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RESEARCH ARTICLE

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Hypoglycaemic, Hypolipidaemic and Antioxidant Properties of *Celastrus paniculatus* Seed Extract in STZ-induced Diabetic Rats

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Background: *Celastrus paniculatus* is a herb used in the Ayurvedic system of medicine that has been reported to show multiple pharmacological properties. In this study, we explored the antioxidative, hypolipidaemic and hypoglycaemic potential of *C. paniculatus* methanolic seed extract (CPMSE) in high-fat diet (HFD)/streptozotocin (STZ)-induced type 2 diabetes mellitus (T2DM) rats.

Materials and methods: Seeds of *C. paniculatus* were extracted in methanol using Soxhlet extraction method. A total of 36 rats were induced with STZ and HFD and treated with glibenclamide or various concentrations of CPMSE. Upon treatment, blood samples were collected and kidney and liver samples were homogenised. Serum biochemical estimation was performed using several diagnostic kits. Protein was estimated by bicinchoninic acid (BCA) method. Oxidative stress was assessed by measuring malondialdehyde level and superoxide dismutase (SOD), catalase (CAT) and glutathione-S-transferase (GST) activity.

Results: CPMSE caused improvements in glucose homeostasis, lipid profile, liver function and oxidative stress parameters in a dose-dependent manner. CPMSE significantly decreased the levels of fasting blood glucose and glycated haemoglobin as well as increased insulin level and total protein content. There was an increase in total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), triglycerides (TG) levels and reduction in high density lipoprotein-cholesterol (HDL-C) level. There was a decrease in serum levels of serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT) and alkaline phosphatase (ALP). CPMSE decreased LPO and increased CAT, SOD and GST activity.

Conclusion: CPMSE has hypoglycaemic, hypolipidaemic and antioxidant properties by reducing the oxidative stress.

Keywords: *diabetes mellitus, Celastrus paniculatus, antioxidant, phytochemicals, phytonutrients, streptozotocin, high-fat diet*

Introduction

Hyperglycaemia or diabetes mellitus (DM) is a chronic metabolic disorder, with an increasing global incidence, especially affecting the obese and aged population.[1] According to the International Diabetes Federation (IDF), approximately 415 million people had DM in 2015. DM is a global public health burden and the number of patients

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is expected to be around 600 million by 2040. Chronic hyperglycaemia can cause damage to various organ systems, leading to the development of disabling and life-threatening health complications, the most prominent of which are microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular complications with an increased risk of cardiovascular diseases.[2,3,4]

The incidence of diabetes and obesity is increasing due to changes in the human environment, behaviour and lifestyle.[5] DM is a group of heterogeneous, hormonal and metabolic disorders, in which insulin action and secretion from pancreatic beta (β)-cells are impaired.[6] Insulin secretion and sensitivity are tightly regulated under normal physiological conditions.[7] DM is classified as type 1, 2, 3 and gestational diabetes mellitus (GDM)[8] by the American Diabetes Foundation (ADA). Type 2 diabetes mellitus (T2DM) accounts for nearly 90-95% of the total diabetic population and is associated with both impaired insulin production and release by the β-cells of the pancreas in response to hyperglycaemia. In type 1 diabetes, insulin replacement therapy is required for patients, while diet and lifestyle modification are essential for treatment and management for T2DM.[9] Chronic hyperglycaemia causes long term complications, dysfunction and failure of many organs, especially kidneys, nerves, eyes, heart, pancreas and blood vessels.[10] The patients have marked hyperglycaemia and insulin deficiency and many suffer from polyuria, polydipsia, polyphagia, weight loss and blurred vision.[8]

Traditional medicinal plants and herbs are utilised as potential alternative sources to prevent and treat DM and its complications.[11] Phytochemicals play an important role in the management of T2DM and its complications due to their lesser side effects.[12] *Celastrus paniculatus* is a woody liana commonly known as *jyotishmati*, *malkangni*, *kangani*, *sphutabandhani*, *svarnalota*, black oil tree, intellect tree and climbing staff plant. It is a herb used in the Ayurvedic system of medicine for thousands of years.[13] *C. paniculatus* is also used against ulcers, scabies, pruritus, wounds, skin diseases, amenorrhoea, dysmenorrhoea, inflammation and epilepsy.[14,15] Compounds extracted from *C. paniculatus* show multiple pharmacological properties, such as antitumor, cytotoxic, anti-inflammatory, anti-microbial, anti-ageing, antioxidative and neuroprotective activities.[16] Hence, the present *in vivo* study explored the antioxidative, hypolipidaemic and hypoglycaemic potential of *C. paniculatus* methanolic seed extract (CPMSE) in high-fat diet (HFD)/streptozotocin (STZ)-induced T2DM rats.

Materials and methods

Preparation of CPMSE

Seeds of *C. paniculatus* were obtained from the local market of Aligarh, India. The seeds were authenticated and validated by Department of Botany, Aligarh Muslim University, Aligarh. The seeds were sun dried and grounded to a coarse powder using a pestle and a mortar. The seeds were extracted in methanol using a Soxhlet extraction apparatus–3840 (Borosil, Mumbai, India). The extract was filtered and evaporated, and a brown residue was obtained. It was weighed and stored at 4°C for further use.

Experimental Animals and Induction of T2DM

Adult Wistar albino rats (120-180 g) were used in the present study. Thirty six rats were housed in the animal house of Interdisciplinary Biotechnology Unit, Aligarh Muslim University, Aligarh, under standard conditions of temperature and humidity with an alternating 12 h light and 12 h dark cycle. The food and water were available to the rats *ad libitum*. Rats were maintained as per the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). Ethical clearance was obtained from the Animal House, Department of Ilmul Advia, Ajmal Khan Tibbiya College, Aligarh Muslim University, Aligarh (No. 1979/GO/Re/S/17/CPCSEA).

A single intraperitoneal injection of STZ (35 mg/kg body weight (bw)) in citrate buffer (pH 4.5) was administered to the rats. STZ is metabolized in the pancreatic β-cells leading to the formation of reactive nitrogen species (RNS) and nitric oxide (NO), which subsequently impairs insulin synthesis and secretion. STZ increases glycated haemoglobin (HbA1c) levels and adversely affects other markers of DM.[17] After 72 h, fasting blood glucose (FBG) level was measured and hyperglycaemic rats were considered to be T2DM and were used in the study.

Animal Treatments

All rats were divided into six groups comprising six rats each. Normal control (NC) group consisted of normal rats that received normal chow diet. Diabetic control (DC) group consisted of diabetic rats that received HFD after STZ injection. Standard control (SD) rats received HFD and glibenclamide (5 mg/kg bw/day) orally post diabetes induction. The other groups consisted of diabetic rats which received HFD and CPMSE 25 (SE-1), 50 (SE-2) and 100 mg/kg bw/day (SE-3) orally for

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4 weeks post diabetes induction. Animal treatments were conducted for four weeks.

Samples Collection and Tissue Preparation

Rats were sacrificed as per standard guidelines under anaesthesia. Blood was collected before sacrificing the animals using cardiac puncture method for biochemical analysis and measurement of FBG and HbA1c. Kidney and liver were rapidly removed and homogenised using mortar-pestle in ice cold phosphate buffered saline (pH 7.4) to form a 10% homogenate. The homogenate was centrifuged at 10,000 rpm for 20 min at 4°C and post-mitochondrial supernatant (PMS) was separated for biochemical analysis.

Serum Biochemical Estimation

Glucose oxidase-peroxidase method[18] was used to measure FBG using a commercial diagnostic kit (Morepen Laboratories Ltd., New Delhi, India). Blood was drawn from the retro-orbital plexus under general anaesthesia to confirm diabetes development and FBG was determined for each group. HbAlc level was assayed by using a diagnostic kit (AGAPPE Diagnostics Ltd., Kerala, India) following the manufacturer's instructions. HbA1c level was calculated from the calibration curve. Insulin level in the serum of rat was estimated by RayBio Rat ELISA kit (Raybiotech, Peachtree Corners, GA, USA) according to the manufacturer's instructions. Lipid profile (total cholesterol, TC; triglycerides, TG; low density lipoprotein-cholesterol, LDL-C and high density lipoprotein-cholesterol, HDL-C) were estimated by using an enzymatic kits (AGAPPE Diagnostics Ltd.). Serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT) and alkaline phosphatase (ALP) were measured using a commercial diagnostic assay kits (AGAPPE Diagnostics Ltd.).

Estimation of Protein

Protein was estimated in homogenate and PMS by bicinchoninic acid (BCA) method. Twenty five µL of samples were mixed with 950 µL BCA solution. The mixture was incubated at 37°C for 30 min and the absorbance was measured at 562 nm. Total protein content was expressed as mg/mL by interpolation of absorbance from the calibration curve.

Assessment of Oxidative Stress

Lipid peroxidation (LPO) was determined in liver homogenate by the amount of malondialdehyde (MDA), a product formed due to the peroxidation of lipids. The amount of MDA formed in the samples was expressed as nmol of MDA formed per mg of protein by using a molar extinction coefficient of 1.56×10^5 $M^{-1}cm^{-1}$. The absorbance of the samples was recorded at 532 nm using Shimadzu 1800 UV-VIS scanning spectrophotometer (Shimadzu, Kyoto, Japan). Superoxide dismutase (SOD) activity was measured using the standard method[19] at 420 nm and expressed as nmol/min/mg protein. One unit of SOD activity is defined as the enzyme activity that inhibits autoxidation of pyrogallol by 50%. Catalase (CAT) activity assay was performed as previously described[20] and expressed as nmol H_2O_2 consumed min^{-1} mg^{-1} protein using a molar extinction coefficient of 43.6 $M^{-1}cm^{-1}$. Samples absorbance was recorded at 240 nm. Glutathione-S-transferase (GST) activity was measured as previously described[21] at an absorbance of 340 nm.

Statistical Analysis

Data was expressed as mean±standard error (SE). Statistical significance between the experimental groups was calculated by one way analysis of variance (ANOVA) followed by Tukey-Kramer test for more than two experimental groups. The two-tail *p*-value was calculated with unpaired t-test for two experimental groups. Statistical analyses were performed using Graph Pad InStat v3 (San Diego, CA, USA) and *p*-value <0.05 was considered as statistically significant.

Results

Determination of Glucose Homeostasis

We demonstrated that CPMSE treatment improved the pathology associated with DM. SE-2 and SE-3 groups showed comparable restoration of biochemical parameters compared to SE-1. The levels of FBG in SE-2 and SE-3 groups were significantly lower compared to the DC group (Figure 1A). In addition, HbA1c percentages in all CPMSE-treated groups were significantly lower compared to the DC group (Figure 1B). CPMSE also improved insulin levels, with the higher increase in insulin level was seen in SE-3 (Figure 1C). The total protein content increased in a dose-dependent manner in the CPMSE-treated groups, indicating normal protein synthesis in the liver (Figure 1D).

Effect of CPMSE on Lipid Profile

The elevation in blood glucose level was followed by a higher TC, LDL-C, TG levels and lower HDL-C level in the DC

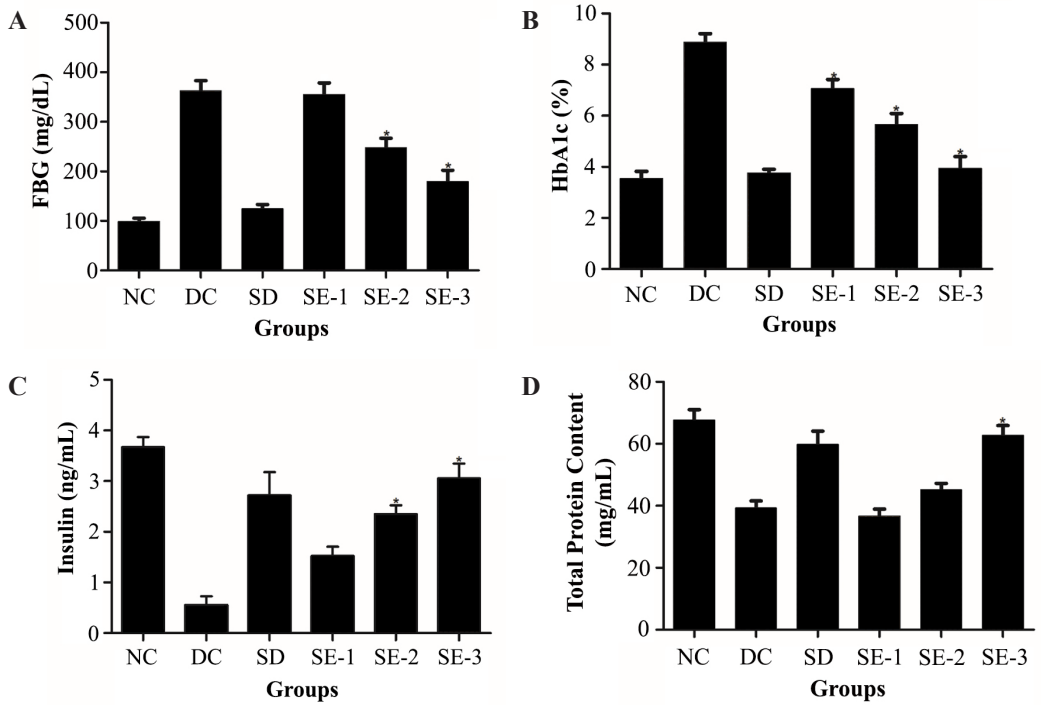

Figure 1. FBG, HbA1c and insulin levels and total protein content of control and CPMSE-treated groups. A: FBG level; B: %HbA1c; C: Insulin level; D: Total protein content. *Significant difference between DC and SE groups (p<0.05, Tukey-Kramer test).

group compared to the NC group. CPMSE improved serum lipid variables in diabetic rats, establishing anti-lipolytic activity of this extract. The higher decrease in the TC, TG and LDL-C levels were observed in SE-3 group. A higher increase in HDL-C level was also observed in the SE-3 group, indicating effective action of CPMSE in restoring lipid profile compared to SE-2 and SE-1 group. TC, LDL-C, TG levels were significantly lower and the HDL-C level was significantly higher in SE-3 group compared to the DC group. The LDL-C level was also significantly lower in the SE-2 group compared to the DC group. However, TC, TG and HDL-C levels in the SE-2 group were not significantly different from the DC group (Figure 2).

Effect of CPMSE on Liver Function

There was a decrease in the serum levels of SGPT, SGOT and ALP in HFD/STZ-induced groups treated with CPMSE. This extract was found to have a protective role in liver function. The greater reduction of liver function parameters could be seen in SE-3 group, reiterating the potent effect of CPMSE in improving liver enzyme levels. SGPT and SGOT levels were comparable in SE-2 and SE-1 groups, indicating their efficacy in improving liver function (Figure 3).

Effect of CPMSE on Oxidative Stress

Oral administration of various doses of CPMSE to hyperglycaemic rats caused a dose-dependent decrease in LPO and increase in CAT, SOD and GST activity (Figure 4).

Discussion

There are several compounds present in the crude seed extract of *C. paniculatus*, such as palmitic acid, phytol, erucic acid, trans-β-copaene and linalool.[13] These compounds may be responsible for the beneficial effect of *C. paniculatus* seed extract against ulcer, asthma, cardiac debility, inflammation, epilepsy, etc.[15] *C. paniculatus* is a herbal plant used for different ailments in the indigenous medicinal system since the ancient times. *C. paniculatus* has several medicinal properties found in the aerial parts of the plant and seeds. It is used in the treatment of rheumatoid arthritis, gout and paralysis in the Ayurvedic system of medicine. It has also been known for its anti-diarrheal, anti-haemorrhagic and anti-cognitive activities.[22]

The present study was designed to evaluate the antidiabetic potential of CPMSE. In this study, the FBG level of rats decreased significantly in a dose-dependent manner

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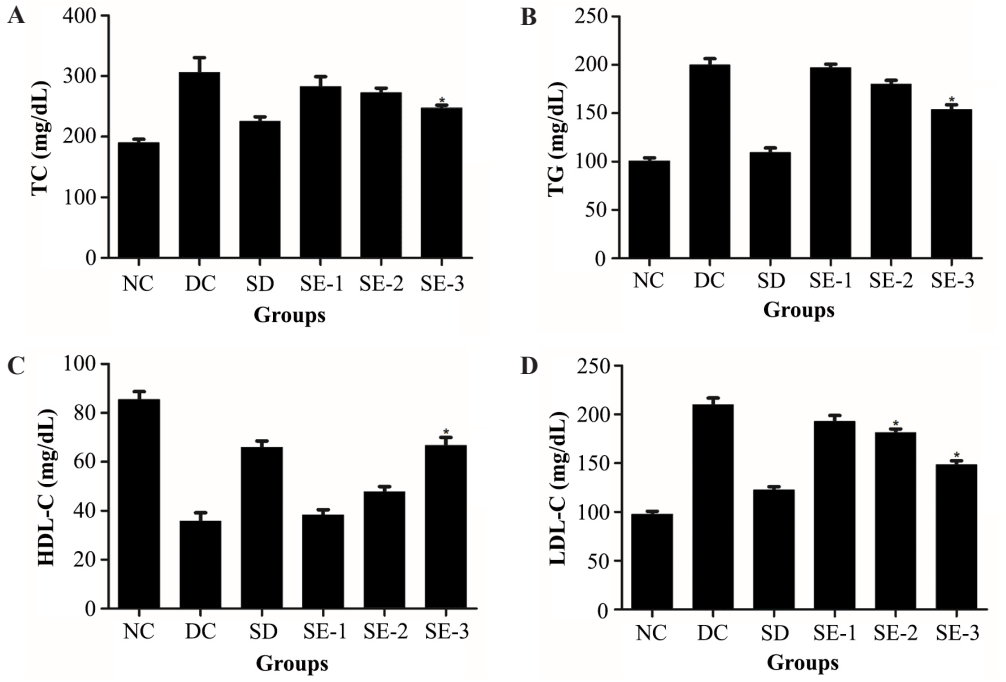

Figure 2. TC, TG, HDL-C and LDL-C levels of control and CPMSE-treated groups. A: TC level; B: TG level; C: HDL-C level; D: LDL-C level. *Significant difference between DC and SE groups (p<0.05, Tukey-Kramer test).

with an increase in the dose of CPMSE. The maximum reduction of FBG was observed at the highest dose, *i.e.* 100 mg/kg bw. HbA1c level significantly decreased in CPMSE-treated groups. CPMSE increased the insulin level in CPMSE-treated groups in a dose-dependent manner as described in earlier studies.[23]

Our results were similar to a previous study, which demonstrated the lipid (TC, TG, LDL, very-low-density lipoprotein; VLDL and cholesterol level)-lowering potential of CPMSE co-administered with HFD. The study also suggested that CPMSE decreased the cholesterol deposition in the aorta of high cholesterol-fed animals, as shown by the normal physiology of aorta.[24] We observed that TC and TG levels in rats treated with 100 mg/kg of CPMSE were significantly lower compared to diabetic group. Similarly, an increase in the level of HDL-C and a decrease in the level of LDL-C was observed compared to hypercholesterolemic or diabetic group. CPMSE also lowered the TC level in blood of animals fed with HFD. Studies have shown a positive correlation of serum LDL-C level and risk of coronary heart diseases.[23-25] Our study also examined the effects of CPMSE on selected markers of liver function in HFD/STZ-induced diabetic rats. CPMSE decreased SGOT, SGPT and ALP levels in a dose-dependent manner. The elevated liver enzymes in the plasma may be due to necrosis of hepatocytes (liver damage) in the diabetic rats.[26] This suggested that CPMSE may improve hepatic functions through its antioxidant and anti-lipidaemic properties.

Excessive production or insufficient removal of free radical molecules is called oxidative stress.[27] Free radicals are highly reactive molecules which are capable of oxidising cellular proteins, nucleic acids, and lipids.[28] Oxidative damage is a complication of DM associated with oxidative degradation of glycated proteins and non-enzymatic protein glycation. Various deleterious effects may be produced by non-enzymatic modification of plasma proteins, leading to defective drug binding, platelet activation, immunomodulation and fibrinolysis.[29,30] LPO was measured by estimation of MDA, which is a byproduct of polyunsaturated fatty acids (PUFA) peroxidation.[31] PUFA forms peroxyl radicals (ROO•) by reacting with oxygen, propagating chain reaction and leading to LPO.[32] We observed a significant decrease in LPO in all CPMSE-treated groups.

SOD, CAT and GST are an important antioxidant defence system that play an important role in protecting cells from free radical-mediated oxidative damage.[33,34] The decrease in antioxidant enzyme activity is either due to their

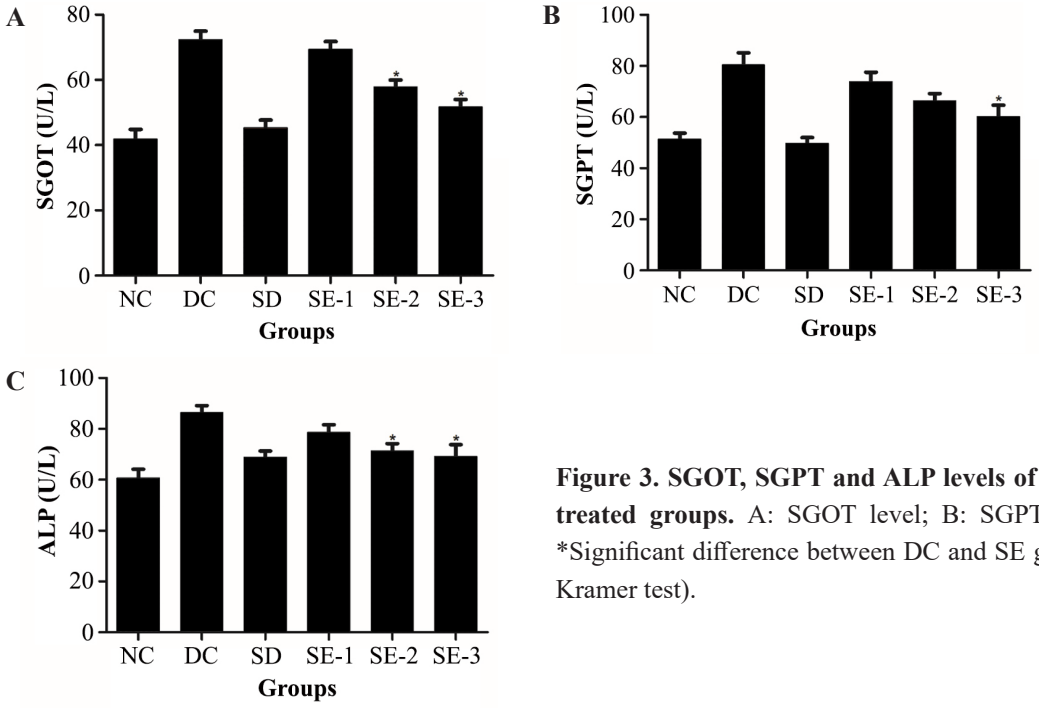

Figure 3. SGOT, SGPT and ALP levels of control and CPMSE-treated groups. A: SGOT level; B: SGPT level; C: ALP level. *Significant difference between DC and SE groups (p<0.05, Tukey-Kramer test).

function against free radicals or their inhibition by free radical species.[35] Likewise, we observed lower antioxidant enzyme activity in diabetic rats compared to normal rats, which was restored by CPMSE treatment.

Conclusion

CPMSE has hypoglycaemic, hypolipidaemic and antioxidant properties by decreasing LPO and augmenting endogenous antioxidant enzymes.

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Authors Contribution

MFA, HA and WAS were involved in concepting and planning the research and designing the methodology. MFA, MAH and NN maintained the research data, conducted the research, performed the data acquisition, and drafted the manuscript. MAH and NN calculated the experimental data and performed the analysis. WAS supervised the research. All authors took parts in giving critical revision of the manuscript and have read and approved the final manuscript.

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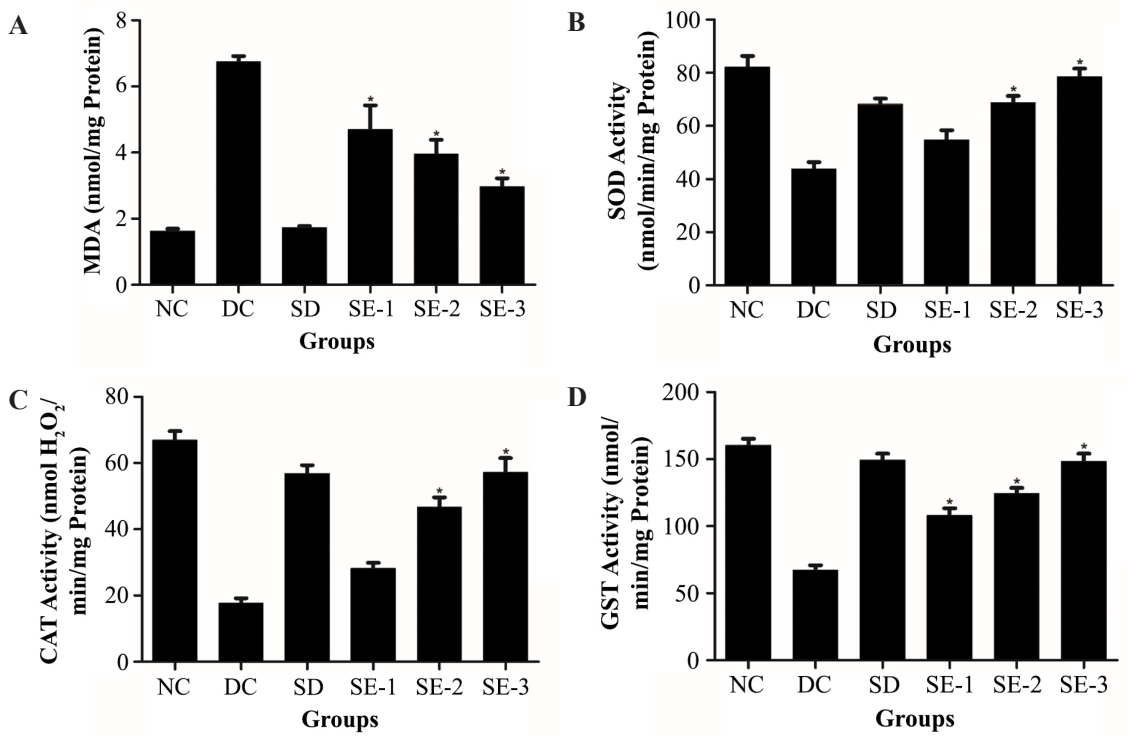

Figure 4. MDA level and SOD, CAT and GST activities of control and CPMSE-treated groups. A: MDA level; B: SOD activity; C: CAT activity; D: GST activity. *Significant difference between DC and SE groups (p<0.05, Tukey-Kramer test).

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