

Antidiabetic Effect of Tetrahydrocurcumin and Gallic Acid on Plasma Antioxidants in Streptozotocin Induced Experimental Diabetes

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ABSTRACT

Background: Diabetes mellitus is a chronic condition associated with vascular damage and complications, whereas Tetrahydrocurcumin (THC)-a stable derivative of curcumin-and Gallic Acid (GA)-a natural plant polyphenol-both possess potent antioxidant and anti-inflammatory properties capable of mitigating oxidative cellular damage. **Objectives:** This study aimed to evaluate the combined impact of THC and GA on antioxidant status, glycaemic indices, and lipid peroxidation in Streptozotocin (STZ)-induced diabetic rats. **Materials and Methods:** Diabetes was induced in rats using STZ, resulting in hyperglycaemia, reduced insulin, decreased antioxidants, and elevated lipid peroxidation. Diabetic rats were orally administered a combination of THC (60 mg/kg) and GA (15 mg/kg body weight) daily for 45 days. Parameters evaluated included plasma insulin levels, lipid peroxidation markers (Thiobarbituric Acid Reactive Substances [TBARS] and lipid hydroperoxides), and antioxidant levels (Vitamin C, Vitamin E, reduced glutathione, and ceruloplasmin). **Results:** STZ-induced diabetic rats exhibited reduced insulin, elevated hyperglycaemia, increased lipid peroxidation (TBARS and lipid hydroperoxides), and decreased antioxidant levels (Vitamin C, Vitamin E, reduced glutathione, and ceruloplasmin). Oral co-administration of THC and GA for 45 days resulted in a significant elevation of plasma insulin and antioxidant levels, along with a marked reduction in lipid peroxidation, demonstrating greater efficacy than either THC or GA administered alone. **Conclusion:** The combined oral administration of THC and GA effectively improves antioxidant defenses, enhances insulin levels, and reduces lipid peroxidation in STZ-induced diabetic rats, outperforming individual treatments.

Keywords: Diabetes mellitus, Gallic acid, Plasma antioxidants, Plasma lipid peroxidation, Streptozotocin, Tetrahydrocurcumin.

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INTRODUCTION

Chronic elevated blood sugar initiates a cascade of events that results in the production of excessive free radicals. These unstable molecules inflict cellular damage and significantly contribute to the development of long-term health issues associated with diabetes, including damage to blood vessels, nerves, and organs (Caturano *et al.*, 2023). The oxidative stress experienced in diabetes is exacerbated as high blood sugar levels generate an overabundance of free radicals while simultaneously diminishing the body's inherent antioxidant defences (Li and Shen, 2019).

In recent years, extensive research has focused on innovative plant-based antioxidants as alternatives to synthetic food additives, aiming to alleviate oxidative stress (Sundaram *et al.*, 2015).

Finding new plant antioxidants is a major goal for science today. Scientists examine leaves, roots, and fruits to identify natural substances that safeguard human cells from harm (Murugan, 2021a; Pung Rozar *et al.*, 2024). The use of natural products for diabetes management has gained considerable popularity, as conventional medications such as insulin and oral tablets may lead to adverse effects, including hypoglycaemia or weight gain. Nevertheless, it is important to note that natural products and herbs can also produce side effects or interact with other medications, indicating that they are not entirely devoid of risks (Manzoor *et al.*, 2026).

Although traditional medicinal plants provide significant therapeutic compounds and have a long-standing history of



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dietary application, the notion that they are completely "free from side effects" is misleading. Herbal and plant-based treatments can still lead to adverse reactions, toxicity, or harmful interactions with synthetic drugs (Murugan *et al.*, 2020; Murugan, 2022; Murugan, 2023). Phytochemicals derived from plant sources are utilised in the prevention and treatment of conditions such as cancer, heart disease, diabetes, and hypertension, among others (Murugan, 2010; Kooti *et al.*, 2016).

GA and THC are both naturally occurring plant phenols recognised for their antioxidant and anti-inflammatory effects. THC is a primary colourless metabolite derived from curcumin. It has been documented that THC shares similar physiological and pharmacological characteristics with curcumin. During intestinal absorption, curcumin is swiftly metabolised into THC, which has demonstrated the most potent antioxidant activity among all curcuminoids (Murugan and Pari, 2007). Numerous studies conducted on experimental animals have indicated that THC can inhibit cancer (Shu *et al.*, 2020), provide protection against inflammation (Zeng *et al.*, 2025), atherosclerotic lesions (Naito *et al.*, 2002), hepatotoxicity (Pari and Murugan, 2004), nephrotoxicity (Pari and Murugan, 2006), and diabetes mellitus (Murugan and Pari, 2006a). GA, a naturally occurring phenolic compound found in a variety of fruits and medicinal plants, exhibits considerable antioxidant, cardioprotective, analgesic, neuroprotective, anti-inflammatory, and anticancer effects (Tsai *et al.*, 2021). Studies have indicated that GA can lower hyperglycaemia, boost insulin secretion, and elevate antioxidant levels (Hadidi *et al.*, 2024). Its ability to modulate gene expression is associated with its antioxidant effects and its influence on transcription factors such as PPAR- γ (Fu *et al.*, 2025).

The integration of natural bioactive compounds with traditional therapies presents a robust medical approach to enhance therapeutic results, address drug resistance, and reduce harmful side effects. Prior research has indicated that the combination of THC and GA enhances glycaemic control, boosts insulin sensitivity, and safeguards pancreatic β -cells (Murugan *et al.*, 2026), lipid metabolism (Gajendhini and Murugan, 2026a), and fatty acid composition (Gajendhini and Murugan, 2026b). To our knowledge, no other biochemical studies have been conducted on the synergistic effects of THC and GA regarding the expression of key genes associated with glucose metabolism and insulin signalling in experimental diabetic rats.

MATERIALS AND METHODS

Animals

Adult male albino Wistar rats (8 weeks), weighing 180 to 200 g bred in the Central Animal House at J.J College of Arts and Science in Pudukkottai, which is affiliated with Bharathidasan University in Tiruchirappalli. These rats were housed in polypropylene cages within a pathogen-free environment, maintained at an ambient temperature of 28 ± 2 °C and a relative

humidity of 45-55%, with a 12-hr cycle of light and dark. The rats were provided with a pellet diet from Hindustan Lever Ltd., India, and had access to water *ad libitum*. The animals were cared for in accordance with the guidelines established by the National Institute of Nutrition, Indian Council of Medical Research, Hyderabad, India, and received approval from the Institutional Animal Ethical Committee at J.J College of Arts and Science in Pudukkottai (JJC/BC/AH/002/2025).

Drugs and chemicals

THC was a gift provided by Sabinsa Corporation, USA. GA was purchased from Sigma Chemical Company, St. Louis, MO, USA, and all other chemicals utilised were of analytical grade sourced from Himedia, Mumbai, India.

Induction of diabetes

Experimental animals were given a freshly prepared solution of STZ (55 mg/kg) in 0.1 M citrate buffer at pH 4.5, administered intraperitoneally at a volume of 1 mL/kg (Furman, 2021). Normal rats received 1 mL of citrate buffer as a control. The animals were allowed to drink a 20% glucose solution overnight to mitigate drug-induced hypoglycaemia. Control rats were provided with the same volume of isotonic saline. After a period of 72 hours, plasma glucose levels were assessed, and those rats with fasting glucose levels exceeding 250 mg/dL were identified as diabetic rats and included in the current study.

Experimental design

The animals were divided into five groups of six animals in each group (24 diabetic and 6 normal). Group I: Normal rats. Group II: Diabetic control rats. Diabetes was induced by intraperitoneal STZ injection (55 mg/kg, pH 4.5 in 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, 2025). Group IV: Diabetic rats given THC (80 mg / kg body weight) in aqueous solution daily using an intragastric tube for 45 days (Pari and Murugan, 2007). Group V: Diabetic rats were given GA (20 mg/kg body weight) in aqueous solution daily using an intragastric tube for 45 days (Wong *et al.*, 2022). At the end of 45 days, the animals were deprived of food overnight and sacrificed by decapitation. Blood was collected in tubes containing potassium oxalate and sodium fluoride mixture for the estimation of blood glucose. Plasma was separated for the estimation of insulin and other biochemical parameters.

Analytical procedure

Measurement of hormone and glucose index parameters

Blood glucose were estimated colorimetrically using commercial diagnostic kits (Sigma Diagnostics (I) Pvt. Ltd., Baroda, India) (Lott and Turner, 1975). Plasma insulin were assayed by ELISA

using a Boehringer-Mannheim kit with an ES300 Boehringer analyzer (Mannheim, Germany).

Estimation of Lipid peroxidation

Lipid peroxidation in plasma was assessed colorimetrically by quantifying Thiobarbituric Acid Reactive Substances (TBARS) and hydroperoxides, utilising the methodologies established by Fraga *et al.* (1988) and Jiang *et al.* (1992), respectively. In summary, 0.5 mL of plasma was combined with 2 mL of a TBA-Trichloroacetic Acid (TCA)-HCl reagent (composed of 0.37% TBA, 0.25 N HCl, and 15% TCA in a 1:1:1 ratio), incubated for 15 min in a water bath, and subsequently cooled. The mixture was then centrifuged for 10 min at 1000 rpm at room temperature, and the resulting clear supernatant was analysed at 535 nm against a reference blank.

Hydroperoxides were quantified in mmoles/dL. A plasma sample of 0.5 mL was combined with 0.9 mL of Fox reagent, which consisted of 88 mg of BHT, 7.6 mg of xylenol orange, and 0.8 mg of ammonium iron sulfate dissolved in 90 mL of methanol and 10 mL of 250 mmoles sulfuric acid. The mixture was incubated at 37 °C for 30 min. The resulting colour intensity was measured at a wavelength of 560 nm.

Estimation of ascorbic acid (Vitamin C)

Vitamin C levels were determined according to the procedure outlined by Omaye *et al.* (1979). A sample of 0.5 mL was mixed with 1.5 mL of 6% TCA and centrifuged for 20 min. From the supernatant, 0.5 mL was taken and combined with 0.5 mL of DNPH reagent, mixed thoroughly, and allowed to stand at room temperature for 3 hr. Afterward, 2.5 mL of 85% sulfuric acid was added, and the mixture was allowed to sit for 30 min. Standards ranging from 10-50 µg of ascorbic acid were processed in the same way, along with a blank, and the absorbance was recorded at 530 nm. The results for ascorbic acid were expressed in mg/dL of plasma.

Estimation of Vitamin E

Vitamin E was analysed using the method established by Baker *et al.* (1951). To 0.1 mL of plasma, 1.5 mL of ethanol and 2.0 mL of petroleum ether were added, mixed thoroughly, and then centrifuged. The resulting supernatant was evaporated to dryness at a temperature of 80 °C. Subsequently, 0.2 mL of a 2,2'-dipyridyl solution and 0.2 mL of a ferric chloride solution were added. The mixture was well combined and kept in the dark for 5 min before adding 2 mL of butanol. The intense red colour that developed was measured at 520 nm. Standard tocopherol concentrations ranging from 10-100 µg were prepared and treated in the same manner, alongside a blank that contained only the reagents. The quantity of α-tocopherol was reported as mg/dL of plasma. The protein content was determined using the method described by Lowry *et al.* (1951).

Estimation of Ceruloplasmin

Plasma ceruloplasmin levels were determined using the method established by Ravin (1961). A volume of 0.05 mL of plasma was introduced. For the control, 1 mL of sodium azide was added and thoroughly mixed. Subsequently, 1.0 mL of p-phenylenediamine was added to both tubes, mixed, and incubated at 37 °C for 1 hr. Following this, 1 mL of sodium azide was added to the test sample. All tubes were then stored at a temperature range of 4 to 10 °C for 30 min. The resulting colour was measured at 540 nm, using the control as a blank. The ceruloplasmin concentrations were reported in mg/dL.

Estimation of reduced glutathione

The determination of Reduced Glutathione (GSH) was conducted using the method established by Ellman in 1959. An aliquot of 1.0 mL from the supernatant was combined with 0.5 mL of Ellman's reagent and 3.0 mL of phosphate buffer (0.2 M, pH 8.0), after which the absorbance was measured at 412 nm. The activity of GPx was quantified as µg of GSH consumed per minute per milligram of protein, while GSH levels were reported in mg per dL of plasma.

Statistical analysis

The data for various biochemical parameters were analysed using Analysis of Variance (ANOVA), and the group means were compared by Duncan's Multiple Range Test (DMRT). Values were considered statistically significant if $p < 0.05$ Duncan (1957).

RESULTS

Changes in blood glucose and plasma insulin

Figure 1 illustrates the blood glucose levels and plasma insulin concentrations across different experimental groups. The diabetic control rats exhibited a notable rise in blood glucose levels, accompanied by a significant reduction in plasma insulin concentrations. The oral administration of a combination of THC and GA to diabetic rats successfully reversed these biochemical alterations. In normal rats, the treatment with THC and GA significantly influenced both blood glucose and plasma insulin levels. The combination therapy of THC and GA demonstrated greater efficacy compared to the administration of either THC or GA alone.

Effect of THC and GA on plasma lipid peroxidation

Diabetic rats that were not treated exhibited a notable rise in the levels of lipid peroxide and TBARS in their plasma (Table 1). In contrast, rats that received a combination treatment of THC and GA displayed significantly reduced levels of plasma lipid peroxide and TBARS when compared to the untreated diabetic rats. Additionally, the simultaneous administration of THC and GA proved to be more effective than administering THC or GA individually.

Effect of THC on plasma antioxidants

Plasma levels of GSH and Vitamin C were markedly reduced in diabetic rats compared to normal rats, while plasma ceruloplasmin and α -tocopherol levels were significantly elevated in diabetic rats relative to their normal counterparts. Conversely, diabetic rats that received a combination treatment of THC and GA exhibited plasma antioxidant levels that were nearly normal (refer to Table 2). The concurrent administration of THC and GA demonstrated greater efficacy than the administration of either THC or GA alone.

DISCUSSION

STZ induces hyperglycaemia by specifically targeting and destroying pancreatic β -cells through the action of Reactive Oxygen Species (ROS). Elevated sugar levels lead to oxidative stress, resulting in lipid peroxidation and a reduction in antioxidant defenses, which is why STZ-rodent models are commonly used for evaluating new antidiabetic and antioxidant therapies (Aboonabi *et al.*, 2014). Pancreatic beta cells are particularly susceptible to nitric oxide and ROS due to their naturally low levels of free

radical scavenging antioxidant enzymes (Eleazu *et al.*, 2013). STZ directly causes lipid peroxidation through the generation of oxygen free radicals (Stadler *et al.*, 2009). Consequently, this study was conducted to evaluate the antiperoxidative effects of THC and GA in STZ diabetic rats. The findings indicated that a 45-day combination treatment with THC at a dosage of 60 mg/kg body weight and GA at 15 mg/kg body weight significantly lowers blood glucose levels in STZ-induced diabetic rats. The potential mechanisms through which THC and GA exert their antihyperglycemic effects may involve stimulating pancreatic insulin secretion from the remaining β -cells, enhancing the transport of blood glucose to peripheral tissues, or decreasing glucose absorption from the gastrointestinal tract.

Non-enzymatic glycosylation leads to the formation of detrimental advanced glycation end-products, while glucose autooxidation results in elevated levels of harmful oxidative stress. Additionally, the polyol pathway reduces protective cellular antioxidants such as NADPH and causes the accumulation of intracellular sorbitol. (Hussain *et al.*, 2025). Hyperglycaemia has a direct impact on the balance between pro-oxidants and antioxidants, producing an overabundance of free radicals that systematically damage both

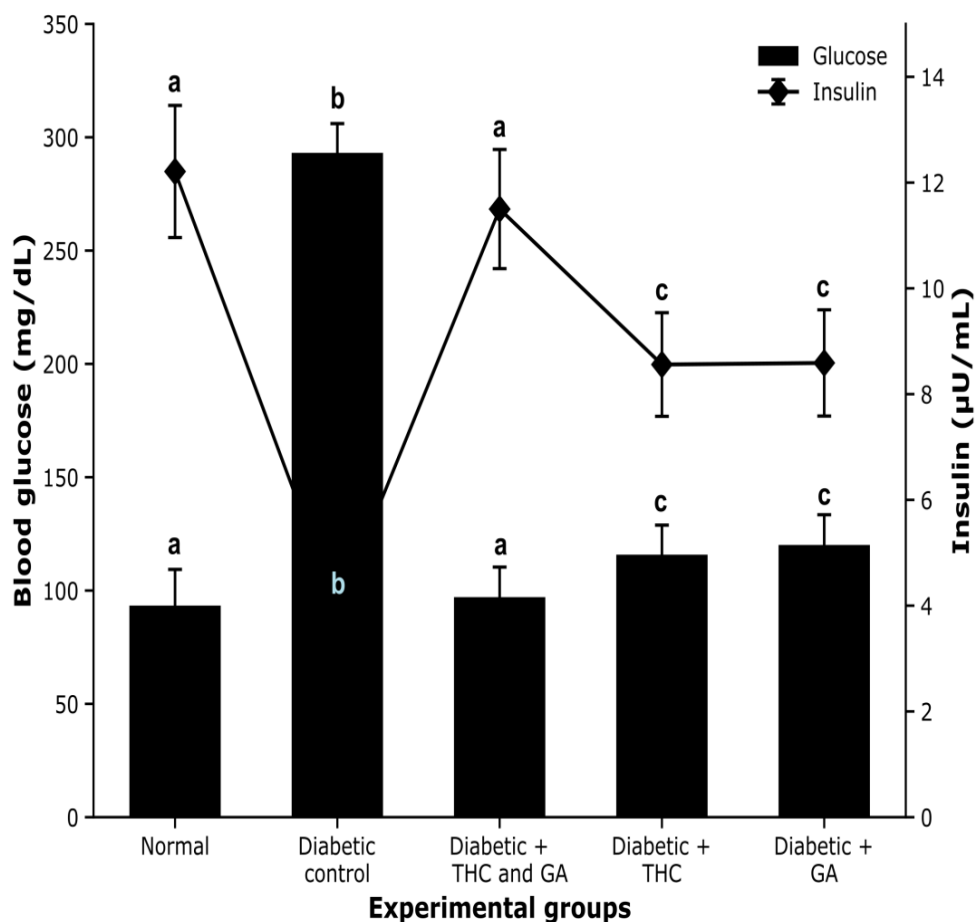


Figure 1: Effect of THC and GA on glucose and insulin in normal and experimental rats. Values are expressed as Mean $\pm$ SD for 6 rats. Statistical analysis of one-way ANOVA, *post hoc* followed by DMRT test using SPSS ver. 24. Mean values are within the row followed by different letters, superscript (homogeneous subsets) are mentioned as statistically significant ($p < 0.05$) while same letter was statistically non-significant ($p > 0.05$) from each other groups.

structural and functional macromolecules throughout the body (Papachristoforou *et al.*, 2020).

Elevated oxidative stress resulting from hyperglycaemia accelerates the generation of ROS and diminishes antioxidant defenses, which ultimately leads to cellular damage and the release of lipid peroxidation products into the bloodstream (Shams *et al.*, 2011). Prior research has indicated an increase in lipid peroxidation in the plasma of diabetic rats (Murugan and Pari, 2006b; Pari and Murugan, 2005; Murugan and Sakthivel, 2022). The combination of THC and GA provides protection to the liver and kidneys by enhancing GSH levels. This mechanism promotes the activity of enzymes that prevent detrimental cellular damage and facilitate the removal of toxic waste in diabetic rats (Pari and Murugan, 2007). THC and GA exhibit an antiperoxidative effect by aiding the body in responding to lipid peroxides. In diabetic rats, elevated plasma levels of ceruloplasmin and α -tocopherol serve as protective agents. Ceruloplasmin acts as a potent free radical scavenger, inhibiting lipid peroxidation (Pari and Murugan,). The administration of the THC and GA combination to STZ-induced diabetic rats resulted in a reduction of plasma levels of TBARS, hydroperoxides, ceruloplasmin, and α -tocopherol, thereby demonstrating the antiperoxidative properties of THC and GA.

Vitamin E is a potent, fat-soluble antioxidant that safeguards cell membranes from damage caused by free radicals. It mitigates oxidative stress by neutralising reactive oxygen species, thereby

maintaining the stability and health of cell walls throughout the body (Wang and Quinn, 1999). It disrupts the chain reaction of lipid peroxidation by interacting with lipid proxy radicals, thus shielding cell structures from harm (Zheng *et al.*, 2024). Additionally, it aids in reducing elevated levels of detrimental cell damage, referred to as lipid peroxidation, which is prevalent in diabetes (Murugan and Pari, 2006c). The oral administration of THC and GA to diabetic rats restored Vitamin E levels to nearly normal.

We have also noted considerable alterations in the levels of plasma antioxidants in diabetic rats. Vitamin C serves as the primary hydrophilic (water-soluble) antioxidant in human blood plasma. When plasma encounters reactive oxygen species, Vitamin C is indeed the first line of defence and is depleted prior to the oxidation of other lipids or antioxidants (Vani *et al.*, 2015). A notable decrease in plasma Vitamin C frequently occurs as a result of elevated oxidative stress. Reactive oxygen species utilise Vitamin C in its role as an antioxidant, or insufficient levels of GSH hinder the recycling of oxidised Vitamin C back to its active state (Kaźmierczak-Barańska *et al.*, 2020).

GSH is a crucial tripeptide found in cells that inhibits lipid peroxidation caused by free radicals. It functions directly as an antioxidant and is a vital cofactor for glutathione peroxidase enzymes, converting harmful lipid peroxides into harmless alcohols while safeguarding cell membranes from oxidative harm (Shi *et al.*, 2014). Elevated blood sugar levels generate numerous free radicals (oxyradicals). The body rapidly depletes GSH and Vitamin C to neutralise these detrimental molecules and shield cells from injury (Phiwayinkosi *et al.*, 2023). GSH serves as a primary defence mechanism for cells against prooxidant environments (Averill-Bates *et al.*, 2023), and its levels were assessed following the administration of THC and GA. GSH systems assist cells in combating oxidative stress by altering the functionality of regulatory enzymes. In this study, THC and GA treatment led to a significant increase in GSH levels. Elevated GSH levels subsequently activate GSH-dependent enzymes such as glutathione peroxidase and glutathione-S-transferase (Brodzka *et al.*, 2024).

Table 1: Changes in the levels of plasma TBARS and hydroperoxides in normal and experimental animals.

Groups	TBARS (mmoles/dL)	Hydroperoxides ($\times 10^{-5}$ mM/100 mL)
Normal	0.20 $\pm$ 0.01a	10.87 $\pm$ 0.60a
Diabetic control	0.46 $\pm$ 0.02b	24.47 $\pm$ 1.27b
Diabetic + THC and GA	0.22 $\pm$ 0.01a	10.98 $\pm$ 0.65a
Diabetic + THC	0.26 $\pm$ 0.01c	12.93 $\pm$ 0.93c
Diabetic+ GA	0.28 $\pm$ 0.01c	13.12 $\pm$ 0.74c

Values are given as Mean $\pm$ S.D for 6 rats in each group. Values not sharing a common superscript letter differ significantly at $p < 0.05$ (DMRT) (Li and Shen, 2019).

Table 2: Changes in levels of Vitamin C, Vitamin E, ceruloplasmin and reduced glutathione (GSH) in plasma of normal and experimental animals.

Groups	Normal	Diabetic control	Diab + THC and GA	Diabetic + THC	Diabetic + GA
Vitamin C (mg/dL)	1.78 $\pm$ 0.11 ^a	0.74 $\pm$ 0.04 ^b	1.81 $\pm$ 0.11 ^a	1.55 $\pm$ 0.11 ^c	1.49 $\pm$ 0.09 ^c
Vitamin E (mg/dL)	1.64 $\pm$ 0.07 ^a	0.72 $\pm$ 0.03 ^b	1.57 $\pm$ 0.09 ^a	1.30 $\pm$ 0.08 ^c	1.27 $\pm$ 0.05 ^c
Ceruloplasmin (mg/dL)	20.33 $\pm$ 1.13 ^a	35.21 $\pm$ 2.12 ^b	22.31 $\pm$ 1.14 ^a	27.12 $\pm$ 1.45 ^c	27.87 $\pm$ 1.32 ^c
Reduced Glutathione (mg / dL)	25.12 $\pm$ 1.44 ^a	12.47 $\pm$ 0.65 ^b	24.01 $\pm$ 1.47 ^a	21.07 $\pm$ 1.38 ^c	20.85 $\pm$ 5.28 ^c

Values are given as Mean $\pm$ S.D for 6 rats in each group. Values not sharing a common superscript letter differ significantly at $p < 0.05$ (DMRT) (Lott and Turner, 1975).

Ceruloplasmin is an essential plasma protein that functions as a ferroxidase, converting harmful Ferrous Iron (Fe^{2+}) into non-toxic Ferric Iron (Fe^{3+}). This enzyme is crucial because the optimal breakdown of fats driven by iron necessitates a balanced ratio of both iron forms at 1:1, thereby preventing cellular damage by eliminating reactive ferrous iron (Patel *et al.*, 2002). During periods of oxidative stress and inflammation, ceruloplasmin levels increase as it serves as a positive acute-phase reactant. Additionally, as a copper-binding antioxidant enzyme, it plays a role in neutralising reactive oxygen species, such as superoxide radicals, thereby mitigating tissue damage (Goldstein *et al.*, 1979). The rise in plasma ceruloplasmin levels observed in diabetic rats may be attributed to elevated lipid peroxides. Furthermore, Murugan and Sakthivel (2020) also noted an increase in ceruloplasmin levels in diabetic rats. The administration of THC and GA to these diabetic rats resulted in the restoration of ceruloplasmin levels to nearly normal values.

CONCLUSION

The combination of THC and GA has strong antioxidant properties. This combination lowers harmful fat breakdown and boosts cell defence systems. It helps protect the body from oxidative stress caused by diabetes. The combination effect of THC and GA was better when compared with that of THC or GA alone.

ABBREVIATIONS

STZ: Streptozotocin; **THC:** Tetrahydrocurcumin; **GA:** Gallic Acid; **STZ:** Streptozotocin; **ROS:** Reactive Oxygen Species; **GSH:** Reduced Glutathione; **TBARS:** Thiobarbituric Acid Reactive Substances; **DMRT:** Duncan's Multiple Range Test.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

Aboonabi, A., Rahmat, A., & Othman, F. (2014). Antioxidant effect of pomegranate against streptozotocin-nicotinamide generated oxidative stress induced diabetic rats. *Toxicology Reports*, 1, 915-922. <https://doi.org/10.1016/j.toxrep.2014.10.022>

Averill-Bates, D. A. (2023). The antioxidant glutathione. *Vitamins and Hormones*, 121, 109-141. <https://doi.org/10.1016/bs.vh.2022.09.002>

Baker, H., Frank, O., Angelis, B., & Feingold, S. (1951). Plasma tocopherol in man at various times after ingesting free or acetylated tocopherol. *Nutritional report Investigation*, 21, 531-536. <https://doi.org/Corpus ID: 82808051>

Brodzka, S., Baszyński, J., Rektor, K., Holderna-Bona, K., Stanek, E., Kurhaluk, N., et al. (2024). The role of glutathione in age-related macular degeneration (AMD). *International Journal of Molecular Sciences*, 25(8), 4158. <https://doi.org/10.3390/ijms25084158>

Caturano, A., D'Angelo, M., Mormone, A., Russo, V., Mollica, M. P., Salvatore, T., et al. (2023). Oxidative stress in type 2 diabetes: Impacts from pathogenesis to lifestyle modifications. *Current Issues in Molecular Biology*, 45(8), 6651-6666. <https://doi.org/10.3390/cimb45080420>

Duncan, D. B. (1957). Multiple ranges tests for correlated and heteroscedastic means. *Biometrics*, 13(2), 164. <https://doi.org/10.2307/2527799https://doi.org/10.2307/2527799>

Eleazu, C. O., Eleazu, K. C., Chukwuma, S., & Essien, U. N. (2013). Review of the mechanism of cell death resulting from streptozotocin challenge in experimental animals, its practical use and potential risk to humans. *Journal of Diabetes and Metabolic Disorders*, 12(1), 60. <https://doi.org/10.1186/2251-6581-12-60>

Ellman, G. L. (1959). Tissue sulfhydryl groups. *Archives of Biochemistry and Biophysics*, 82(1), 70-77. [https://doi.org/10.1016/0003-9861\(59\)90090-6](https://doi.org/10.1016/0003-9861(59)90090-6)

Fraga, C. G., Leibovitz, B. E., & Tappel, A. L. (1988). Lipid peroxidation measured as thiobarbituric acid-reactive substances in tissue slices: Characterization and comparison with homogenates and microsomes. *Free Radical Biology and Medicine*, 4(3), 155-161. [https://doi.org/10.1016/0891-5849\(88\)90023-8](https://doi.org/10.1016/0891-5849(88)90023-8)

Fu, M., Sik Yoon, K., Ha, J., Kang, I., & Choe, W. (2025). Crosstalk between antioxidants and adipogenesis: Mechanistic pathways and their roles in metabolic health. *Antioxid (Basel)*, 14(2), 203. <https://doi.org/10.3390/antiox14020203>

Furman, B. L. (2021). Streptozotocin-induced diabetic models in mice and rats. *Current protocols in pharmacology*, 70(1), 5-47. <https://doi.org/10.1002/cpz1.78>

Gajendhini, S., & Murugan, P. (2025). Combined and comparative antioxidant effect of tetrahydrocurcumin and gallic acid in streptozotocin induced diabetic rats. *Current Topics in Peptide and Protein Research*, 26, 47-59. <https://doi.org/10.31300/CTPPR.26.2025.47-59>

Gajendhini, S., & Murugan, P. (2026a). Effect of tetrahydrocurcumin and gallic acid on lipids in streptozotocin induced diabetic rats. *Research Journal of Biotechnology*, 6(21), 201-207. <https://doi.org/10.25303/216rjbt2010207>

Gajendhini, S., & Murugan, P. (2026b). Protective role of tetrahydrocurcumin and gallic acid on changes in the fatty acid composition in streptozotocin diabetic rats. *International Journal of Zoological Investigations*, 12(1), 778-788. <https://doi.org/10.33745/ijzi.2026.v12i01.076>

Goldstein, I. M., Kaplan, H. B., Edelson, H. S., & Weissmann, G. (1979). A new function for ceruloplasmin as an acute-phase reactant in inflammation: A scavenger of superoxide anion radicals. *Transactions of the Association of American Physicians*, 92, 360-369. <https://doi.org/10.3390/antiox14020203>

Hadidi, M., Liñán-Atero, R., & Tarahi, M. (2024). The potential health benefits of gallic acid: Therapeutic and food applications. *Antioxid (Basel)*, 13(8), 1001. <https://doi.org/10.3390/antiox13081001>

Hussain, A. (2025). Chronic hyperglycemia and cardiovascular dysfunction: An in-depth exploration of metabolic and cellular pathways in type 2 diabetes mellitus. *Cardiovasc Diabetol. endocrinol. Rep.* 12. *Cardiovascular Diabetology. Endocrinology Reports*, 11(1), 39. <https://doi.org/10.1186/s40842-025-00247-3>

Jiang, Z. Y., Hunt, J. V., & Wolff, S. P. (1992). Ferrous ion oxidation in the presence of xylenol orange for detection of lipid hydroperoxide in low density lipoprotein. *Analytical Biochemistry*, 202(2), 384-389. [https://doi.org/10.1016/0003-2697\(92\)90122-N](https://doi.org/10.1016/0003-2697(92)90122-N)

Kaźmierczak-Barańska, J., Boguszewska, K., Adamus-Grabicka, A., & Karwowski, B. T. (2020). Two faces of Vitamin C-antioxidative and pro-oxidative agent. *Nutrients*, 12(5), 1501. <https://doi.org/10.3390/nu12051501>

Kooti, W., Farokhipour, M., Asadzadeh, Z., Ashtary-Larky, D., & Asadi-Samani, M. (2016). The role of medicinal plants in the treatment of diabetes: A systematic review. *Electronic Physician*, 8(1), 1832-1842. <https://doi.org/10.19082/1832>

Li, J., & Shen, X. (2019). Oxidative stress and adipokine levels were significantly correlated in diabetic patients with hyperglycemic crises. *Diabetology and Metabolic Syndrome*, 11(1), 13. Li and Shen *Diabetol Metab Syndr., Article 13*. <https://doi.org/10.1186/s13098-019-0410-5>

Lott, J. A., & Turner, K. (1975). Evaluation of trinder's glucose oxidase method for measuring glucose in serum and urine. *Clinical Chemistry*, 21(12), 1754-1760. <https://doi.org/10.1093/clinchem/21.12.1754>

Lowry, O. H., Roesborough, M. J., Farr, A. L., & Randall, R. J. (1951). Protein measurement with Folin-phenol reagent. *Journal of Biological Chemistry*, 193, 265-275. <https://pubmed.ncbi.nlm.nih.gov/14907713/>

Manzoor, J., Jan, K., Akgöl, C., Wani, K. A., Soni, A., & Wani, B. A. (2026). Chapter 20. Natural Remedies for diabetes management: Benefits and drawbacks. In *Diabetes, aging, and management strategies* (pp. 263-279). Elsevier. <https://doi.org/10.1016/B978-0-443-44665-8.00013-4>

Murugan, P. (2022). Antioxidant effect of tetrahydrocurcumin compared pterostilbene in streptozotocin - nicotinamide induced diabetic rats. *Journal of Pharmaceutical Negative Results*, 13, 04, 2190-2196. <https://doi.org/10.47750/pnr.2022.13.04.295>

Murugan, P. (2023). Effect Cassia auriculata on lipid peroxidation and lipids in streptozotocin - nicotinamide induced diabetic rats. *Journal of Population Therapeutics & Clinical Pharmacology*, 30, 4, 638-648. <https://doi.org/10.53555/jptcp.v30i4.2400>

Murugan, P., & Pari, L. (2006a). Antioxidant effect of tetrahydrocurcumin in streptozotocin-Nicotinamide induced diabetic rats. *Life Sciences*, 79(18), 1720-1728. <https://doi.org/10.1016/j.lfs.2006.06.001>

Murugan, P., & Pari, L. (2006b). Effect of tetrahydrocurcumin on lipid peroxidation and lipids in streptozotocin-nicotinamide-induced diabetic rats. *Basic and Clinical Pharmacology and Toxicology*, 99(2), 122-127. https://doi.org/10.1111/j.1742-7843.2006.pto_447.x

Murugan, P., & Pari, L. (2006c). Effect of tetrahydrocurcumin on plasma antioxidants in streptozotocin- nicotinamide induced experimental diabetes. *Journal of Basic and Clinical Physiology and Pharmacology*, 17(4), 231-244. <https://doi.org/10.1515/JBCPP.2006.17.4.231>

Murugan, P., & Pari, L. (2007). Influence of tetrahydrocurcumin on erythrocyte membrane bound enzymes and antioxidant status in experimental type 2 diabetic rats. *Journal of Ethnopharmacology*, 113(3), 479-486. <https://doi.org/10.1016/j.jep.2007.07.004>

- Murugan, P., & Sakthivel, V. (2020). Influence of *Cassia auriculata* leaves on plasma antioxidants in streptozotocin- nicotinamide induced experimental diabetes. *Journal of Population Therapeutics and Clinical Pharmacology*, 27(03), 89-97. <https://doi.org/10.53555/jptcp.v27i3.2502>.
- Murugan, P., & Sakthivel, V. (2022). Effect of tetrahydrocurcumin compared pterostilbene on plasma antioxidants in streptozotocin- nicotinamide induced experimental diabetes. *Journal of Pharmaceutical Negative Results*, 13(09), 11215-11221. <https://doi.org/10.47750/pnr.2022.13.509.1319>.
- Murugan, P., Gajendhini, S., Malarvili, T., Marudhadurai, T., Suganthi, K., & Sakthivel, V. (2026b). Enhanced antidiabetic efficacy of tetrahydrocurcumin and Gallic acid on hepatic and renal functional markers and protein levels: A comparative study in Albino Wistar Rats. *Asian Journal of Biological and Life Sciences*, 15(2), 303-311. <https://doi.org/10.5530/ajbls.20260001>
- Murugan, P. (2010). Taner's *Cassia (Cassia auriculata* L.) extract prevents hemoglobin glycation tail tendon collagen properties in experimental diabetic rats. *Cell and Tissue Research*, 10(1), 2109-2114. <https://doi.org/10.1007/s12019-2114.2010>.
- Murugan, P., Sakthivel, V., Jawahar, S. (2020). Effect of *Cassia auriculata* flowers, leaves and seeds dose dependent study in streptozotocin - induced diabetic rats. *Journal of Population Therapeutics and Clinical Pharmacology*, 27, 4, 74-82. <https://doi.org/10.53555/jptcp.v27i4.2496>.
- Naito, M., Wu, X., Nomura, H., Kodama, M., Kato, Y., Kato, Y., et al. (2002). The protective effects of tetrahydrocurcumin on oxidative stress in cholesterol-fed rabbits. *Journal of Atherosclerosis and Thrombosis*, 9(5), 243-250. <https://doi.org/10.5551/jat.9.243>
- Omaye, S.T., Turnbull, J.D., & Sauberlich, H.E. (1979). Selected method for the determination of ascorbic acid in animal cells, tissues and fluids. *Methods in Enzymology* D. B. McCormic & D. L. Wright (Eds.) [Methods]. *Enzymol Academic Press*, 62, 3-11. [https://doi.org/10.1016/0076-6879\(79\)62181-x](https://doi.org/10.1016/0076-6879(79)62181-x)
- Papachristoforou, E., Lambadiari, V., Maratou, E., & Makrilakis, K. (2020). Association of glycemic indices (hyperglycemia, glucose variability, and hypoglycemia) with oxidative stress and diabetic complications. *Journal of Diabetes Research*, 2020(1), 7489795. <https://doi.org/10.1155/2020/7489795>
- Pari, L., & Murugan, P. (2004). Protective role of tetrahydrocurcumin against erythromycin estolate-induced hepatotoxicity. *Pharmacological Research*, 49(5), 481-486. <https://doi.org/10.1016/j.phrs.2003.11.005>
- Pari, L., & Murugan, P. (2006). Tetrahydrocurcumin: Effect on chloroquine-mediated oxidative damage in rat kidney. *Basic and Clinical Pharmacology and Toxicology*, 99(5), 329-334. https://doi.org/10.1111/j.1742-7843.2006.pto_503.x
- Pari, L., & Murugan, P. (2007a). Changes in glycoprotein components in streptozotocin-Nicotinamide induced type 2 diabetes: Influence of tetrahydrocurcumin from *Curcuma longa*. *Plant Foods for Human Nutrition*, 62(1), 25-29. <https://doi.org/10.1007/s11130-006-0037-1>
- Pari, L., & Murugan, P. (2007a). Tetrahydrocurcumin prevents brain lipid peroxidation in streptozotocin-induced diabetic rats. *Journal of Medicinal Food*, 10(2), 323-329. <https://doi.org/10.1089/jmf.2006.058>
- Pari, L., & Murugan, P. (2007b). Antihyperlipidemic effect of curcumin and tetrahydrocurcumin in experimental type 2 diabetic rats. *Renal Failure*, 29(7), 881-889. <https://doi.org/10.1080/08860220701540326>
- Pari, L., & Murugan, P. (2005). Effect of tetrahydrocurcumin on blood glucose, plasma insulin and hepatic key enzymes in streptozotocin induced diabetic rats. *Journal of Basic & Clinical Physiology & Pharmacology*, 2005, 16, 257-274. <https://doi.org/10.1515/jbcp.2005.16.4.257>.
- Patel, B. N., Dunn, R. J., Jeong, S. Y., Zhu, Q., Julien, J.-P., & David, S. (2002). Ceruloplasmin regulates iron levels in the CNS and prevents free radical injury. *The Journal of Neuroscience*, 22(15), 6578-6586. <https://doi.org/10.1523/JNEUROSCI.22-15-06578.2002>
- Phiyawinkosi, V. D., Khanyisani, Z., Sihle, E., Sithandiwe, E. M., Sidney, H., Bongani, B. N., et al. (2023). Dietary supplements potentially target plasma glutathione levels to improve cardiometabolic health in patients with diabetes mellitus: A systematic review of randomized clinical trials. *Nutrients*. 15(4), 944. <https://pubmed.ncbi.nlm.nih.gov/232945/>
- Pung Rozar, K., Kumar, S., Rajnish, S., Shijagurumayum, B., & Sharma Milica, M. (2024). Comparison of Phenolic Content, Flavonoid Content and Antioxidant Activities of L. From North-Phyllanthus emblica East, India. *Nongrum and Jyoti Jopir. Indian Journal of Ecology*, 51(4), 732-737. <https://doi.org/https://indianjournals.com/article/ije1-51-4-005>
- Ravin, H. A. (1961). An improved colorimetric enzymatic assay of ceruloplasmin. *The Journal of Laboratory and Clinical Medicine*, 58(1), 161-168. <https://doi.org/10.55362/IJE/2024/4301>
- Shams, M. E. E., Al-Gayyar, M. M. H., & Barakat, E. A. M. E. (2011). Type 2 diabetes mellitus-induced hyperglycemia in patients with NAFLD and normal LFTs: Relationship to lipid profile, oxidative stress and pro-inflammatory cytokines. *Scientia Pharmaceutica*, 79(3), 623-634. <https://doi.org/10.3797/scipharm.1104-21>
- Shi, Y., Kovacs-Nolan, J., Jiang, B., Tsao, R., & Mine, Y. (2014). Peptides derived from eggshell membrane improve antioxidant enzyme activity and glutathione synthesis against oxidative damage in Caco-2 cells. *Journal of Functional Foods*, 11, 571-580. <https://doi.org/10.1016/j.jff.2014.08.017>
- Shu Lai, C.-S., Ho, T., & Pan, M.-H., Pan, M.-H. C., Hsiung Pan M. (2020). The cancer chemopreventive and therapeutic potential of tetrahydrocurcumin. *Biomolecules*, 10(6), 831. <https://doi.org/10.3390/biom10060831>
- Stadler, K., Dallas Bonini, M. G., Jiang, J., Radi, R., Mason, R. P., & Kadiiska, M. B. (2009). Involvement of inducible nitric oxide synthase in hydroxyl radical-mediated lipid peroxidation in streptozotocin-induced diabetes. *Free Radic. Biol. Med*, 45(6), 866-874. *PMC: 2009 Sep 15*.
- Sundaram, R., Shanthi, P., & Sachdanandam, P. (2015). Oxidative stress and adipokine levels were significantly correlated in diabetic patients with hyperglycemic crises. *Journal of Functional Foods*, 16, 315-333. <https://doi.org/10.1016/j.jff.2015.03.024>
- Tsai, Y.-Z., Tsai, M.-L., Hsu, L.-Y., Ho, C.-T., & Lai, C.-S. (2021). Tetrahydrocurcumin upregulates the adiponectin-AdipoR pathway and improves insulin signaling and pancreatic β -cell function in high-fat diet/streptozotocin-induced diabetic obese mice. *Nutrients*, 13(12), 4552. <https://doi.org/10.3390/nu13124552><https://doi.org/10.3390/nu13124552>
- Vani, R., Soumya, R., Carl, H., et al. (2015). Prospects of Vitamin C as an additive in plasma of stored blood. *Advances in Hematology*, 2015(1), 961049.
- Wang, X., & Quinn, P. J. (1999). Vitamin E and its function in membranes. *Progress in Lipid Research*, 38(4), 309-336. [https://doi.org/10.1016/S0163-7827\(99\)00008-9](https://doi.org/10.1016/S0163-7827(99)00008-9).
- Wong, T., Mohamed Tap, F., Hashim, Z., Abdul Majid, F., Hafizah Zakaria, N., Siahaan, P., Mogadem, A. (2022). Dual actions of gallic acid and andrographolide trigger AdipoR1 to stimulate insulin secretion in a streptozotocin-induced diabetes rat model. *Journal of Traditional and Complementary Medicine*, 28,13(1),11-19. <https://doi.org/10.1016/j.jtcme.2022.09.002>.
- Zeng, A., Quan, Y., Tao, H., Dai, Y., Song, L., & Zhao, J. (2025). The role of tetrahydrocurcumin in tumor and neurodegenerative diseases through anti-inflammatory effects. *International Journal of Molecular Sciences*, 26(8), Article 3561. <https://doi.org/10.3390/ijms26083561>
- Zheng, Y., Sun, J., Luo, Z., Li, Y., & Yongbo, H. (2024). Emerging mechanisms of lipid peroxidation in regulated cell death and its physiological implications. *Cell Death and Disease*, 15(11):859.

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