

Protective effect of Glutathione Against D-Galactos Induced Physiological and Lipid Alterations in the Central Nervous System of Female Rats

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Received: 27/11/2025

Accepted: 10/12/2025

Published: 15/3/2026

Abstract— This study is carried out to investigate the protective role of decreased glutathione female rats' central nervous systems from harm brought on by D-galactose excess. Ten of the forty adult female rats, both weighting two hundred grams, had been separated among 4 distinct groups. The initial grouping (G1) received a control injection of normal saline intraperitoneal (IP) for 40 days, Within the latter category (G2), D-galactose was injected during an amount about one hundred milligrams per kilogram of B.W. on a daily basis IP in forty days; within the next group (G3), glutathione (GSH) was injected via the peritoneum (IP) for forty days at a daily dosage of 100 mg/kg B.W. every day to stay for forty days in addition, in the final group (G4), D- galactose and the antioxidant glutathione were combined (G4).

The research study was carried out at the laboratories of the College of Veterinary Medicine at the University of Kerbala in Iraq. By analyzing fasting plasma samples taken by the heart puncture procedure at 40 forty-one days throughout the research, the composition of lipid profile (total cholesterol levels (TC), triglycerides, (TAG), and levels in the serum of high- density cholesterol from lipoprotein (HDL-C), extremely low-density cholesterol from lipoprotein (LDL-C), and exceptionally low density cholesterol from lipoprotein (VLDL C) have been determined. In comparison to the control and G3 groups, The findings showed a significant by p 0.05 raised serum pain in the second generation category and a considerable (p<0.01) elevation in plasma beta amyloid concentrations among the second phase and The fourth group categories. Serum cholesterol levels in the G2 category were significantly higher (p<0.05) than in the G1, G3, and G4 categories.

When comparing the G2 group to the G1, G3, and G4 groups, there was a substantial (p<0.05) rise in serum triglycerides. In contrast to the 1 categories , 3 categorie, and 4 categories classifications, the G2 group there was a substantial (p<0.01) drop in serum high-density lipoproteins and cholesterol. In

contrast to the initial group, the third group, and G4 categories groups, the second group there was a significant (p<0.01). rise in serum low-density lipoproteins and cholesterol. A serum A significant difference (p<0.05) was seen between the second group and the G1 group. Group3, and G4 groups rise in very low-density lipoproteins and cholesterol.

Keywords — lipid profile, female rats, D-galactose, glutathione, serum beta-amyloid, and acetylcholine esterase.

INTRODUCTION

The monosaccharide D-galactose (D-gal) shares the same molecular formula as glucose, which is C₆H₁₂O₆, structure is identical to that of glucose, with the exception of one hydroxyl group, which gives galactose distinct chemical and biological characteristics from glucose (1). A reducing sugar called D-gal causes oxidative stress, which changes mitochondrial dynamics and causes neurones to die (2). With average concentrations, D-gal is converted to galactose-1-phosphate by an enzyme called D-galactokinase or galactose-1-phosphate uridyl-transferring enzymes, although not at high doses, Instead, at greater doses, d-gal is converted to galactitol, the latter of that accumulates in cellular and results in reactive oxygen species (ROS) and osmotic strain (3).

Through raising the rate of apoptosis, oxidative stress, and inflammatory reactions, an endogenous doses of D-galactose, given at levels around standard might have an aging adverse impact on a number of tissues (2, 4). D-galactose administration to animals can cause brain ageing in many ways similar to human brain ageing effects, such as memory deficit, neuronal degeneration and apoptosis, increased oxidative stress, reduced ATP synthesis, elevated mutations in DNA contained in mitochondria, compromised respiratory function, and regulation of aberrant gene transcription in the brain (4, 5, 6). In addition to being targets for ROS, mitochondria are a major source of intracellular ROS production. Oxidative damage brought on by ROS can result in mitochondrial dysfunction, which produces more ROS. Both oxidative mitochondrial

damage and the harmful effect of the ROS yielding process greatly accelerate aging (7).

Chronic inflammation and oxidative stress brought on by long-term D-galactose (D-gal) injections can accelerate aging. Studies on anti-aging have frequently employed models of rapid aging associated with prolonged D-gal administration to account for the increase in persistent inflammatory processes and cognitive impairment, which are similar to the normal aging of animals. Rats aged by D-gal have enhanced vascular development, reduced inflammatory and apoptosis rates, and better cognition and blood-brain barrier functioning. (8). The primary non-protein thiol that protects toward damage from oxidation is glutamate (GSH), a tripeptide that's made up of L-glutamyl-L-cysteinylglycine which is present throughout every tissues of mammals at amounts between 1 to 10 mM (with the greatest concentrations in the liver). Glutathione is also a key regulator of electrochemical signaling; it controls inflammation, immune function, the death of cells, and cell proliferation and is necessary for international detoxifying Glutathione (GSH) is an antioxidant found in plants, mammals, fungi, as well as some bacteria and archaea, Glutathione can protect critical cellular components from damage caused by reactive oxygen species such as free radicals, peroxides, lipid peroxides, and heavy metals. (Pompella et al., 2003).

GSH can lower ROS and lipid peroxidation levels, as well as neutrophil infiltration (10). Several pathologic conditions including hypoxia, ischemia/reperfusion damage, aging, liver illnesses, and neurological illnesses, are influenced by GSH, indicating that it plays a significant role in pathophysiology and biomedical therapies aiming at increasing GSH levels. (11). Glutathione is the most commonly used oral dietary supplement; it can also be utilized as a lotion (12). The study aimed to assess the impact of D-galactose as an oxidative stressor on the CNS and the protective role of glutathione. The following parameters were measured, serum beta amyloid levels. Measuring serum Acetylcholine Esterase levels. Lipid profile (TC, TG, HDL, LDL, and VLDL).

MATERIALS AND MTHODS

Experimental protocol:

The study used 40 white female albino rats weighing between 190 and 210g from the College of Pharmacy at the University of Kerbala in Iraq. The rats were aged between 12 and 14 weeks and were housed in special plastic cages with adequate ventilation. Twelve hours per day plus a relative humidity of fifty percent five percent were the settings for the light arrangement. During a two-week period, animals were housed to become used to the standard experimental arrangement.

Experimental Design:

Forty white albino rats were randomly assigned to four groups (10 per group) and treated as follows for six weeks. G1 (injection intraperitoneal): Rats in this group were injected with merely regular saline (0.1 ml) as a control. G2: With this particular population of animals, one hundred mg/kg of B.W. of D-galactose was injected intraperitoneal (13). G3: one hundred mg/kg of by weight of glutamate was injected

intraperitoneally into the animals in this group (14) G4: Subcutaneous doses of one hundred mg/kg of B.W. of D-galactose and Hundred mg/kg B.W. of Glutathione were administered to the animals in this category.

Collect of the blood samples :

The creatures were starved before samples of their blood were obtained. The chloroform injection was used to anesthetize the animals following subsequent 6 weeks study in order to quiet and supervise animals earlier than the final sample collection. Using sterilized medicinal instruments, (5m/L) of plasma was drawn directly from the animal's circulation through a heart puncture while it was lying on its back. The resultant blood was subsequently placed in The serum had been separated by centrifuged around (50) thousand r/min for (10 min) in a customized gel container without an anticoagulant being added, Following separation, the serum was put in Eppendorf tubes and kept frozen between -20 and -22 °C until the measurements were finished.

1. Plasma beta amyloid evaluation: an ELISA kit was used to assess serum mouse caspase-3. The Sandwich-ELISA testing technique is applied in this Immunoassay kit. An antibody designed for rats has been coated beforehand onto the micro ELISA plate included within this kit.

Serum acetylcholine esterase (AChE) amount determination: An ELISA kit was employed to determine the amount of blood rats AChE. The ELISA sandwich technique is applied in this particular Immunoassay kit. An antibody specific to Rat AChE was recently coated beforehand onto the micro-ELISA plates included by this package.

Serum cholesterol evaluation: Measurement of Serum Total Cholesterol (TC) Amount (milligrams per deciliter): The chromatographic approach outlined by the researchers Allain and colleagues (15) has been employed for detecting the level of total cholesterol (TC).

Serum Triglycerides (TAG) Amount in milligrams per deciliter Measurement: The The researchers Fossati and Prencipe technique, which is linked to the Trinder phenomenon, was used to detect the amount of total serum triglycerides. Mechanism of process (16).

The highest-density lipoprotein (HDL-C) concentration in serum (mg/dL) can be found by: The blood's lower density lipoprotein concentration was determined by enzymes using a high density cholesterol (HDL-C) kit in the research study with (17).

Calculating the Serum Lower Density Protein Cholesterol (LDL-C) Percentage (mg/dL): The serum LDL cholesterol percentage was determined using the (LDL -C = Total cholesterol - (HDL -C + TG/5) (18) equation.

Serum Extremely low-density lipoprotein cholesterol (VLDL-C) measurement Percentage (mg/dL): Using a formula (18), the serum very low density cholesterol-lipoprotein content was determined.

Statistical analysis: The results from each of the 5 procedures in the current research were statistically analyzed (SPSS) utilizing a one-way analysis of variance (ANOVA) with statistically significant values (P<0.01) as well as (P<0.05).

RESULT AND DISCUSSION

a substance called beta-galactose, and their combined effects on a few neurometer in adult female rats.

Effects against beta amyloid (pg /mL) in adult female rats of D-galactose, the antioxidant glutathione and the combination of them.

Following six weeks, the primary plasma beta-amyloid value in G1 (control) and all 3 groups receiving treatment throughout the experimental investigation demonstrates, the serum beta-amyloid value in the G2 treated group increases significantly ($p \leq 0.01$) compared to the group's first phase, G 3, and fourth group G4. However, compared to the G1 and third groups, there is an important rise ($p \leq 0.01$) in the fourth group. However, there is no statistically significant distinction between the first group and G3 grouping categories ($p \geq 0.01$). At the conclusion of the trial, the mean values for the Control, D-gal, Clusters of Glutathione and Glutathione+D-gal were 12.7 ± 3.33 , 26.78 ± 4.47 , 8.55 ± 1.37 , and 20.31 ± 1.95 , respectively. (LSD = 8.2499).

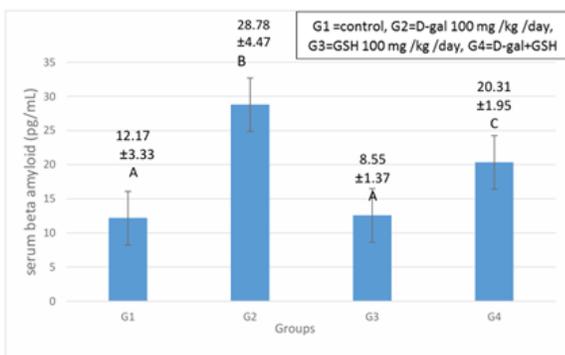


Figure 1. Effects on adult female rats of D- galactose, glutathione, and their combination beta amyloid (pg/ml).

Effect of D-galactose, glutathione and their combination on Acetylcholinesterase (AChE) in adult female rats.

After six weeks, the G2 treated group's primary blood AChE concentration value reveals a substantially higher ($p \leq 0.05$) value than the G1, G3, and G4 groups. In contrast to G1 and G3, G4 shows a substantial rise ($p \leq 0.05$). However, there is no discernible difference ($p \geq 0.05$) between G1 and G3. For groups Control, D-gal, GSH, and GSH+D-gal, the primary acetylcholinesterase values were 6.17 ± 0.77 , 21.12 ± 2.19 , 5.21 ± 0.75 , and 13.15 ± 3.55 , respectively (LSD=6.9706).

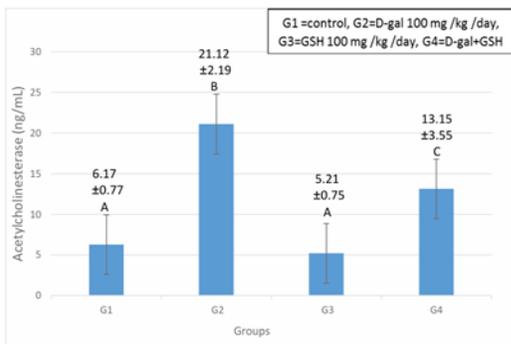


Figure 2. Impact of the antioxidant glutathione, D-galactose, and the two together on adult female rats' acetylcholinesterase, also called AChE

Impact of glutathione and D-galactose together on the serum lipid profile in older female rats:

Effects of D-galactose, glutathione and related combined on Serum Cholesterol (mg/dl) in adult female rats:

Compared to the first group, G3, and G4 groups, the primary cholesterol level value of the second category is considerably higher ($p \leq 0.05$). Additionally, no significant ($p \geq 0.05$) difference is observed within the first category, G3, and The fourth categories. The experiment's mean values for the Control, D-gal, and 309.67 groups were 311.20 ± 29.01 , 338.52 ± 13.79 , and 317.60 ± 38.91 , respectively. respectively, GSH and GSH+D-gal (LSD=104.81).

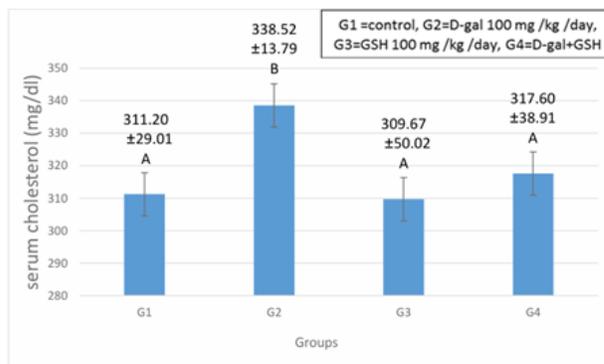


Figure 3. Effect of D-galactose, glutathione and their combination serum cholesterol (mg/dl) concentration in female rats.

Impact of the individual components of the antioxidant glutathione, and their combined use on adult female rats' circulating triglycerides (TG) (mg/dl):

According to Comparing the participants in the G2 (D-gal) category to the 1 group, 3group, as well as G4 groups, the primary serum TG value indicates a substantial rise ($p \leq 0.05$) as well as the differences among controls) G1(control), (G3)GSH, and (G4) D-gal + GSH are not significant ($p \geq 0.05$). At the conclusion of the investigation, the average results were 89.51 (G2), 59.87 (G1) ± 1.45 .

LSD=20.819 for categories controls, D-gal, GSH, and GSH+D-gal, whereas the values were ± 10.80 , 47.15 ± 3.79 , and 64.89 ± 8.06 .

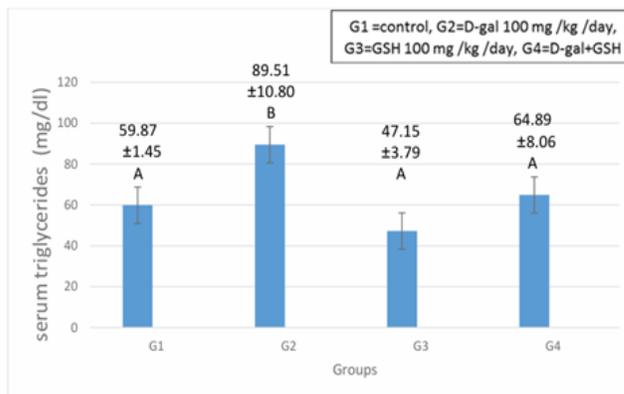


Figure 4. Effect of D-galactose, glutathione and their combination serum triglycerides concentration(mg/dl) in female rats.

Effect of D-galactose, glutathione and their combination on serum High-density lipoproteins-cholesterol (HDL-c) concentration (mg/dl) in male rats:

Comparing group G2 to groups G1, G3, and G4, the mean value of serum HDL-c shows a substantial drop ($p < 0.01$). The G1, G3, and G4 groups do not vary significantly ($p \geq 0.01$) however, At the conclusion of the trial, the mean values for the Control, D-gal, GSH, and GSH+D-gal groups were 105.18 ± 15.95 , 89.29 ± 12.71 , 110.54 ± 15.14 , and 100.63 ± 14.81 , respectively (LSD=11.286).

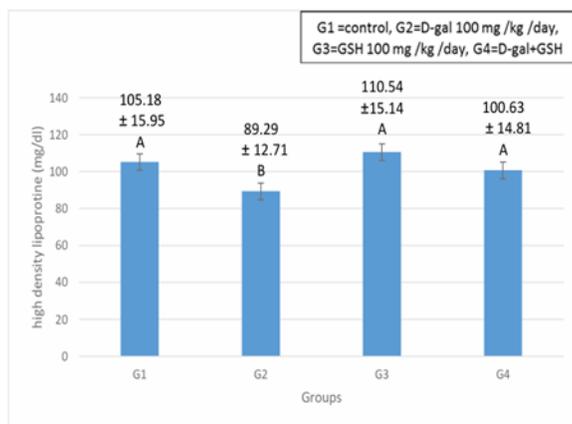


Figure 5. The impact of D- galactose, glutathione, and their combination on the percentage of cholesterol in HDL-c (milligrams per deciliter) in female rats' serum.

Impact of amino acids glutathione and D-galactose, and their combined consumption on the blood blood levels of lipoproteins with a low density and cholesterol (LDL-c) (milligrams per decilitre) in female rats:

The fundamental serum LDL-c level of the second group exhibits a significant increase ($p < 0.05$), in comparison with the G1, the third group, as well as The fourth recommendation categories. There is no significant variation ($p \geq 0.05$) among the 1, 3, and 4 groups. AtFollowing the end of the trial, the overall mean results for the categories control, D-gal, GSH, as well as GSH combined with D- gal were 172.27 ± 21.57 , 200 ± 17.21 , 169.81 ± 34.14 , and 175.99 ± 33.3 , correspondingly (LSD=21.277).

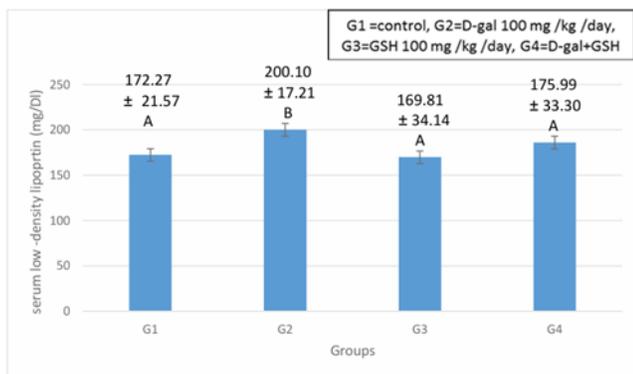


Figure 6. Impact of the antioxidant glutathione, D-galactose, and the combination of them on the quantity of lipoproteins

with a low density and cholesterol (LDL-c) in female rodents' serum (milligrams per deciliter).

amino acids Glutathione and D-galactose, and their combination's effects on serum VLDL-c (very lower-density lipoproteins) cholesterol The level in female rats (milligrams per deciliter)

Compared to the G1, G3 and G4 groups, the G2 group's primary serum VLDL-c value shows a substantial rise ($p \leq 0.05$). G1 and G3 do not differ significantly ($p \geq 0.05$) from one another. The Control, D-gal, GSH, and GSH+D-gal groups had mean values of 11.97 ± 0.30 , 17.90 ± 2.16 , 9.43 ± 0.75 , and 12.97 ± 1.61 at the conclusion of the trial, respectively (LSD=4.1638).

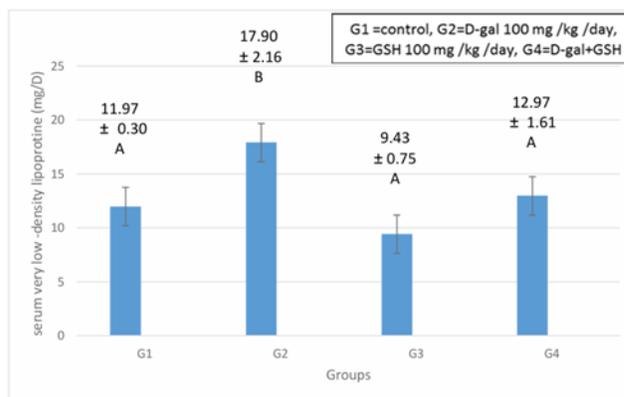


Figure 7. Effects of glutathione, D-galactose, and their combination on the amount of very low-density lipoproteins-cholesterol (VLDL-c) in female rats' blood (milligrams per deciliter).

Glutathione, D-galactose and their interaction's impact on serum beta-amyloid levels.

In contrast with the remaining category, the D-gal-injected subgroup's beta amyloid concentrations were noticeably greater ($p \leq 0.01$). Additionally, this finding concur with (19). Increases in beta amyloid are caused by an increase in ROS, which causes brain ageing and neuronal degeneration (20). The incomplete reduction of molecular oxygen produces radicals and compounds known as ROS. They are created in modest quantities during oxygen metabolism, resulting from four sequential 1-electron reductions of O_2 that lead to the creation of H_2O . They are essential for signalling and for preserving cellular homeostasis (21).

Free radicals can induce the production of $A\beta$, This implies that the pathophysiology of sporadic Alzheimer's disease involves mitochondrial malfunction at an early stage. Mitochondrial dysfunction and increased ROS production are linked to the ageing process, $A\beta$ may hasten the processing of amyloid-genic APP by causing oxidative stress and mitochondrial dysfunction (22). The enzyme β -secretase cleaves APP at position 671 in the extracellular domain, releasing the soluble ectodomain (sAPP- β), γ secretase processes the remaining C-terminal fragment (CTF- β) to release the $A\beta$ peptide and AICD fragment (23).

Glutathione, D-galactose, and their combination's effects on serum acetylcholinesterase (AChE):

When contrasted with the other study participants, the D-gal injected group showed a significant ($p \leq 0.01$) increase in (AChE) levels. Additionally, this is in line the (24,25). Amyloid plaques encircled by elevated acetylcholinesterase (AChE) activities are found in the central nervous system of AD patients (26, 27). In recent years, acetylcholinesterase (AChE) in Alzheimer's disease sufferers' brains has attracted a lot of attention; AChE activity increases close to beta-amyloid plaque, and the beta-amyloid peptide (Abeta) can change AChE levels, even though the AD brain generally declines. There is evidence that AChE and amyloid levels may change simultaneously in Alzheimer's disease (28,29).

Cytochemical studies have shown that the AChE associated with senile plaques is enzymatically distinct from the AChE associated with neurones in various ways, Biochemical investigations have shown that AChE causes amyloid fibril production and the creation of highly poisonous AChE-Abeta complexes. Although AChE can accelerate amyloid production, AChE inhibitors may be a viable therapy option for Alzheimer's disease because of the neurotoxicity produced by AChE-Abeta complexes, which showed that they induce higher neurodegeneration than the Abeta peptide alone (30).

Impact on the serum cholesterol levels of D-galactose, glutathione, and their combo:

According to our research, the D-gal group had a significantly decreased HDL-c concentration and a substantially greater lipid profile (TG, TC, and VLDL-c) than the remainder of the groups. Beta-cell malfunction affects the metabolism of lipids and its micro- and macro-vascular ramifications, and dyslipidaemia has a reciprocal influence on the beta-cell functioning. It's unknown how each of these distinct yet detrimental effects interact. collaborating, researchers will outline According to recent research, controlling the quantities of the two kinds of cholesterol in the blood is essential for lowering cardiovascular risk, but it ought to be taken into account to prevent beta-cell dysfunction and the development of type 2 diabetes (31).

According to studies, low HDL-C and LDL-C high levels are separate risk factors for beta-cell dysfunction. In light of this, several researchers have elucidated the presence of particular LDL-C receptors, specifically LRP, in pancreatic islets and shown that LDL-C particles are highly selectively integrated into the metabolic pathway of beta-cells. This enhanced bioavailability of LDL-C in pancreatic cell metabolism seems to have a cytotoxic effect and may result in an increase in beta-cell apoptosis (32).

Circulating LDL-C levels are determined by hepatic production, intestinal absorption, and biliary excretion. Furthermore, these cholesterol levels are controlled by the intracellular pool and cholesterol uptake via the activation of the particular membrane receptor for LDL lipoproteins. However, the control of lipid metabolism in diabetes is exceedingly complex, including several carrier lipoproteins and enzyme systems that are only poorly understood. Low HDL-C

levels are frequently associated with hypertriglyceridemia, particularly in those with insulin resistance (33).

CONCLUSION

Based on the results and analysis of this investigation, it may be inferred that: A 6-week intraperitoneal injection in female rats of one hundred milligrams per kilogram B.W. of D-galactose resulted in oxidative stress, a marked increase in serum levels of beta amyloid, acetyl, TC, TG, LDL, and VLDL, and a marked decrease in serum HDL concentrations. The glutathione group that received an adequate dosage did not differ significantly from the control group.

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