Asian J Biol Life Sci., 2026; 15(2):303-311.
https://ajbls.com

Review Article

Enhanced Antidiabetic Efficacy of Tetrahydrocurcumin and Galiic Acid on Hepatic and Renal Functional Markers and Protein Levels: A Comparative Study in Albino Wistar Rats

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ABSTRACT

Background: Diabetic hepatopathy and nephropathy is the leading cause of end stage hepatic and renal disease in the Western world. In Streptozotocin (STZ)-induced diabetic male albino rats, the antidiabetic and hepato-renal protective combined effects of Tetrahydrocurcumin (THC) and Gallic Acid (GA) were examined. **Materials and Methods:** The combination of Tetrahydrocurcumin (THC) and Gallic Acid (GA) shows a greater effect on antidiabetic and antioxidant effect. The present study aimed to investigate the modulatory effects of THC and GA on liver and kidney markers and protein levels in Streptozotocin (STZ) - induced diabetic rats. **Results:** When diabetic rats were given a combination of THC (60 mg/kg) and GA (15 mg/kg body weight) orally for 45 days, their blood glucose levels significantly decreased and their plasma insulin levels significantly increased. Serum bilirubin, Alanine Transaminase (ALT), Aspartate Transaminase (AST), Alkaline Phosphatase (ALP), urea, and creatinine levels were significantly higher in the diabetic rats treated with THC and GA at the end of treatment compared to the diabetic control rat group. When compared to the diabetic control rat group, the serum levels of these liver and kidney-related indicators were considerably lower in the diabetic rats treated with THC and GA. In addition, compared to control rats, the diabetic rats showed decreased levels of plasma total protein, albumin, globulin, and albumin/globulin ratio. Total protein, albumin, globulin, and the albumin/globulin ratio restored nearly normal levels after treatment with a combination of THC and GA. When compared to control rats, the activities of hepatic and renal indicators were significantly higher in diabetic rats; however, THC and GA treatment decreased these parameters restored to near normal levels. **Conclusion:** Treatment with THC and GA reversed these parameters to almost normal levels in diabetic rats, which reduced levels of urea, uric acid, and creatinine with increasing levels. Histopathological analysis of the liver and kidney sections complemented these analytical findings. The combination of THC and GA was more potent than treatment with THC or GA alone in the rats.

Keywords: Gallic Acid, Kidney Markers, Liver Markers, Tetrahydrocurcumin, Uric Acid.

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Received: 02-04-2026;
Revised: 22-05-2026;
Accepted: 17-07-2026.

INTRODUCTION

Diabetes mellitus constitutes a major global health concern, affecting hundreds of millions of people. The main causes consist of a deficiency in insulin, insulin resistance, or a combination of these two factors. The resulting hyperglycemia is closely linked to serious macrovascular and microvascular complications, which encompass cardiovascular diseases, retinopathy, neuropathy, and nephropathy (American Diabetes Association 2009). The International Diabetes Federation reports that there are presently 589 million adults between the ages of 20 and 79 who are living with diabetes. This number is projected to rise to 853 million by 2050, with diabetes responsible for 3.4 million fatalities in 2024, which translates to one death every 9 sec. According to data from the World Health Organization, approximately 830 million individuals globally are affected by diabetes, with a significant proportion residing in low and middle income nations. Alarmingly, more than half of those diagnosed with diabetes are not receiving appropriate treatment. In recent decades, there has been a steady increase in both the prevalence of diabetes and the number of cases that remain untreated (Gupta *et al.*, 2026). The STZ-induced

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DOI: 10.5530/ajbls.20260001

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diabetes model in experimental animals is extensively utilized to investigate the pathophysiology of diabetes as well as potential treatment approaches. STZ is a naturally occurring nitrosourea compound that specifically targets pancreatic β-cells by means of DNA alkylation and the production of Reactive Oxygen Species (ROS), resulting in β-cell necrosis and a deficiency in insulin (Murugan *et al*., 2008). Additionally, STZ-induced diabetes results in significant alterations in gene expression across various tissues, such as the pancreas, liver, kidney, adipose tissue, and skeletal muscle, reflecting systemic metabolic dysregulation (Sudarshan *et al*., 2025).

Hepatopathy and nephropathy are major contributors to end-stage renal disease, and together with the rising global incidence of diabetes, they create a significant strain on healthcare systems. Diabetes mellitus is the most prevalent of the endocrine disorders and poses a significant risk to global health care. The rise of toxicity mediated by free radicals is well established in rats with streptozotocin-induced diabetes. The liver is the primary organ responsible for regulating plasma glucose levels within a tight range. Hyperglycemia can create a redox imbalance within the cells, particularly in the liver (Gallou *et al*., 1993). An ideal antidiabetic medication must exhibit both hypoglycemic and antioxidant characteristics, free from any negative side effects. Plant-based drugs are often regarded as being less harmful than synthetic alternatives (Ramesh and Pugalendi, 2000).

The liver and kidneys significantly contribute to the development of type 2 diabetes. Nephrotoxicity is a significant adverse effect of pharmacological treatment in clinical settings, often resulting in acute kidney injury. Numerous physiological mechanisms have been associated with renal damage induced by streptozotocin in diabetes (Murugan and Pari, 2007a; Murugan *et al*., 2022). In diabetes mellitus, numerous proteins undergo non-enzymatic glycation and are believed to play a role in the disease's long-term complications (Murugan and Pari, 2006[a]). Increased focus on alternative medicines and natural therapies has sparked a fresh wave of research interest in conventional practices, highlighting the necessity to seek more effective agents with reduced side effects. There is an increasing interest in herbal treatments lately because of the side effects linked to the current oral hypoglycemic drugs used for managing diabetes mellitus (Kim *et al*., 2006).

THC is one of the major colourless metabolite of curcumin. THC has been reported to exhibit the same physiological and pharmacological properties of curcumin (Pari and Murugan 2007[a]). Curcumin is rapidly metabolized during absorption from the intestine, yielding THC, which has shown the strongest antioxidant activity among all curcuminoids (Murugan and Pari 2006[a]). Several studies in experimental animals indicated that anti-inflammatory, anti-cancer, anti-aging, hepatoprotective (Pari and Murugan 2004), renal-protective (Pari and Murugan 2006[b]), neuron-protective (Pari and Murugan 2007[b]), fatty acid composition (Murugan and Pari 2007[a]), brain lipid peroxidation (Murugan, 2023[a]), glycoprotein components (Pari and Murugan 2007[b]) and the status of insulin receptors in type 2 diabetes (Murugan, 2023[b]). Reports indicate possible effects of THC on collagen levels in tail tendons (Pari and Murugan 2007[c]), hyperlipidemia (Murugan and Pari, 2006[b]) and erythrocyte membrane bound enzymes (Murugan and Pari 2007[c]). Several studies have highlighted the hypoglycemic effects of THC, suggesting it may enhance insulin secretion and reduce hepatic gluconeogenic enzyme activities in diabetic animals (Pari and Murugan, 2005; Gajendhini and Murugan, 2025[b]). Consequently, THC demonstrates several advantageous effects against human diseases (Lai *et al*., 2020). GA, a naturally occurring phenolic compound present in various fruits and medicinal plants, demonstrates significant antioxidant, cardioprotective, analgesic, neuroprotective, anti-inflammatory and anticancer properties (Tsai *et al*., 2021). Research has shown that GA can reduce hyperglycemia, enhance insulin secretion, and increase antioxidant levels (Hadidi *et al*., 2024). Its capacity to regulate gene expression is linked to its antioxidant properties and its effect on transcription factors like PPAR-γ and NF-κB (Fu *et al*., 2025).

Recent research suggests that employing combination therapy with natural compounds may provide enhanced therapeutic benefits due to their additive interactions (Akinwumi and Ambali 2026). Previous studies have shown that combination of THC and GA improve glycemic control, increase insulin sensitivity, and protect pancreatic β-cells, in addition to improving antioxidant status (Gajendhini and Murugan 2025[b]), lipid metabolism and fatty acid composition (Gajendhini and Murugan 2026[a,b]).

To our knowledge, no other biochemical studies have yet examined the combined impact of THC and GA on hepatic and renal functional markers and protein levels in experimental diabetic rats. The current study was conducted to examine the combined impact of THC and GA on liver and kidney function indicators and protein levels in rats with diabetes induced by STZ.

MATERIALS AND METHODS

Animals

Eight-week-old male albino Wistar rats, weighing between 180 and 220 g, were sourced from the Central Animal House at J.J College of Arts and Science in Pudukkottai, affiliated with Bharathidasan University, Tiruchirappalli. All animal studies received approval from the ethical committee (JJC/BC/AH/002/2025) at J.J College of Arts and Science and complied with the protocols set by the National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, India. The animals were kept in polycarbonate enclosures within a room that had a 12-hr light-dark cycle, a temperature of 24±2°C, and humidity levels ranging from 45 to 64%. Throughout the entire experimental duration, the animals were provided with a balanced

commercial diet (Hindustan Lever Ltd., Mumbai, India) and had free access to water.

Chemicals

THC was provided by Sabinsa Corporation, USA. GA was acquired from Sigma Chemicals Corporation, St.

Experimental induction of diabetes

Experimental animals were administered a newly prepared solution of STZ (55 mg/kg) in 0.1 M citrate buffer at pH 4.5, delivered intraperitoneally at a volume of 1 mL/kg. Normal rats were administered 1 mL of citrate buffer as the vehicle. Blood glucose levels were measured 72 hr following STZ administration. The experiment involved rats exhibiting moderate diabetes characterized by glycosuria and hyperglycemia (blood glucose levels between 200-300 mg/dL).

Experimental design

Group I: Normal rats.

Group II: Diabetic control rats (Diabetes was induced by intraperitoneal STZ injection (55 mg/kg, pH 4.5in citrate buffer solution).

Group III: Diabetic rats administered with combined phytochemicals THC (60 mg/kg body weight) and GA (15 mg/kg body weight) in aqueous solution daily using an intragastric tube for 45 days (Gajendhini and Murugan, 2026c).

Group IV: Diabetic rats given THC (80 mg/kg body weight) in aqueous solution daily using an intragastric tube for 45 days (Murugan *et al*., 2026a).

Group V: Diabetic rats given GA (20 mg/kg body weight) in aqueous solution daily using an intragastric tube for 45 days (Yu *et al*., 2021).

After 45 days, the animals were starved for one night and then euthanized by decapitation. Blood was drawn into tubes with a potassium oxalate and sodium fluoride combination for blood glucose measurement. Plasma was isolated for the measurement of insulin. Gathering urine through the use of metabolic cages with animals housed overnight.

Analytical methods

Blood glucose and HOMA were measured colorimetrically using commercial diagnostic kits from Sigma Diagnostics (I) Pvt Ltd, Baroda, India (Lott and Turner, 1975). Plasma insulin, leptin, and QUICKI were measured by ELISA with a Boehringer-Mannheim kit using an ES300 Boehringer analyzer (Mannheim, Germany).

Total protein and albumin kit, Biuret and BCG Dye Binding method for *in vitro* estimation- Diagnostics. Serum enzymatic activities of aspartate transaminase, alanine transaminase, alkaline phosphatase, and gamma glutamyl transpeptidase were determined on fully automated chemistry analyzer Roche/Hitachi-912 (Roche Diagnostics, Manheim, Germany) using Roche Diagnostics GmbH kits. The values were expressed as IU/L serum.

The levels of urea, ureic acid, creatinine, albumin and total protein were estimated spectophotometrically according to the standard procedures using commercially available diagnostic kits (Sigma Diagnostics (I) Pvt Ltd, Baroda, India).

Histopathological study

The liver and kidney samples fixed for 48hr in 10% formal-saline were dehydrated by passing successfully in different mixture of ethyl alcohol - water, cleaned in xylene and embedded in paraffin. Sections of liver and kidney (4-5 μm thick) were prepared and then stained with hematoxylin and eosin dye, which mounted in neutral Deparaffinated Xylene (DPX) medium for microscopic observations.

Statistical analysis

The biochemical parameter data were evaluated through analysis of variance, and Duncan's multiple range test was utilized to compare the group means. Values were deemed statistically significant when $p<0.05$ (Duncan, 1957)

RESULTS

Table 1 presents the blood glucose levels and plasma insulin concentrations for various experimental groups. The rats with diabetic control exhibited a notable rise in blood glucose, leptin, and HOMA levels, accompanied by a significant decline in plasma insulin and QUICKI levels. The oral administration of a combination of THC and GA to diabetic rats notably reversed the biochemical alterations mentioned above. The administration of THC and GA to normal rats revealed a substantial impact on blood glucose, leptin, HOMA, QUICKI, and plasma insulin levels. The combination of THC and GA administration demonstrated greater effectiveness than THC alone or GA alone.

Table 2 displays the levels of total protein, albumin, and globulin in the plasma of both normal and diabetic rats. The diabetic rats exhibited lower levels of plasma total protein, albumin, globulin, and albumin/globulin ratio in comparison to normal rats. Following treatment with a combination of THC and GA, total protein, albumin, globulin, and the albumin/globulin ratio were restored to levels close to normal. The protective effect of THC was stronger in comparison to GA

Table 3 illustrates the impact of tetrahydrocurcumin on alterations in the activities of serum aspartate transaminase, alanine transaminase, alkaline phosphatase, and gamma glutamyl transpeptidase in both normal and experimental rats. The levels of hepatic markers were notably increased in diabetic rats in comparison to control rats. The treatment with THC and GA for

diabetic rats significantly reversed the aforementioned changes in comparison to the diabetic control rats. The impact of THC was more noticeable in comparison to GA.

Table 4 displays the serum levels of urea, uric acid, and creatinine in both control and diabetic rats. In our research, the concentrations of urea, uric acid, and creatinine are significantly higher in the serum of diabetic rats than in control rats. Diabetic rats administered a combination of THC and GA exhibited a restoration of these parameters to nearly normal levels. The impact of THC was stronger than GA.

Table 5 presents the urine output along with the concentrations of urea, uric acid, creatinine, and albumin found in the urine of diabetic rats. Diabetic rats exhibited reduced urea, uric acid, and creatinine levels, along with elevated albumin levels; treatment with THC and GA restored these parameters to nearly normal levels

Pathological changes of liver (Figure 1a) include sinusoidal congestion and fatty degeneration in the form of fat lake in diabetic control rats (Figure 1b). The above pathological changes were remarkably reduced in rats combination treated with THC and GA, with mild portal inflammation with near normal appearance (Figure 1c). Diabetic rats treated with THC showed mild sinusoidal dilatation and focal kupffer cell hyperplasia (Figure 1d) and GA showed mild sinusoidal dilatation and congestion (Figure 1e).

Diabetic control rat kidney (Figure 2a) showed fatty infiltration (Figure 2b). The above pathological changes were remarkably reduced in rats combination treated with THC and GA, with mild parenchymal inflammation (Figure 2c). Diabetic rats treated with THC showed parenchymal inflammation and necrotic areas (Figure 2d) and GA showed cloudy swelling of tubules (Figure 2e).

DISCUSSION

Complications from diabetes typically result in liver and kidney impairments, which explains the common occurrence of diabetic hepato- and nephropathies in persons with type 1 and type 2 diabetes mellitus (Murugan and Pari, 2007[a]). Non-alcoholic fatty liver disease is typically marked by increased serum concentrations of aspartate and alanine aminotransferases, γ-glutamyl transferase, alkaline phosphatase, and bilirubin (Sattar *et al.*, 2014; Murugan and Sakthivel, 2021; Murugan *et al.*, 2022). It is linked to an increased occurrence of chronic kidney disease and retinopathy in individuals with type 1 and type 2 diabetes, regardless of various confounding factors (Murugan and Pari, 2007[a]).

Table 1: Effect of THC and GA on hormone and glucose index parameters in normal and experimental animals.

Parameters	Normal	Diabetic control	Diabetic + THC and GA	Diabetic + THC	Diabetic + GA
Glucose (mg/dL)	86.87±4.87[a]	141.54±4.54[b]	88.54±4.45[a]	102.65±4.25[c]	99.41±4.50[c]
Leptin (ng/mL)	0.57±0.02[a]	1.83±0.03[b]	0.59±0.03[a]	0.75±0.02[c]	0.70±0.03[c]
Insulin (μU/mL)	48.70±3.60[a]	85.13±4.16[b]	50.45±3.70[a]	68.40±3.71[c]	64.70±3.30[c]
HOMA	11.12±1.20[a]	31.55±2.31[b]	12.15±1.37[a]	16.52±1.55[c]	16.01±1.41[c]
QUICKI	1.59±0.11[a]	0.90±0.02[b]	1.50±0.11[a]	1.17±0.04[c]	1.22±0.06[c]

Values are expressed as Mean ± SD for 6 rats. Statistical analysis of one-way ANOVA, post-hoc followed by DMRT test using SPSS ver. 24. Mean values are within the row followed by different letters, superscript (homogeneous subsets) are mentioned as statistically significant ($P<0.05$) while same letter was statistically non-significant ($P>0.05$) from each other groups.

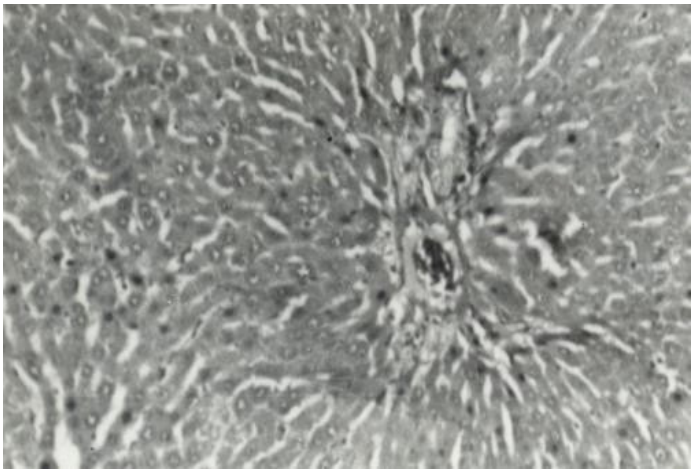

Figure 1a: Normal rat liver. Normal architecture of liver.

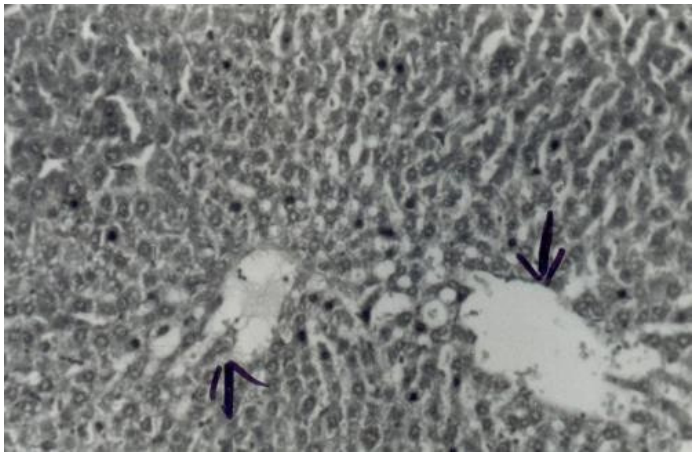

Figure 1b: Diabetic rat liver. Sinusoidal congestion and fatty degeneration in the form of fat lake ( ).

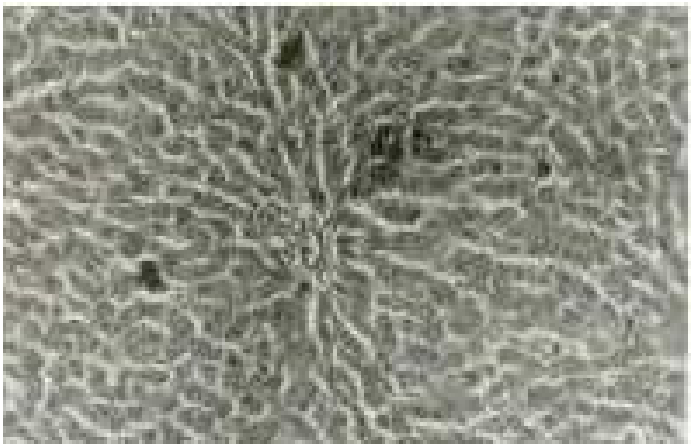

Figure 1c: Diabetic + THC and GA treated rat liver. Mild portal inflammation with near normal appearance.

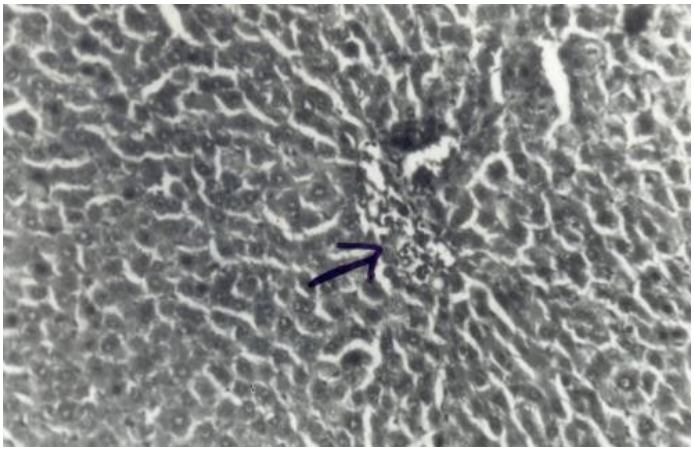

Figure 1d: Diabetic + THC treated rat liver. Mild sinusoidal dilatation and focal kupffer cell hyperplasia.

Table 2: Effect of THC and GA total protein, albumin, globulin and albumin/globulin ratio in plasma in normal and experimental animals.

Groups	Total protein (g/dL)	Albumin (g/dL)	Globulin (g/dL)	A/G ratio
Normal	7.63±0.33a	4.00±0.06a	3.63±0.26a	a 1.15 ± 0.01
Diabetic control	4.44±0.2b	2.16±0.07b	2.28±0.20b	b 0.89 ± 0.04
Diabetic + THC and GA	7.58±0.25a	3.92±0.11a	3.61±0.14a	a 1.14 ± 0.01
Diabetic + THC	7.07±0.19c	3.64±0.07c	3.46±0.12c	c 1.05 ± 0.01
Diabetic + GA	7.15±0.22c	3.78±0.09c	3.49±0.13c	c 1.04 ± 0.01

Values are given as Mean ± S.D for 6 rats in each group. Values not sharing a common superscript letter differ significantly at $p<0.05$ (Duncan's multiple range test).

The liver has been linked to the development of type 2 diabetes. It is crucial for the regulation of normal glucose levels, and liver impairment due to insulin resistance syndrome has been proposed as a precursor to type 2 diabetes. In diabetes, increased liver enzymes such as ALT, AST, GGT, and ALP are typical hepatic indicators of liver stress, damage, and Non-Alcoholic Fatty Liver Disease (NAFLD), which is closely associated with insulin resistance and metabolic syndrome. These markers, notably GGT and ALT, may indicate the risk of diabetes, as elevated levels frequently associate with a heightened risk; however, it's essential to monitor liver health in uncontrolled T2DM for improved management and to exclude liver complications (Nguyen *et al.*, 2011). Earlier research indicates that protein synthesis diminishes across all tissues due to reduced ALP production in cases of absolute or relative insulin deficiency (James *et al.*, 2017), potentially leading to lower plasma protein levels, including albumin and globulin, which may be associated with elevated plasma insulin levels in diabetics undergoing treatment with a combination of THC and GA. Takeuchi *et al.* (2021) indicated that the A/G ratio in plasma was decreased in diabetic animals. Elevated protein breakdown in diabetics may have caused a direct negative impact on albumin production and release. Diabetic rats administered a combination of THC and GA returned their A/G ratio to almost normal levels

Multiple observational studies have shown that liver enzymes such as Aspartate Aminotransferase (AST), alanine aminotransferase (ALT), and Gamma-Glutamyl Transferase (GGT) are positively associated with the risk of diabetes mellitus and metabolic syndrome, particularly serum GGT (Zheng *et al.*, 2022; Nano *et al.*, 2017). The liver is essential for regulating glucose metabolism homeostasis, and levels of liver enzymes are positively linked to liver injury. Serum ALT and AST are released from damaged liver cells. GGT is abundantly found on cell membrane surfaces and plays a crucial role in glutathione metabolism. Glutathione serves as a crucial antioxidant within cells, closely linked to tissue inflammation and oxidative stress (Van Beek *et al.*, 2013; Hogg *et al.*, 1997; Wickham *et al.*, 2011), both of which significantly contribute to the onset of insulin resistance (Yan *et al.*, 2019).

In our study, the activities of serum transaminases were found to be elevated in diabetic rats. In this context, several investigators reported the increase in the activities of AST and ALT in the liver

Table 3: Effect of THC and GA on serum Aspartate Transaminase (AST), Alanine Transaminase (ALT), Alkaline Phosphatase (ALP) and Gamma Glutamyl Transpeptidase (GGT) in normal and experimental animals.

Parameters	Normal	Diabetic control	Diabetic + THC and GA	Diabetic + THC	Diabetic + GA
ALT (IU/dL)	26.13±0.48[a]	46.97±1.89[b]	27.91±0.44[a]	34.24±0.81[c]	34.31±0.36[c]
AST (IU/dL)	58.38±0.53[a]	86.70±1.35[b]	59.12±0.63[a]	62.61±0.75[c]	61.98±0.71[c]
ALP (IU/dL)	60.20±1.23[a]	92.40±2.58[b]	61.80±1.07[a]	78.30±1.48[c]	76.81±0.52[c]
GGT (IU/L)	a 12.25±0.65	b 31.26±1.55	a 13.34±0.77	c 17.65±1.08	c 18.78±1.05

Values are given as Mean ± S.D for 6 rats in each group. Values not sharing a common superscript letter differ significantly at $p<0.05$ (Duncan's multiple range test).

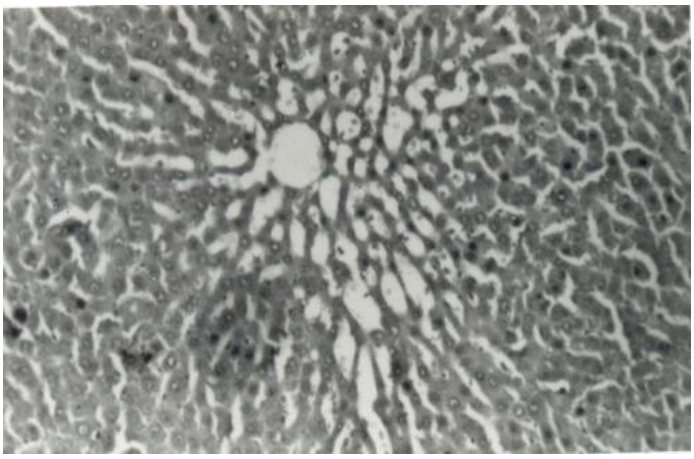

Figure 1e: Diabetic+GA treated rat liver. Mild sinusoidal dilatation and congestion. Histopathological changes in liver of normal and experimental rats. All the sections are in H&E x 20

and serum of STZ diabetic rats (Ghanbari *et al.*, 2013; Singh *et al.*, 2001; Prakasam *et al.*, 2004). The alterations in serum enzyme levels are directly linked to shifts in the metabolism in which these enzymes participate. The heightened protein breakdown associated with gluconeogenesis in the diabetic condition could explain the increased activities of these enzymes, which were nearly normalized by THC and GA administration. This outcome indicates that the combination effects of THC and GA normalize hepatocellular injury and inhibit gluconeogenesis.

In diabetes, increased Alkaline Phosphatase (ALP) usually indicates complications such as vascular calcification, bone disorders (diabetic bone disease), liver issues, and deteriorating kidney function, serving as an indicator for heart disease and mortality; however, elevated ALP levels might also be connected to inflammation, highlighting the importance of ALP isoenzyme (bone, liver, intestinal) analysis for pinpointing the origin and extent of the disease (Zhao *et al.*, 2020). Under this condition, elevated activity has been observed for glucose-6-phosphatase and fructose-1,6-bisphosphatase in the liver. These phosphatases are different enzymes from ALP. Vella *et al.* (2017) noted that due to overlapping substrate specificity exhibited by the phosphatases and the potential presence of an increased ALP in the tissues of diabetic individuals. The serum ALP activity was noted to rise in rats with STZ-induced diabetes. Conversely, the administration of THC to diabetic rats brought ALP activity back to its normal levels.

Based on the findings mentioned, STZ-induced diabetes plays a crucial role in modifying liver functions, as the activities of AST, ALT, ALP, and GGT showed significant increases. Nonetheless, the THC therapy for diabetic rats greatly diminished the functions of serum enzymes. In our earlier report, it was noted that THC treatment showed no significant alterations in serum enzyme activities in normal rats (Adelakun *et al.*, 2024; Ghanbari *et al.*, 2016), indicating that the drug is non-toxic to the mammalian system.

Increased Gamma-Glutamyl Transferase (GGT) levels serve as a robust, independent indicator for the onset of Type 2 Diabetes and are associated with insulin resistance, oxidative stress, and inflammation, even when within normal limits, possibly indicating early metabolic issues. Although GGT shows liver health, its increased levels in diabetes imply it signifies metabolic problems such as fatty liver and oxidative stress, thus serving as a valuable biomarker for evaluating risk (Bo *et al.*, 2005). GGT is a cytosolic enzyme present in extremely high levels in the liver. This aligns with previous studies (Cho *et al.*, 2023), which demonstrated a significant rise in GGT expression in the livers of diabetic rats. Increased GGT activity in serum occurs due to oxidative damage in the liver (Whitfield, 2001). Moreover, hepatocellular injury or cholestasis might also play a role in the increase in activity. The elevated GGT activity in STZ-induced diabetic rats was reduced to nearly normal levels by THC and GA treatment, suggesting that THC and GA may help prevent necrosis.

Creatine is a compound that serves as a high-energy phosphate source that tissues can use for ATP (Adenosine Triphosphate) production. Creatine is obtained from dietary sources or produced from the amino acids arginine, glycine, and methionine, with this production taking place mainly in the liver and kidneys, though other organs might also play a role. Creatine and phospho-creatine non-enzymatically transform into the metabolite creatinine, which diffuses into the bloodstream and is eliminated by the kidneys. Creatinine is produced naturally from

phospho-creatine and is exclusively removed from the body by the kidneys (Kreider and J Stout, 2021).

Urea is synthesized in the liver through the urea cycle to eliminate surplus nitrogen from the body. Urea enters the blood, accumulates in the kidneys, and is eliminated through urine. Urea is present in various bodily fluids, including gastric acid, sweat, and saliva. Under typical circumstances, twenty to thirty percent of the synthesized urea is broken down by bacterial urease activity in the gastrointestinal system (Zhou *et al.*, 2019). Diabetic hyperglycemia and creatinine are viewed as key indicators of kidney function (Butt *et al.*, 2024), along with reduced urea, uric acid, and creatinine levels, and elevated urine output, which mirror the current findings. THC and GA treatment mirrors the current outcome. THC and GA treatment

Table 4: Effect of THC and GA on urea, ureic acid, creatinine, sodium and potassium in normal and experimental animals.

Parameters	Normal	Diabetic control	Diabetic + THC and GA	Diabetic + THC	Diabetic + GA
Urea (mg/dL)	24.01±0.63[a]	44.78±1.36[b]	23.50±0.61[a]	27.21±0.40[c]	26.97±0.42[c]
Ureic acid (mg/dL)	1.15 ± 0.05[a]	2.45 ± 0.14[b]	1.17 ± 0.05[a]	1.38 ± 0.07[c]	1.41 ± 0.06[c]
Creatinine (mg/dL)	0.71±0.02[a]	1.36±0.05[b]	0.73±0.01[a]	0.89±0.02[c]	0.91±0.02[c]
Sodium (mEq/L)	155.91±2.93[a]	187.52±4.36[b]	157.49±3.26[a]	165.13±2.58[c]	163.28±2.77[c]
Potassium (mEq/L)	4.95±0.14[a]	2.71±0.15[b]	4.87±0.11[a]	4.12±0.09[c]	4.25±0.10[c]

Values are given as Mean ± S.D for 6 rats in each group. Values not sharing a common superscript letter differ significantly at $p<0.05$ (Duncan's multiple range test).

Table 5: Effect of THC and GA on urea in urine, ureic acid, creatinine and albumin, urine in normal and experimental animals.

Groups	Urea in urine (mg/dL)	Ureic acid (mg/dL)	Creatinine (mg/dL)	Albumin (μg/dL)	Urine volume (mL/day)
Normal	a 149.87±7.45	a 8.15±4.47	a 2.88 ±0.16	a 151.56±7.15	a 9.98±0.42
Diabetic control	b 115.71±7.45	b 5.45±0.35	[b] 1.79± 0.11	b 319.78 ± 14.47	b 21.42± 1.39
Diabetic+ THC and GA	[a] 144.45±8.47	a 7.95±4.79	a 2.81±0.15	a 147.47±7.43	a 9.39 ± 0.50
Diabetic+ THC	C 130.19 ± 8.87	c 7.14±0.37	c 2.59±0.15	c 164.38±9.35	c 11.84± 0.65
Diabetic + GA	c 128.43 ± 7.05	c 7.03±0.12	c 2.55±0.12	c 159.17± 9.01	c 11.51± 0.60

Values are Mean ± SD for 6 rats in each group. Values not sharing a common superscript letter differ significantly at $p< 0.05$ (Duncan's multiple range test).

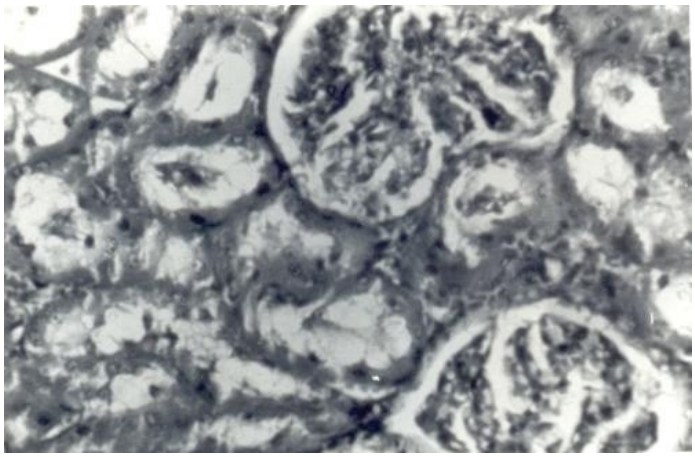

Figure 2a: Normal rat kidney. Normal architecture of kidney.

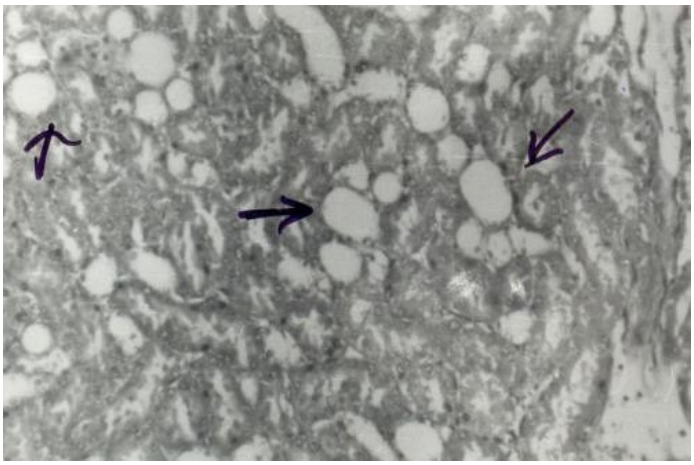

Figure 2b: Diabetic rat Kidney. Fatty infiltration (→).

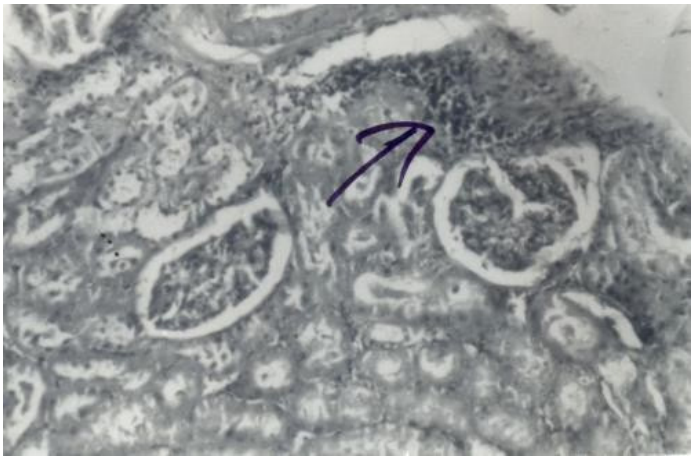

Figure 2c: Normal + THC and GA treated rat kidney. Mild parenchymal inflammation (→).

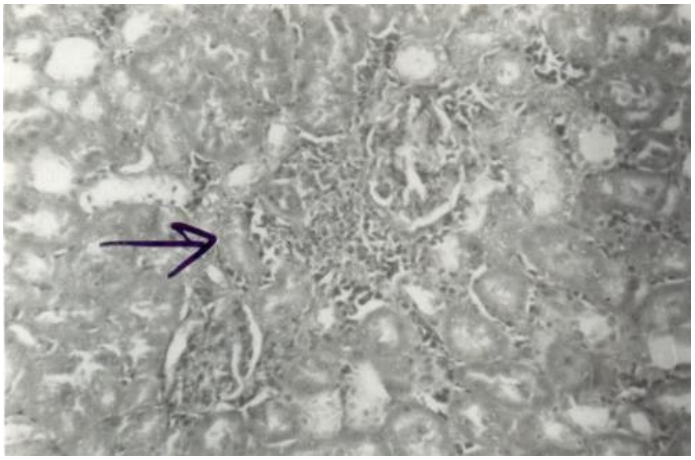

Figure 2d: Diabetic+ THC treated rat kidney. Parenchymal inflammation and necrotic areas (→).

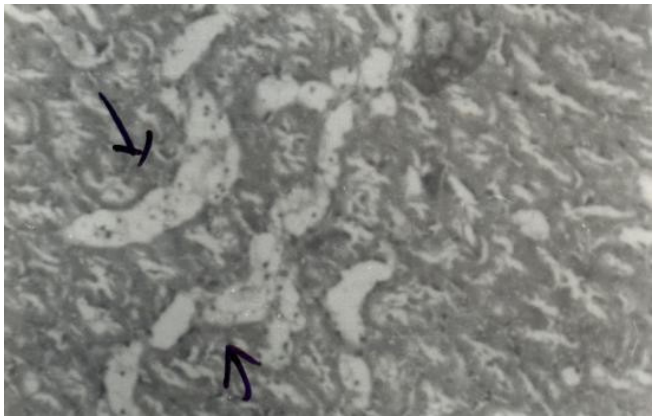

Figure 2e: Diabetic+ GA treated rat kidney. Cloudy swelling of tubules (→). Histopathological changes in kidney of normal and experimental rats. All the sections are in H & E x 20.

restored these parameters to nearly normal levels, likely due to reduced metabolic irregularities in other pathways like protein and nucleic acid metabolism, as indicated by enhanced glycemic control.

CONCLUSION

The activities of hepatic and renal markers were significantly elevated in diabetic rats when compared to normal rats. Combination treatment with THC and GA reduced the liver markers and recover the kidney tissue from the damage by hyperglycemia induced oxidative insult, by improve in glycemic control and defense mechanisms. From the results, it is concluded that combination of THC and GA has possessed a strong protective effect against hepatic and renal function in diabetic rats. The combination of THC and GA administration showed more effective than THC and GA.

ABBREVIATIONS

STZ: Streptozotocin; **THC:** Tetrahydrocurcumin; **GA:** Gallic Acid; **ALT:** Alanine Transaminase; **AST:** Aspartate Transaminase; **ALP:** Alkaline Phosphatase; **HOMA:** Homeostatic Model Assessment; **QUICKI:** Quantitative Insulin Sensitivity Check Index.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Cite this article: Murugan P, Gajendhini S, Malarvili T, Marudhadurai T, Suganthi K, Sakthivel V. Enhanced Antidiabetic Efficacy of Tetrahydrocurcumin and Galiic Acid on Hepatic and Renal Functional Markers and Protein Levels: A Comparative Study in Albino Wistar Rats. Asian J Biol Life Sci. 2026;15(2):303-11.