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ANTI-HYPERGLYCAEMIC, ANTI-LIPIDAEMIC AND ANTI-FLAMMATORY POTENTIAL OF L-ARGININE AND GLUTAMATE ON STREPTOZOTOCIN INDUCED DIABETIC ALBINO RATS

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ABSTRACT

Diabetes mellitus is one of the most common metabolic disorders globally. L-arginine and glutamate have promising beneficial effects against metabolic disorders. The study investigated the anti-hyperglycaemic, anti-lipidaemic and anti-inflammatory potential of l-arginine and glutamate on streptozotocin induced diabetic albino rats. A total of 73 adult albino rats were used. Out of this, 13 rats were used for LD_{50} study while 60 rats were used for the proper study. They were grouped into 6, Group 1 served as Normal control, Group 2-6 were diabetic rats induced with streptozotocin (120mg/kg bwt) served as Diabetic control (administered only 0.2 ml normal saline daily). Groups 3, 4, 5 and 6 rats were diabetic rats given Glibenclamide (3 mg/kg bwt), L-Arginine (50 mg/kg bwt), Glutamate (50 mg/kg bwt), L-Arginine and Glutamate (50 mg/kg bwt), respectively for 30 days. After the treatment period, the animals were sacrificed; blood sample collected, and serum separated for determination of liver function status, lipid profile, kidney function markers, cardiac function markers, The acute effect of L-arginine and glutamate on blood sugar levels showed a significant increase ($P<0.05$) across all groups, after 4 hours post-treatment. Animals in Glibenclamide control group showed a decrease in blood sugar level followed by the L-arginine group and that of co-treated group when compared to diabetic control group. There were significant ($P<0.05$) decrease in the activities of AST and ALT when the treatment groups were compared to the diabetic group, the L-arginine group showed the lowest AST activity followed by the Glibenclamide control group then the group co-treated with L-arginine and glutamate. The effects of L-arginine and glutamate on renal function; urea, creatinine showed a significant decrease ($p<0.05$) in the co-treated group when compared to the diabetic group, and in sodium, potassium and chloride levels when compared to the drug control group. The result of lipid profile status showed significant decrease ($P<0.05$) in triglyceride, LDL, VLDL of L-arginine and glutamate groups when compared to the co-treated group. The LDH activity significantly ($P<0.05$) decreased across the co-treated group compared to diabetic control group. The result of serum levels of inflammatory cytokines concentrations showed significant ($P<0.05$) decrease across the treated groups compared to that of the diabetic control group. TNF-α concentration showed significant decrease ($P<0.05$) across the treatment groups when compared to the diabetic control group. It could be concluded that L-arginine and glutamate have anti-hyperglycemic, anti-inflammatory and anti-hyperlipidemic potential.They also showed reno-protective and hepato-protective potentials.

INTRODUCTION

BACKGROUND OF THE STUDY

l- Arginine and glutamate supplementation on streptozotocin induced albino rat has been widely studied in the context of oxidative stress, diabetes and Metabolic syndrome (MES), which is clustering of abnormalities including obesity, lipid and glucose disorders that confer an increased risk of developing not only cardiovascular disease but also type 2 diabetes mellitus (Wilson *et al.,* 2017) and colorectal cancer (Siddiqui, 2015; Pelucchi *et al.,* 2016). Although the pathogenesis of the metabolic syndrome is multifaceted, reports suggest a significant impact from impaired nitric oxide synthesis that could lead to insulin resistance and, possibly, vice versa. Even though nitric oxide (NO) is the principal mediator of endothelium-dependent vasodilatation and could play an important role in the host defense mechanism, many disease conditions in humans, including components of the metabolic syndrome, could occur as a result of either deficient or excessive production of NO (Lokhande *et al.,* 2016).

Streptozotocin is widely used to induce experimental diabetes related symptom. L-arginine the major substrate of nitric oxide and the activities of L-glutamate which possibly enhance the calcium-calmodulin complex formation activates the neuronal and endothelial isoforms of the catalyzing enzymes. Nitric oxide acts as a pleiotropic intracellular messenger, exerting a variety of biological actions under both physiological and pathological conditions. While low levels of Nitric oxide are beneficial for several physiological and cellular functions keeping vascular tonus, coagulation and inflammation well balanced, high levels of Nitric oxide may cause detrimental effects. L arginine plays a role in insulin sensitivity and oxidative stress regulation. Similarly glutamate an excitatory neurotransmitter has also been implicated in pancreatic beta cell function.

GLIBENCLAMIDE

Glibenclamide is a second-generation sulfonylurea that reduces blood glucose by increasing insulin secretion from pancreatic beta cells. It undergoes significant hepatic metabolism and renal and biliary excretion. Rydberg *et al*., (2022) reported that it has a long duration of action and metabolites with hypoglycemic activity that confer an increased risk of prolonged hypoglycemia. Glibenclamide-induced hypoglycemia is more likely in the elderly, in patients with irregular eating habits, and in renal impairment. Matsuda *et al*., (2014)

TYPE 2 DIABETES?

Type 2 diabetes occurs when the body does not produce enough insulin, or when the cells are unable to use insulin properly, which is called insulin resistance. Type 2 diabetes is commonly called “adult-onset diabetes” since it is diagnosed later in life, generally after the age of 45. It accounts for 90-95 percent of people with diabetes. In recent years, Type 2 diabetes has been diagnosed in younger people, including children, more frequently than in the past. (Roden and Shulman, 2019)

L-ARGININE (ARG) BIOAVAILABILITY

L-arginine is considered a conditionally essential amino acid because endogenous L-arginine synthesis may not be sufficient to meet metabolic needs, especially during growth (infants and children) (Wu *et al*., 2014) and during highly catabolic conditions such as sepsis and burns. ARG could enhance the production and release of glucagon and insulin (Harold, 2017), reduce hypertension (Alexander *et al*., 2004), increase lipid peroxidation levels (Lubec *et al*., 2018), and induce vasodilation (Rang *et al*., 2013). ARG inhibited the oxidation of low-density lipoproteins to oxidized LDL, which is an early step in atherogenesis (Rang *et al*., 2013) and reduce hypercholesterolemic effect in animals. In addition, Arginine plays a key role in many metabolic processes in health and disease (van Waardenburg *et al*., 2017) including the synthesis of nitric oxide (Morris, 2016).

GLUCOSE METABOLISM IN ENDOTHELIAL CELLS

Glucose is actively metabolized in endothelial cells (Gerritsen and Burke 2018) and sustains anaerobic and aerobic metabolism (i.e 20–50 nmol ATP_mg protein_1_min_1.

Kumagai, (2019).In the presence of 5 mM D-glucose, catabolism of amino acids, palmitate, and lactate is reduced significantly, with oxidation rates for L-glutamine, L-alanine, and L-arginine decreased significantly (Kumagai, 2019).
In rat coronary microvascular endothelial cells, 98% of incorporated glucose is metabolized to lactate. At physiological concentrations of glucose, the contribution of the hexose monophosphate pathway accounts for 1.2% of glucose metabolism and the Krebs cycle for only 0.04%, suggesting that in microvascular endothelial cells, almost all of the energy obtained from the catabolism of glucose is generated glycolytically. At lower glucose concentrations (1 mM), oxidation of glucose via the Krebs cycle is higher. Thus oxidative metabolism in endothelial cells is inhibited at physiological concentrations of glucose, demonstrating that endothelial cells express the Crabtree effect (i.e., an inhibitory effect of glucose on mitochondrial respiration (Kumagai, 2019).

Glutamate is a naturally occurring amino acid found in protein-rich foods like milk, tomatoes, mushrooms, fish, meat, and various vegetables. It functions as an excitatory amino acid and serves as a key precursor in the synthesis of the neurotransmitters glutamine and gamma-aminobutyric acid (GABA). These neurotransmitters play essential roles in brain function. Glutamate is heavily involved in excitatory signal transmission within the central nervous system (CNS),

making it a crucial component in neural communication and brain activity regulation, as supported by various studies (Rang et al., 2003; Cotman et al., 2015; Harold, 2017).

MATERIALS AND METHODS

ANIMALS

A total of 73 male adult albino rats were used for the study. Out of this 13 rats were used for LD_{50} study while 60 were used for the study proper. Adult male albino rats weighing between 150-200g were obtained from the Animal House of the Department of Zoology and Environmental Biology, Federal University Gashua Yobe State, housed in Aluminum cages and allowed to acclimatize for two weeks to allow for proper adaptation to their new environment and living conditions before commencement of the study. The experimental rats were fed at liberty with Vita Finisher's mash (Vital Feeds, Nigeria) and clean water at libitum starved for 12 hours before the commencement of the experiment. All animal experiments were conducted in compliance with international guidelines for the care and use of laboratory animals (Orieke *et al*., 2019). The study was conducted in the Department of Biochemistry Federal University Gashua Yobe State.

INDUCTION OF DIABETES MELLITUS

Animals were made diabetic via single intraperitoneal administration of Streptozotocin (120 mg/kg body weight) and diabetes mellitus was confirmed 72hrs after induction. sample were collected for 2hrs pre induction and 4hrs post induction by determining blood sugar levels of all induced animals using a single touch glucometer (ACCUCHEK ACTIVE). Animals with blood glucose levels of 180 mg/dl and above were considered diabetic and were used for the study.

EXPERIMENTAL DESIGN FOR THE ANTI-DIABETIC STUDY

The rats were assigned to 6 groups of 10 rats each and were treated according to the order below: Group 1 rats were not made diabetic and remained normal throughout the period of the study. Animals in groups 2-6 were made diabetic and treated as indicated.

Group 2: Diabetic control (administered only 0.2 ml normal saline daily)
Group 3: Diabetic + Glibenclamide (3 mg/kg)
Group 4: Diabetic + L-Arginine (50 mg/kg bw)
Group 5: Diabetic + Glutamate (50 mg/kg bw)
Group 6: Diabetic + L-Arginine and Glutamate (50 mg/kg bw)

At the end of the 7th, 14th and 28th days' treatment period, the sugar levels of rats were determined using a single touch ACCU CHECK glucometer on blood collected from each animal's tail by tail snip. Body weights of all animals were also measured using an electronic balance at the beginning and end of treatment. All animals were also sacrificed after 30 days and blood was collected into EDTA and plain bottles for hematological and biochemical analyses respectively.

SAMPLE COLLECTION AND PREPARATION

A known quantity, 1g of the powdered form of the L-Arginine and Glutamate supplements each was dissolved in 50ml of water and allowed to stand for 2 hours. The resulting solutions were then prepared to a concentration of 25mg/ml per body weight of the rats. The volume of supplement was administered based on body weight was calculated using the formula. (Laxminatrain and Hildbert, 2007).

Volume=D×P⁄C

Where D= Dose to be administered.
P= body weight of animal weight .
C= concentration of the stock.

ACUTE TOXICITY (LD_{50}) TESTS OF SUPPLEMENTS

The acute, sub-acute and chronic toxicity of the supplements were observed for 7th to 14th days in the rats using the method of Lorke (1983), as reported by Orieke *et al*. (2019).The tests involved two phases. In the first phase, 9 rats assigned to 3 groups were given 10, 100 and 1000 mg/kg body weight oral doses of the supplement. The death or survival records in first phase determined the doses used for the second phase. In the second phase, another set of 3 rats also assigned to 3 groups of 1 rat each were assigned treated with 1600, 2900 and 5000 mg/kg body weight of the extract respectively. The treated animals were observed for 24hours for signs of toxicity and lethality. With no mortality observed after 24 hours, 5000 mg/kg body of the supplement was administered to yet another set of 1 rat as confirmatory tests. The animals were thereafter observed for 24 hours and a further 7 days. Acute toxicity dose of the supplement was calculated using the expression below:

$LD_{50} = \sqrt{A \times B}$

A= Maximum dose that produced no mortality
B= Minimum dose that killed all animals in a group

STATISTICAL ANALYSIS

Results obtained were expressed as Mean±SEM. One-way analysis of variance (ANOVA) was used to analyze the result using statistical product, service and solutions (SPSS) version 25. Duncan multiple range test was used as post-hoc tool to compare P- Values less than 0.05 were considered statistically significantly different between the test and control groups as well as among test groups for measured value.

RESULT

3.1.1The result of the total cholesterol showed significant ($p \leq 0.05$) decrease in the concentration of the co-treated groups compared to that of the diabetic group. Furthermore, the result of the L-Arginine group showed the lowest concentration (102.88±1.73) followed by that of the drug control group (106.17±0.82) then the group co-treated L-Arginine and glutamate (108.12±0.91) and then the glutamate group (117.90±1.25). The result of the HDL showed significant ($p \leq 0.05$) increase in the concentration of the co-treated groups compared to that of the diabetic group. The result of the L-Arginine group showed the highest concentration (60.22±0.75) followed by that of the drug control group (60.33±0.63) and the group co-treated L-Arginine and glutamate (59.59±0.18) and then the glutamate group (59.30±0.31). The result of the triglyceride showed significant ($p \leq 0.05$) decrease in the concentration of the co-treated groups compared to that of the diabetic group. Furthermore, the result of the drug control group showed the lowest concentration (92.10±1.27) followed by that of the L-Arginine group (99.28±0.82) and the group co-treated L-Arginine and glutamate (100.52±0.49) while the glutamate group was the highest (111.43±0.50). The result of the LDL showed significant ($p \leq 0.05$) decrease in the concentration of the co-treated groups compared to that of the diabetic group. Furthermore, the result of the L-Arginine group showed the lowest concentration (21.51±1.76) followed by that of the drug control group (26.81±1.18) and the group co-treated L-Arginine and glutamate (28.30±0.94) and then the glutamate group (36.07±1.45). The result of the VLDL concentration showed significant ($p \leq 0.05$) decrease across the co-treated groups compared to that of the diabetic group. The result of the standard drug group showed the lowest concentration (18.02±0.55) followed by that of L-Arginine group (18.99±0.75) then the group co-treated L-Arginine and glutamate (20.02±0.15) and then the glutamate group (22.13±0.22).

Result of effect of L-Arginine and Glutamate on lipid profile parameters in streptozotocin-induced diabetic rats

Treatments	Total cholesterol (mg/dl)	HDL-C (mg/dl)	Triglycerides (mg/dl)	LDL-C (mg/dl)	VLDL-C (mg/dl)
Normal control	96.31±0.58^{a}	62.34±0.33^{d}	80.41±1.00^{a}	17.70±0.80^{a}	15.96±0.25^{a}
Diabetic control	120.41±0.62^{d}	55.78±0.65^{a}	123.78±1.13^{e}	39.37±1.01^{e}	24.42±0.47^{e}
Diabetic + Glibenclamide (3 mg/kg)	106.17±0.82^{c}	60.33±0.63^{b}	92.10±1.27^{b}	26.81±1.18^{c}	18.02±0.55^{b}
Diabetic + L-Arginine (50 mg/kg bw)	102.88±1.73^{b}	60.22±0.75^{b}	99.28±0.82^{c}	21.51±1.76^{b}	18.99±0.75^{bc}
Diabetic + Glutamate (50 mg/kg bw)	117.90±1.25^{d}	59.30±0.31^{b}	111.43±0.50^{d}	36.07±1.45^{e}	22.13±0.22^{d}
Diabetic + L-Arginine and Glutamate (50 mg/kg bw)	108.12±0.91^{c}	59.59±0.18^{b}	100.52±0.49^{c}	28.30±0.94^{d}	20.02±0.15^{c}

Result were presented as mean ± SEM (n = 6); and Values within a column having the same superscripts letter are not significantly different at $p \leq 0.05$

THE RESULT OF THE EFFECT OF L-ARGININE AND GLUTAMATE ON BLOOD SUGAR LEVELS OF STREPTOZOTOCIN INDUCED DIABETIC RATS

The table showed general increase in the blood sugar levels across all groups in streptozotocin-induced diabetic rats 4 hours post treatment. However, the animals in the drug group showed the highest percentage fall in blood sugar level (37.26±6.27%) followed by that of the animals in L-arginine (29.95±0.0%), then those co-treated both L-arginine and glutamate (11.90±8.86 %).

Table 4.1.5: Result of sub-acute effect of L-Arginine and Glutamate on blood sugar levels of streptozotocin-induced diabetic rats

Treatments	Pre-induction blood sugar level (mg/dl)	7 days Post-induction blood sugar level (mg/dl)	2 H Post-treatment blood sugar level (mg/dl)	4 H Post-treatment blood sugar level (mg/dl)	Percentage fall in blood sugar level %
Normal control	80.33±0.91^{bc}	79.33±0.79^{a}	78.00±0.26^{a}	72.33±0.54^{a}	-11.92±2.33^{a}
Diabetic control	75.33±1.08^{a}	316.00±18.31^{b}	289.33±2.33^{d}	307.67±4.05^{d}	42.64±0.019^{bc}
Diabetic + Glibenclamide (3 mg/kg)	78.66±0.39^{b}	317.00±6.73^{b}	241.33±8.92^{b}	198.89±9.64^{b}	37.26±6.27^{d}
Diabetic + L-Arginine (50 mg/kg bw)	79.32±0.91^{bc}	301.66±4.51^{b}	265.66±6.37^{c}	211.32±5.54^{b}	29.95±0.0^{cd}
Diabetic + Glutamate (50 mg/kg bw)	78.66±1.08^{b}	296.99±3.24^{b}	291.32±2.09^{d}	295.66±2.78^{d}	0.45±3.45^{b}
Diabetic + L-Arginine and Glutamate (50 mg/kg bw)	81.96±1.13^{c}	310.96±8.77^{b}	291.63±11.06^{d}	273.96±8.00^{c}	11.90±8.86^{bcd}

Results were presented in Percentage fall in blood and values with different letter superscripts are significantly different from any paired mean within the group. $p \leq 0.05$

EFFECT OF L-ARGININE AND GLUTAMATE ON SERUM LEVELS OF INFLAMMATORY CYTOKINES IN STREPTOZOTOCIN-INDUCED DIABETIC RATS.

The result of the IL-1β concentration showed significant ($p \leq 0.05$) decrease in across the treatment groups compared to that of the diabetic group. The result indicated that the drug control group showed the lowest concentration (0.24±0.01), followed by the L-Arginine group (0.22±0.03), then the group co-treated with both L-Arginine and glutamate (0.36±0.02), and finally the glutamate group (0.43±0.03).

The TNF-α concentration showed significant ($p \leq 0.05$) decrease in across the treatment groups compared to that of the diabetic group. The result indicated that the drug control group showed the lowest concentration (49.41±1.56), followed by the L-Arginine group (49.94±1.48), then the group co-treated with both L-Arginine and glutamate (54.31±1.16), and finally the glutamate group (67.90±0.98).

Result of effect of L-Arginine and Glutamate on serum levels of inflammatory cytokines in streptozotocin-induced diabetic rats

Groups	Treatments	IL-1β (pg/ml)	TNF-α (pg/ml)
1	Normal control	0.20±0.01^{a}	30.91±0.61^{a}
2	Diabetic control	0.50±0.07^{d}	69.44±0.90^{d}
3	Diabetic + Glibenclamide (3 mg/kg)	0.24±0.01^{a}	49.41±1.56^{b}
4	Diabetic + L-Arginine (50 mg/kg bw)	0.22±0.03^{a}	49.94±1.48^{b}
5	Diabetic + Glutamate (50 mg/kg bw)	0.43±0.03^{bc}	67.90±0.98^{d}
6	Diabetic + L-Arginine and Glutamate (50 mg/kg bw each)	0.36±0.02^{b}	54.31±1.16^{c}

Results were presented as mean ± SEM (n = 6); and Values within a column having the same superscripts letter are not significantly different at $p \leq 0.05$

DISCUSSION

Type 2 diabetes mellitus (T2DM) affects about 85% of patients with diabetes mellitus. It can be brought on by environmental factors, genetic predisposition, or a combination of the two (Jafari-Vayghan et al., 2020). Anti-hyperglycaemic, Anti-lipidaemic and Anti-flammatory potential of l-arginine and glutamate on streptozotocin induced diabetic albino rats.

Insulin is the primary regulator of glucose homeostasis, which is defined as the equilibrium between hepatic glucose production and peripheral glucose uptake and utilization (Yari *et al.,* 2020). Reduced insulin secretion, decreased glucose utilization, and increased glucose production are the factors that lead to hyperglycemia (Simon and Wittmann, 2019). Via the glucose transporter (GLUT2), streptozotocin enters the B cell and causes DNA to be alkylated. DNA damage triggers the activation of poly ADP-ribosylation, a process that is more crucial to streptozotocin's ability to cause diabetes than DNA damage itself. (Ghasemi and Jeddi, 2023).
The more significant reduction in the glucose concentration 2hours after induction and 4 hours induction as seen in the

L-Arginine group compared to that of the Control group and glutamate is indicative of its higher anti-diabetic potential. Though the mechanism for this is not clear, it could possibly be that L-Arginine reduced the carbohydrate digestion by altering the activity of digestive enzymes leading to reduction in the concentration of the blood sugar, or inhibited the activity of the enzyme glucose-6-phosphatase which also led to reduced circulatory blood glucose. Another mechanism through which the L-arginine caused reduction in the blood glucose concentration in the group 6 by increasing the activity of glucose transporter especially GLUT 4 leading to mopping up the circulating glucose for storage hence, the reduced blood glucose concentration seen in the groups (Saka *et al*., 2022) Previous study showed that L-arginine increases the GLUT 1 in diabetic patients (Saka *et al*., 2022) while its substrate; Nitric oxide (NO) has been shown to play vital role in the up-regulation of GLUT 4 through 5'-AMP-activated protein kinase (AMPK) pathways (Lira *et al.,* 2007). This is further buttressed by higher percentage fall in blood glucose seen at 14 days post treatment suggesting that L-Arginine could have higher anti-hyperglycemic potential more than Glibenclamide the standard drug after 14 days. The higher blood glucose seen in the group treated with both L-Arginine and L-glutamate could be indicative of antagonistic reaction caused by drug-drug interaction of both supplements which caused reduced anti-hyperglycemic potential.

Dietary cholesterol causes increase in the serum concentration of total cholesterol, low density lipoprotein, very low density lipoprotein while causing reduced high density lipoprotein hence, hyperlipidaemia which has been implicated in the pathogenesis of diseases including arteriosclerosis, hypertension, diabetes mellitus, cardiovascular diseases and hemispheric stroke (Titchenell *et al*., 2016). The significant decrease in the cholesterol concentration of the L-Arginine group and L-Glutamate group when compared to the diabetic group could be indicative of anti-hyperlipidaemic potential The anti-hyperlipidaemic effects observed may be due to several underlying mechanisms. One possible explanation is the suppression of the activity of HMG-CoA reductase, a key regulatory enzyme that plays a central role in the synthesis of cholesterol within the body. By inhibiting this enzyme, cholesterol production may be significantly reduced. Another contributing mechanism might involve the inhibition of fat absorption in the intestines, thereby limiting the amount of dietary lipids entering systemic circulation. Both of these processes help decrease the overall lipid buildup and fat storage in tissues, which are commonly associated with metabolic disturbances seen in Streptozotocin-induced diabetic rats. Other mechanisms could be that L-Arginine and L-Glutamate bound to cholesterol, forming complexes thereby making it unable to be absorbed from the intestinal tract resulting to increased excretion of cholesterol (Atangwo *et al.,* 2012). Alternatively, it could be that the supplements could have caused this feat by reduction of enterohepatic circulation of bile acids leading to increased conversion of cholesterol to bile acids which is enhanced by the liver; an overall action which will cause reduced serum cholesterol.

The fact that the cholesterol concentration of the L-Arginine group showed more significant reduction compared to that of L-Glutamate group could be indicative that L-Arginine has higher affinity to cholesterol hence binds more strongly leading to formation of complexes which renders more cholesterol moieties unavailable for absorption (Tall *et al*., 2022). Another possible explanation is that L-Arginine inhibited the activity of HMG-COA reductase more than L-Glutamate which led to a more significant reduction in serum total cholesterol concentration as seen in the result.
High density lipoprotein is known to incite its artherogenic potential either by reversing cholesterol pathway through removing low density lipoprotein from the plasma and non-hepatic cells, or by inhibiting oxidation of low density lipoprotein (Tall *et al*., 2022). High density lipoprotein binds to cholesterol in the blood and transport it to the liver where they bind to specific receptors (SR-B1 receptors) hence, transferring the cholesterols and its esters to the liver. Cholesterol is converted to bile salts within the liver and secreted to the gall bladder for storage (Madsen *et al.,* 2017). The free high density cholesterol is then returned to the plasma for another cycle of cholesterol transport. The higher concentration of high density lipoprotein seen in the groups treated with *L*-Arginine compared to that of the group treated with L-Glutamate could be indicative that L-Arginine may have better atherogenic index potential and might prevent lipid peroxidation more than L-Glutamate.

Low density lipoprotein (LDL) has been implicated as a leading predisposing factor in the pathogenesis of cardiovascular diseases as it aids in the transport of cholesterol via the arteries (Pradhan et al., 2022). LDL has been shown to invade the endothelium where they induce endothelial damage, causing oxidative stress, inflammation and

worsen obesity especially in oxidized state (Roffi *et al*., 2016). Increases LDL concentration has also been linked to other conditions including atherosclerosis, stroke, peripheral vascular diseases and heart attack.

The reduced concentration of low density lipoprotein as seen in the groups treated with L-Arginine and L-Glutamate is indicative of their anti-hyperlipidaemic potential and agrees with the result of Eraga *et al*., (2022) that stated that administration of anti-hyperlipidemic materials leads to reduced serum LDL-cholesterol concentration. The reductions in concentration of low density lipoprotein was more pronounced and significantly lower in the group treated with L-Arginine compared to that of the group treated with L-Glutamate. This could be indicative that L-Arginine had more anti-hyperlipidemic activity compared to L-glutamate and could be a good management therapy for the prevention of LDL-induced disease conditions such as stroke, arteriosclerosis, cardiovascular diseases and obesity. Since (Obidike *et al*., 2023) has shown correlation between anti-diabetic properties and anti-hyperlipidemic potentials in medicinal plants, it could also be said that L-Arginine and L-glutamate could have antidiabetic properties and could be used in the management of diabetes mellitus. Pancreatic β-cells produce ROS as a result of the toxic effects of the hyperglycemic environment, which also compromises the mitochondrial respiratory chain and NADPH oxidase (Zheng *et al*., 2018). Pro-inflammatory cytokines and inflammatory markers, such as TNF-α and anti-inflammatory cytokines, are also produced in greater amounts (Wronka *et al.,* 2022). Excessive oxidant levels also cause the pro-inflammatory cytokines IL-1 and IL-18 to be expressed, which accelerates ageing and worsens cellular damage (Martinez de Toda *et al.,* 2021). Elevated levels of reactive oxygen species (ROS) and pro-inflammatory cytokines hinder mitochondrial function, augment insulin resistance, and trigger pancreatic β-cell apoptosis, all of which culminate in type 2 diabetes (T2DM) (Oguntibeju, 2019).

An increase in TNF-α and IL-1 B have been linked with the pathogenesis of diabetic neuropathy (Pușcașu *et al*., 2023). The significant reduction in TNF-α with concomitant reduction in IL-1B noticed across the treatment groups could be indicative of reversal of the toxicity and reduction in inflammation caused by Streptozotocin which agrees with the report of Pușcașu *et al*., (2023) that antioxidant factor reduces the toxicity and could further be indicative that the supplements could have anti-inflammatory potentials. It is noteworthy to indicative that L-arginine showed the most anti-inflammatory potential shown by the lowest IL-1B and TNF-α as seen in the result.

LDH plays a role in catalyzing pyruvate into lactic acid through the process of glycolysis in which $NADH_2$ acts to donate electrons (Malicka *et al*., 2016). Though the activity of LDH and its isoenzymes help in screening the progression of diseases including some tumours such as lymphoma and myocardial infarction, recent studies have shown that LDH activities increase in worsening diabetes mellitus hence could be used as a biomarker to determine the progression of DM (Dmour *et al*., 2020). The significant increase noticed in the Streptozotocin group is indicative of DM while the significant decrease in the activity of LDH across the treatment groups is indicative of reversal of the toxicity hence, ameliorative effect of the supplements. The most significant decrease of LDH activity in the L-Arginine group compared to the L-Glutamate group and the group co-treated L-Arginine and L-Glutamate could be indicative that L-Arginine has higher anti-hyperglycemic potential compared to L-glutamate.

CONCLUSION

From the study above, it could be concluded that L-Arginine and L-glutamate both have anti-hyperglycemic, anti-inflammatory and anti-hyperlipidemic potential. However, it could be better concluded that L-Arginine showed higher ability to reverse the toxicity induced by Streptozotocin compared to L-Glutamate, hence, showed higher anti-hyperglycemic, anti-inflammatory and anti-hyperlipidemic potential compared to L-Glutamate. Meanwhile, the combination of L-Arginine and L-Glutamate showed antagonist effect compared to L-Arginine alone.

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