, the ALP levels were measured as follows: Normal control - 86.33 ± 7.25 IU/L, DNJ-20 - 87.55 ± 6.25 IU/L, Diabetic control - 144.16 ± 11.84 IU/L, Diabetic + DNJ 10 - 126.00 ± 10.28 IU/L, Diabetic + DNJ 20 - 100.33 ± 9.72 IU/L, and Diabetic + glibenclamide 0.6 - 97.50 ± 8.24 IU/L **(Table 4)**.

ALP is commonly included in blood tests as an indicator of liver and bone health. Elevated ALP levels in blood tests can indicate liver disease, bone abnormalities, or certain types of cancer. In liver conditions such as hepatitis, cirrhosis, or biliary obstruction, high ALP levels may be observed. Additionally, it may be elevated in cases of bone metastases or bone abnormalities such as osteomalacia and Paget's disease.[34,51] In addition, a slight increase in ALP can be caused by pregnancy or certain medications. It is important to note that elevated ALP levels require further investigation to determine the underlying cause. Additional tests, imaging scans, and medical evaluations may be necessary to accurately diagnose the condition responsible for the elevated ALP levels.[52-54]

Table 4; Effect of DNJ on serum diagnostic marker enzymes in control, and high glucose-induced experimental tilapia.

Treatment Groups (mg/kg)	AST (IU^x/l)	ALT (IU^x/l)	ALP (IU^y/l)	γ-GT (IU^z/l)
Normal control	86.33 ± 8.53^a	31.16 ± 5.27^a	86.33 ± 7.25^a	22.64 ± 3.72^a
DJN- 20	85.41 ± 7.27^a	32.88 ± 4.23^a	87.55 ± 6.25^a	22.12 ± 3.76^a
Diabetic control	120.46 ± 10.55^b	66.66 ± 7.05^b	144.16 ± 11.84^b	34.65 ± 4.25^b
Diabetic + DJN 10	104.35 ± 9.75^c	51.16 ± 5.71^c	126.00 ± 10.28^c	28.64 ± 3.84^c
Diabetic + DJN 20	94.22 ± 8.73^d	41.83 ± 4.12^d	100.33 ± 9.72^d	26.85 ± 3.64^c
Diabetic + glibenclamide 0.6	94.57 ± 7.56^d	37.66 ± 3.25^e	97.50 ± 8.24^d	26.40 ± 3.21^c

Values are given as mean ± S.D. for groups of ten fish each. Values not sharing a common superscript (a–d) differ significantly at $p < 0.05$, Duncan's multiple range test (DMRT). U^x =µmol of pyruvate liberated/h; U^y = µmol of phenol liberated/min; U^z = mol of *p*-nitroanilide liberated/min.

ALT, also known as serum glutamate-pyruvate transaminase, is a liver-specific enzyme that plays a critical role in amino acid metabolism by facilitating the transfer of an amino group from alanine to alpha-ketoglutarate, resulting in the production of pyruvate and glutamate. ALT is primarily found in the liver and is a sensitive indicator of liver damage. Elevated levels of ALT in the bloodstream may indicate the presence of hepatitis or liver cirrhosis.[55,56] The normal control range for ALT is 31.16 ± 5.27 IU/L, while for DJN-20 it is 32.88 ± 4.23 IU/L. For diabetic control, the range is 66.66 ± 7.05 IU/L, for diabetic +

DNJ 10 it is 51.16 ± 5.71 IU/L, for diabetic + DNJ 20 it is 41.83 ± 4.12 IU/L, and for diabetic + glibenclamide 0.6 it is 37.66 ± 3.25 IU/L **(Table 4)**.

ALT is commonly included in blood tests to evaluate liver function in clinical practice. An increase in ALT levels in the blood indicates liver cell damage or injury. Compared to other liver enzymes, such as AST, ALT is more specific to liver damage. The most common cause of elevated ALT values is liver disease, including viral hepatitis, NAFLD, alcoholic liver disease, autoimmune hepatitis, drug-induced liver damage, or liver cirrhosis. However, non-hepatic diseases such as muscular damage, pancreatitis, or certain drugs can also cause an increase in ALT levels.[32] Gamma-glutamyl transferase (GGT) is another liver-specific enzyme that is also present in the kidneys, pancreas, and intestines. It plays a role in the metabolism of glutathione, which is crucial for detoxifying cells and maintaining redox balance. GGT is primarily found in the liver and is particularly sensitive to liver damage caused by alcohol consumption or certain drugs.[57,58]

Elevated GGT levels may indicate alcohol addiction, liver disease, or bile duct obstruction. The normal control range for GGT is 22.64 ± 3.72 IU/L, while for DJN-20 it is 22.12 ± 3.76 IU/L. For diabetic control, the range is 34.65 ± 4.25 IU/L, for diabetic + DNJ 10 it is 28.64 ± 3.84 IU/L, for diabetic + DNJ 20 it is 26.85 ± 3.64 IU/L, and for diabetic + glibenclamide 0.6 it is 26.40 ± 3.21 IU/L **(Table 4)**. Blood tests are often used to assess GGT as a marker of liver function in clinical practice. GGT blood tests can detect liver disorders or diseases that affect liver function, such as alcoholism, bile duct obstruction, or liver inflammation. GGT is commonly used in conjunction with other liver enzymes, such as ALT and AST, to evaluate liver function and identify liver abnormalities.[59,60]

DNJ on liver and kidney transaminases

While DNJ has been studied for its potential health benefits, including its impact on diabetes and liver function, there is limited information available on how it specifically affects liver and kidney transaminases. AST can be detected in various tissues, including the liver, heart, skeletal muscle, kidneys, and brain. While elevated AST levels can indicate liver damage, it is less specific to the liver than ALT. Elevated AST values may indicate liver conditions such as viral hepatitis, alcoholic liver disease, or drug-induced liver damage. However, other conditions such as myocardial infarction, muscular damage, pancreatitis, or renal disease can also cause an increase in AST levels.[61,62]

Table 5: Effect of DNJ on liver and kidney transaminases in control, and high glucose-induced experimental tilapia.

Treatment Groups (mg/kg)	AST (U^x /mg protein)		ALT (U^x /mg protein)	
	Liver	Kidney	Liver	Kidney
Normal control	664.0 ± 17.46[a]	800.0 ± 12.54[a]	947.73 ± 15.46[a]	901.36 ± 16.82[a]
DJN- 20	684.0 ± 19.45[a]	820.0 ± 13.54[a]	947.73 ± 14.46[a]	908.36 ± 17.82[a]
Diabetic control	890.2 ± 21.02[b]	980.25 ± 11.60[b]	1270.36 ± 19.24[b]	851.62 ± 19.28[b]
Diabetic + DJN 10	768.9 ± 19.37[c]	769.15 ± 10.90[c]	1061.62 ± 17.55[c]	881.66 ± 14.96[a]
Diabetic + DJN 20	695.4 ± 16.74[a]	771.97 ± 10.91[a]	1022.62 ± 11.35[c]	884.32 ± 15.16[a]
Diabetic + glibenclamide 0.6	664.7 ± 17.93[a]	781.23 ± 9.80[a]	965.40 ± 14.44[d]	890.76 ± 14.48[a]

Values are given as mean ± S.D. for groups of ten fish each. Values not sharing a common superscript (a–d) differ significantly at $p<0.05$, Duncan's multiple range test (DMRT). U^x =µmol of pyruvate liberated/h.

The analysis of AST in different treatment groups showed that normal control levels were 664.0 ± 17.46 Ux/mg for the liver and 800.0 ± 12.54 Ux/mg for the kidney. For DJN-20, the levels were 684.0 ± 19.45 Ux/mg for the liver and 820.0 ± 13.54 Ux/mg for the kidney. For diabetic control, the levels were 890.2 ± 21.02 Ux/mg for the liver and 980.25 ± 11.60 Ux/mg for the kidney. For diabetic + DJN 10, the levels were 768.9 ± 19.37 Ux/mg for the liver and 769.15 ± 10.90 Ux/mg for the kidney. For diabetic + DJN 20, the levels were 695.4 ± 16.74 Ux/mg for the liver and 771.97 ± 10.91 Ux/mg for the kidney. For diabetic + glibenclamide 0.6, the levels were 664.7 ± 17.93 Ux/mg for the liver and 781.23 ± 9.80 Ux/mg for the kidney **(Table 5)**. ALT, being primarily found in the liver, is considered a more accurate indicator of liver damage. Elevated ALT levels in the blood often indicate liver disease or liver cell damage. Common causes of high ALT levels include viral hepatitis (such as hepatitis B or C), NAFLD or alcoholic fatty liver disease, drug-induced liver damage, autoimmune hepatitis, and liver cirrhosis.[63]

The ALT levels were analyzed for the liver and kidney in different treatment groups. In the normal control group, the ALT levels were 947.73 ± 15.46 Ux/mg for the liver and 901.36 ± 16.82 Ux/mg for the kidney. Similarly, in the DJN-20 group, the ALT levels were 947.73 ± 14.46 Ux/mg for the liver and 908.36 ± 17.82 Ux/mg for the kidney. In the diabetic control group, the ALT levels were 1270.36 ± 19.24 Ux/mg for the liver and 851.62 ± 19.28 Ux/mg for the kidney. The diabetic + DJN 10 group showed ALT levels of 1061.62 ± 17.55 Ux/mg for the liver and 881.66 ± 14.96 Ux/mg for the kidney **(Table 5)**. In the

diabetic + DJN 20 group, the ALT levels were 1022.62 ± 11.35 Ux/mg for the liver and 884.32 ± 15.16 Ux/mg for the kidney. Lastly, the diabetic + glibenclamide 0.6 group exhibited ALT levels of 965.40 ± 14.44 Ux/mg for the liver and 890.76 ± 14.48 Ux/mg for the kidney **(Table 5)**. These results provide information about the ALT levels in each treatment group for both the liver and kidney. ALT levels can be used to assess liver function and indicate liver damage or disease.

When liver cells are damaged or injured, ALT and AST, which are primarily found in hepatocytes, are released into the bloodstream. AST is considered a less specific diagnostic for liver damage than ALT due to its presence in other tissues. Elevated levels of ALT and AST in the blood can indicate liver conditions such as viral hepatitis, NAFLD, alcoholic liver disease, or drug-induced liver injury.[64-66] The kidneys contain alanine-glyoxylate aminotransferase (AGT), an enzyme involved in the metabolism of glyoxylate and pyruvate. The proper functioning of the kidneys is highly dependent on AGT. Elevated levels of AGT in the blood can indicate kidney injury or dysfunction, as in the case of primary hyperoxaluria, a genetic disorder that causes the buildup of oxalate crystals in the kidneys.[67-69]

DNJ on liver and kidney ALP and y-GT

Elevated levels of ALP in the blood can indicate biliary blockage or liver disease. ALP is primarily produced in the liver, biliary system, and bones. Liver conditions such as hepatitis, cirrhosis, or primary biliary cholangitis can lead to increased ALP levels due to impaired liver function or reduced bile flow (cholestasis). Bile duct obstruction, often caused by gallstones, can also result in elevated ALP levels. Additionally, ALP levels may rise in bone disorders like Paget's disease or bone metastases due to accelerated bone turnover.[70-72]

The ALP and GGT levels were analyzed for the liver and kidney in different treatment groups. The normal control group showed ALP levels of 0.38 ± 0.02 Uy/mg for the liver and 0.44 ± 0.03 Uy/mg for the kidney. In the DJN-20 group, the ALP levels were 0.32 ± 0.02 Uy/mg for the liver and 0.48 ± 0.03 Uy/mg for the kidney. The diabetic control group exhibited ALP levels of 0.48 ± 0.03 Uy/mg for the liver and 0.67 ± 0.04 Uy/mg for the kidney. The diabetic + DJN 10 group showed ALP levels of 0.42 ± 0.02 Uy/mg for the liver and 0.56 ± 0.04 Uy/mg for the kidney. In the diabetic + DJN 20 group, the ALP levels were 0.42 ± 0.04 Uy/mg for the liver and 0.54 ± 0.04 Uy/mg for the kidney. Lastly, the diabetic

+ glibenclamide 0.6 group exhibited ALP levels of 0.41 ± 0.02 Uy/mg for the liver and 0.48 ± 0.04 Uy/mg for the kidney **(Table 6)**. The liver, bile ducts, and GGT are the primary sources of the enzyme ALP, while GGT is mainly found in the liver and kidney. The analysis of ALP levels in different treatment groups provides information about the liver and kidney function and can indicate liver or biliary system disorders. GGT levels can also be used as a marker for liver and kidney function.[73-75]

Table 6: Effect of DNJ on liver and kidney ALP and y-GT in control, and high glucose-induced experimental tilapia.

Treatment Groups (mg/kg)	ALP (U^y /mg protein)		*y*-GT (U^z /mg protein)	
	Liver	Kidney	Liver	Kidney
Normal control	0.38 ± 0.02^a	0.44 ± 0.03^a	4.33 ± 1.25^a	3.63 ± 0.88^a
DJN- 20	0.32 ± 0.02^a	0.48 ± 0.03^b	4.21 ± 1.85^a	3.74 ± 0.76^a
Diabetic control	0.48 ± 0.03^b	0.67 ± 0.04^c	6.46 ± 1.44^b	6.36 ± 0.89^b
Diabetic + DJN 10	0.42 ± 0.02^c	0.56 ± 0.04^c	5.33 ± 1.38^c	4.83 ± 0.64^c
Diabetic + DJN 20	0.42 ± 0.04^c	0.54 ± 0.04^c	4.53 ± 1.26^d	4.36 ± 0.58^d
Diabetic + glibenclamide 0.6	0.41 ± 0.02^c	0.48 ± 0.04^d	4.54 ± 1.24^d	4.06 ± 0.55^d

Values are given as mean ± S.D. for groups of ten fish each. Values not sharing a common superscript (a–d) differ significantly at $p<0.05$, Duncan's multiple range test (DMRT). U^y = µmol of phenol liberated/min; U^z = mol of *p*-nitroanilide liberated/min.

Elevated GGT levels are often associated with liver conditions such as hepatitis, alcoholism, NAFLD, and drug-induced liver damage. Alcohol misuse can also be indicated by increased GGT levels, which are highly sensitive to alcohol intake. Biliary obstruction and certain medications can cause an increase in GGT levels.[9,76] The GGT levels for the different treatment groups were also analyzed. The normal control group showed GGT levels of 4.33 ± 1.25 Uz/mg for the liver and 3.63 ± 0.88 Uz/mg for the kidney. In the DJN-20 group, the GGT levels were 4.21 ± 1.85 Uz/mg for the liver and 3.74 ± 0.76 Uz/mg for the kidney. The diabetic control group exhibited GGT levels of 6.46 ± 1.44 Uz/mg for the liver and 6.36 ± 0.89 Uz/mg for the kidney. The diabetic + DJN 10 group showed GGT levels of 5.33 ± 1.38 Uz/mg for the liver and 4.83 ± 0.64 Uz/mg for the kidney. In the diabetic + DJN 20 group, the GGT levels were 4.53 ± 1.26 Uz/mg for the liver and 4.36 ± 0.58 Uz/mg for the kidney. Lastly, the diabetic + glibenclamide 0.6 group exhibited GGT levels of 4.54 ± 1.24 Uz/mg for the liver and 4.06 ± 0.55 Uz/mg for the kidney **(Table 6)**. The analysis of GGT levels in different treatment groups provides information about the liver and kidney function and can indicate liver or biliary system disorders. The results can

be used to diagnose and monitor liver conditions and to assess the effectiveness of treatments.

While ALP and GGT can be found in the kidneys, they are primarily associated with the liver. Elevated levels of ALP and GGT may indicate liver dysfunction or impairment in liver disorders. However, in kidney disorders, these enzymes can also be affected due to specific metabolic changes that increase proteolysis and decrease protein synthesis, leading to a negative nitrogen balance.[77,78] Oxidative stress is one of the primary causes of diabetes and actively promotes cellular damage. It can occur before the onset of many diabetic complications.[79,80] When individuals are exposed to high glucose levels over an extended period, ROS are produced more frequently. It is widely accepted that oxidative stress plays a causal role in the development of insulin resistance and the consequences of diabetes. Overall, the analysis of ALP and GGT levels can provide insights into liver and kidney function, as well as the presence of liver and kidney disorders.[80] Additionally, oxidative stress is a significant factor in diabetes and its complications.

CONCLUSION

The study focused on investigating the effect of DNJ on protein synthesis and marker enzymes in experimental diabetic tilapia, induced by high glucose levels. The findings of the study suggest that DNJ has a positive impact on marker enzymes and protein metabolism in this experimental model of diabetes. DNJ therapy in diabetic tilapia showed beneficial effects on protein metabolism, potentially enhancing protein synthesis and decreasing protein breakdown. The regulation of key enzymes involved in protein metabolism pathways may be responsible for this impact. Furthermore, the study also revealed positive increases in marker enzymes associated with liver and renal function. DNJ therapy in the diabetic tilapia model showed potential for reducing liver and renal damage caused by high glucose levels. These results highlight the potential of DNJ as a therapeutic agent for treating aberrant protein metabolism and marker enzyme changes associated with diabetes in tilapia.

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