*Original Research*

# Green synthesized silver nanoparticles for the treatment of diabetes and the related complications of hyperlipidemia and oxidative stress in diabetic rats

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### Impact statement

Using biological nanoparticle sources is important for nanoscale material development, and emerging technical tools have been created to develop eco-friendly and reliable methodologies to synthesize nanoscale materials. Accordingly, we aimed to synthesize green silver nanoparticles using cinnamon extracts (C-Ag-NPs) and to study the physical and chemical characteristics of the composite nanoparticles, and to assess their biological ecofriendliness while controlling for hyperglycemic conditions and related complication disorders in streptozotocin (STZ)-induced diabetic rats. The C-Ag-NPs played a protective role against hyperglycemia and hyperlipidemia in diabetic rats and modulated liver function enzyme biomarkers and antioxidant enzyme activities.

### Abstract

This study was conducted to compare the impact of cinnamon silver nanoparticles (C-Ag-NPs) and cinnamon aqueous extract (CAE) on the total body weight (TBW), body weight gain (BWG), blood count (BC), fasting blood glucose (FBG), triglycerides (TGs), total cholesterol (TC), low-density (LDL-C) and high-density (HDL-C) lipoprotein cholesterol, liver function enzymes, superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) of normal and streptozotocin (STZ) diabetic rats. The CAE was administered to rats at different doses (50.0 and 100.0 mg/kg bw), whereas the C-Ag-NPs were ingested at doses of 25.0 and 50.0 mg/kg bw for 30 days. At the end of the experiment, the administration of high or low dosages of CAE or C-Ag-NPs to diabetic rats significantly reduced the FBG, TC, TG, and LDL-C and significantly increased the HDL-C compared with the diabetic control rats. The highest dose (50.0 mg/kg bw) of the C-Ag-NPs was the most efficient at significantly reducing ($P < 0.05$) the levels of all the analyzed parameters compared with the CAE. However, the treated and normal rats did not show any hypoglycemic activity after ingesting the CAE or C-Ag-NPs. Such effects were associated with considerable increases in their BWG. The diabetic rats that ingested the CAE or C-Ag-NPs showed a gradual decrease in their FBG, TC, LDL, and TG levels, but they were still higher than those in the normal rats. Furthermore, the C-Ag-NPs and CAE considerably enhanced the hepatic (GPT, GOT, ALP, and GGT) and antioxidant biomarker enzyme activities (SOD, CAT, and GPx) in diabetic rats. Relative to the untreated diabetic control, the C-Ag-NPs were more effective than the CAE in the diabetic rats. The C-Ag-NPs exhibited a protective role against hyperglycemia and hyperlipidemia in the diabetic rats and modulated their liver function enzyme biomarkers and antioxidant enzyme activities more than the CAE.

**Keywords:** Cinnamon bark, extract, nanoparticles, antioxidant, diabetic control, chronic

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## Introduction

Diabetes mellitus (DM) is a chronic disease characterized by hyperglycemia and is triggered by insulin resistance, pancreatic dysfunction, or both because of insulin resistance. This disease is responsible for 2.9 million deaths worldwide every year, which makes it the third leading cause of death.[1] Type 1 diabetes (T1DM; insulin-dependent) and type 2 diabetes (T2DM; non-insulin-dependent) are two major types of diabetes. By 2030, 366 million people are expected to have diabetes, and approximately 90% of them will have T2DM; that is, about 5% of the global population will have T2DM.[2] However, T2DM is associated with both microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular cardiovascular complications.[3,4] A two- to fourfold higher incidence of cardiovascular diseases exists among people with T2DM.[5] Although T2DM and cardiovascular disease have multifactorial causes, diet has a considerable effect on

their incidence and severity. The damage and failure of multiple organs are the long-term effects of this disease.[6] Several drugs derived from plants contain alkaloids, glycosides, and flavonoids that have strong antioxidant properties (to treat diabetes). To minimize diabetes symptoms and increase diabetic patients' quality of life, blood glucose levels need to be effectively controlled. Public awareness of this endocrine disorder has led to the identification of the risk factors associated with it, and the ways to prevent and treat it.

Blood glucose levels and lipid profiles can be lowered via pharmacologic drugs and dietary and lifestyle changes. However, some severe side effects are associated with the drug treatment. The natural food products that are used in traditional medicine have been focused on to identify antihyperglycemic agents.[7] Numerous medicinal herb extracts have been used to treat DM due to their minimal side effects and affordability.[8] However, many of the phytochemicals present in these plants are hypoglycemic due to their metabolic or hepatic toxicity. Approximately one- to two-thirds of the 1223 plants that were tested for their ability to lower blood glucose levels might be harmful to humans.[9] Using rat epididymal adipocyte assays, 49 herbs, spices, and medicinal plant extracts were examined to determine their potential effects on insulin-dependent glucose utilization, and cinnamon was the most active product.[8] Cinnamon is one of the most popular and important spices used on a daily basis without side effects, and it is extracted from the inner bark of trees of the Lauraceae family genus *Cinnamomum*. Cinnamon is one of the most important spices and medicinal materials used throughout the world. Many vital oils and derivatives of cinnamon exist, including cinnamaldehyde, cinnamic acid, and cinnamate, which play a vital role in the antioxidant, anti-inflammatory, antidiabetic, antimicrobial, anticancer, and cholesterol-lowering properties of cinnamon.[10–12] In addition, scholars have hypothesized that cinnamon (*Cinnamomum cassia*) and nanocinnamon have health benefits as they effectively lower blood glucose and serum lipid levels[13,14] and that the active component cinnamaldehyde is mainly responsible for the effect of cinnamon on blood glucose.[15]

Researchers have been conducting research on cinnamon since the 1990s when peroxisome proliferator–activated receptors (PPARs) were recognized as potential therapeutic targets for diabetes and dyslipidemia.[16] The results of *in vitro* studies have shown that cinnamon extracts increase glucose uptake, glycogen synthesis, insulin receptor phosphorylation, and insulin cascade systems, which are also crucially important for lipid metabolism.[17] In addition, Subhasree et al.[18] reported that zinc oxide nanoparticles that are reinforced with cinnamon extract have potential as an anticancer, anti-inflammatory, and antioxidant agent and can be used as an alternative to commercially available products. To increase the bioavailability of cinnamon to targeted organs and organ systems, efforts must be made to enhance the actions of cinnamon toward these organs and organ systems. This provoked a search for new nanotechnology methods to provide broad knowledge of applied science and technology to control matter on an atomic and molecular nanoscale, and this matter is thought to be less toxic and free of side effects than the original matter; thereby, its use can increase health care quality.[19] Using the biological nanoparticle sources is important for nanoscale material development, and technical tools that can be used to develop ecofriendly and reliable methodologies to synthesize such materials.[20–22] Accordingly, we aimed to synthesize green silver nanoparticles using cinnamon extracts (C-Ag-NPs) and study the physical and chemical characteristics of the composite nanoparticles, and to assess the biological ecofriendliness of the nanoparticles when controlling the hyperglycemic conditions and related complications disorders in streptozotocin (STZ)-induced diabetic rats.

## Materials and methods

### Ethical approval

Ethical approval for this study was provided by the Institutional Animal Care and Use committee (CU-IACUC) Reviewers, Cairo University, Sep 1, 2022, Expiration Date: Sep 2024.

### Biosynthesis of C-Ag-NPs using cinnamon zeylanicum plants

Initially, the cinnamon aqueous extract (CAE) was prepared by dissolving 10 g of the cinnamon bark powder (Figure 1(A) and (B)) of the zeylanicum plants in 100 mL of distilled water in a 500 mL flask and boiled for 5 min. The CAE was then filtered using Whatman no.1 filter paper, and according to the recommended guidelines, the final solution of CAE was stored at 4°C during the experiment.[23] The silver nitrate ($AgNO_3$) solution (1 mM) was prepared by dissolving 1.7 g of silver nitrate in 40.0 mL of double distilled water. To prevent the auto-oxidation of the silver, the solution was thoroughly mixed and stored in dark bottles. The CAE (1 mL) was then added to 50 mL of 1 mM aqueous $AgNO_3$ solution and kept at room temperature for 8 h to produce the C-Ag-NPs.[24] Initially, the solution was yellowish, but once the silver ($Ag^+$) was reduced to its reduced form ($Ag^0$), the color became dark.

### Identification and separation of C-Ag-NPs

The formation and stability of the silver nanoparticles in the sterile distilled water was confirmed via a UV–vis spectrophotometer analysis by applying a range of wavelengths from 100 to 700 nm. The prepared C-Ag-NPs were centrifuged at 10,000 rpm for 30 min. The pellet was washed three times with 20 mL of distilled water and finally dried at 60°C to remove the free proteins and enzymes that were not capping the C-Ag-NPs.[25]

### Fourier transform infrared spectroscopy studies

Fourier transform infrared spectroscopy (FTIR) was used to measure all the lyophilized samples using a Thermo Nicolet FTIR Spectrometer (Model No. 5700, Madison, USA). All the analyzed spectra were recorded using an ATR accessory and ZnSe as the internal element of reflection. The spectra were recorded in transmission mode with 4 $cm^{-1}$ resolutions and an average of 32 scans.


**Figure 1.** Cinnamon (A) *Zeylanicum* barks and (B) powder.

### Morphological characterization of C-Ag-NPs

Transmission electron microscopy (TEM) imaging was used to morphologically characterize the synthesized materials, whereby a drop of the C-Ag-NP solution was placed on the carbon-coated copper grids and the films were left to stand for 2 min. The extra film solution was removed using blotting paper and then dried the grid. The size distribution of the C-Ag-NPs was estimated according to the basis of the TEM images.[26]

### Animals and biochemical assay

Male Wistar albino rats with a 200 g ± 5.0 body weight (TBW) were obtained from Veterinary College, Cairo University, Giza, Egypt. The animals were kept in the laboratory animal house at a temperature of 22–24°C and humidity of 40–60% with 12-h light and 12-h dark cycles. A standard diet in the form of dry pellets and water was frequently supplied to the animals.[20] The National Institutes of Health (NIH) guides were adhered to when handling all the animals used in this study; specifically, we adhered to the guides on the caring and use of animals: NIH Publication revised (1985), NIPRD standard operating procedures (SOPs).

### STZ Administration

Overall, 100 male albino rats that were about 15 weeks old (Wistar strain) with an average weight of 200 g ± 5 were used in this experiment, and 50 were preserved as normal, non-diabetic rats. In the remaining 50 rats, STZ was intraperitoneally injected at a dosage of 70 mg/kg TBW to induce diabetes (Pari and Venkateswaran, 2002). The development of diabetes was confirmed 72 h after the STZ induction using the Roche Diagnostics Accu-Chek Active Glucometer and blood glucose test strips. Rats with a fasting blood glucose (FBG) level greater than 9.7 mmol/L (175 mg/dL) were included in this study.[27] The success ratio of establishing the diabetic rats is 9.7 mmol (175 mg/dL) sugar of rats. However, other researchers consider blood above 150 mg/dL as diabetes depending on the STZ dosage from 60 to 70 mg/kg and the age of the rats.[28]

### Experimental design

The normal (non-diabetic rats) *were divided into five equal groups (10 rats each) that were numbered* Group 1–Group 5. The Group 1 rats (control) only received a standard diet. The rats in both Groups 2 and 3 were provided a standard diet and ingested 50.0 and 100.0 mg/kg b. wt./day of the CAE, respectively. The rats in Groups 4 and 5 were provided a standard diet and ingested 25.0 and 50.0 mg/kg. b.wt./day of the C-Ag-NPs, respectively. The other 50 diabetic rats that were injected with STZ were equally divided into five groups (Group 6–Group 10) of 10 rats each as well. The Group 6 (diabetic control) rats were only provided a standard diet. The Group 7 and 8 diabetic rats were provided a standard diet and ingested 50.0 and 100.0 mg/kg. b.wt. of the CAE, respectively. The last two groups of diabetic rats (Groups 9 and 10) were provided a standard diet and ingested 25.0 and 50.0 mg/kg of C-Ag-NPs, respectively. Both the TBW and body weight gain (BWG) were recorded at the start of the experiment and on a weekly basis. The experiment was conducted for 30 days. The silver group was excluded, according to our previous studies, which indicate that silver nanoparticles coated with cinnamon had no toxicity or any side effects when used as antioxidant and anticancer at normal and cancer cells[11] or when used to control the hyperglycemia in diabetic rats.[28]

### Collection of blood samples for serum preparation

At the beginning and, after 10, 20, and 30 days of the experiment, blood samples (3 mL) were collected from the retro-orbital plexus of the treated rats and were centrifuged at room temperature at 1500 rpm for 10 min. After separation,

the serum samples were stored in clean Eppendorf Tubes at −20°C until analysis.

### Determination of hematological parameters

The hematological parameters, total red blood cells (RBCs), and hemoglobin concentration (HGB), white blood cells (WBCs), and other hematological parameters (hematocrit [HCT], mean cell volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], red blood cell distribution width coefficient of variation [RDW-CV], red blood cell distribution width standard deviation [RDW-SD], mean platelet volume [MPV], platelet distribution width [PDW], and plateletcrit [PCT]) of the blood were determined using a BC-3200 Auto Hematology Analyzer in the biochemistry department, King Saud University.

### Determination of serum glucose and lipid profiles

The serum levels of the FBG were quantitatively analyzed using a Vitros Analyzer (Ortho-Clinical Diagnostics Inc., Johnson and Johnson) following the standard protocols reported by Tietz.[29] The total cholesterol (TC), triglycerides (TGs), and high-density lipoprotein cholesterol (HDL-C) were analyzed using a Randox diagnostic kit,[30] and the Friedwald et al.'s[31] method was followed to calculate the low-density lipoprotein cholesterol (LDL-C) in the blood samples.

### Biochemical parameters of hepatic marker enzymes

We followed the kinetic methodology described by Reitman S. Frankel[32] to estimate the serum aspartate transaminase (AST) and alanine transaminase (ALT) activities, whereas the serum alkaline phosphatase (ALP) activity was determined using commercial kits as described by Schumann and his group.[33] An effective colorimetric method was adopted to determine the serum gamma-glutamyl transferase (GGT) level by following the reported method.[34] All the obtained results are expressed as units per liter (U/L) throughout the article.

### Antioxidant enzymes activity

The superoxide dismutase (SOD) activity (SOD, $CuZnSO_4$, EC 1.15.1.1) in the serum was analyzed using spectrophotometrical technique where the lambda max was set at 560 nm to measure the absorbance. The catalase (CAT) activity (CAT, EC1.11.1.6) in the serum was assessed by following the method outlined by Aebi,[35] and $H_2O_2$ was used as the substrate. The disappearance of $H_2O_2$ was investigated at 240 nm, and the CAT activity was expressed in U/L. Regarding the glutathione peroxidase (GPx) activity, the method employed by Paglia and Valentine[36] was used to estimate the GPx (EC 1.11.1.9) activity in the serum.

### Statistical analysis

Statistical Package for the Social Sciences (SPSS; computer software version 17) was employed to analyze the data, and the data are displayed as mean ± SD. The paired Student's *t*-test was adopted to compare the mean values of each group. Multiple comparisons of the mean between the treatments and negative control were obtained by analyzing the data with a one-way analysis of variance (ANOVA) and Bonferroni's *post hoc* test. The correction method was investigated, and statistical probabilities of $P < 0.5$ were considered significant. The accuracy of the method was dependent on repeated determination of the parameters in triplicates. For this, we take blood samples from 10 rats and each sample was analyzed in triplicates and the mean from 30 determination was calculated with ± SD.

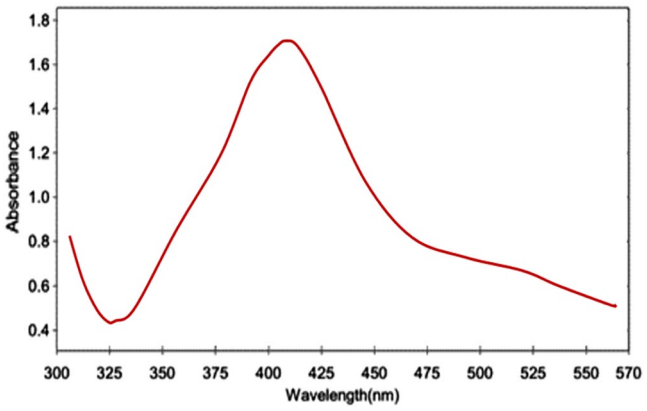


**Figure 2.** UV–visible absorption spectra of synthesized C-Ag-NPs, showing the SPR peak of silver nanoparticles at 410 nm.

## Results

### Spectrophotometry

The formation of silver nanoparticles was monitored by observing the color change and via UV–vis spectroscopy. The color was caused by the excitation of the surface plasmon resonance (SPR) due to the reduction of $Ag^+$ to $Ag^0$. The absorption spectra of the silver nanoparticles solution consisted of a single sharp SPR band at 410 nm, which is an indication of the reduction of silver (Figure 2). The most characteristic part of the silver solution was a narrow plasmon absorption band that was observable in the 300–570 nm regions.

### TEM analysis

The TEM images of the biosynthesized C-Ag-NPs are shown in Figure 3. The TEM images showed that the largest NPs attained a spherical shape. The different sizes of the NPs determined the dispersed nature of the synthesized NPs. The disperse nature is attributed to the presence of biomolecules. The biosynthesized NPs attained a polydisperse nature and the size was 37 nm, which matched the crystallite size. The images showed that on the surface of the roughly sphere-shaped polydisperse particles, the nanoparticles were deposited and its surface morphology was smooth and homogeneous. The electron diffraction in the images revealed that the spherical nanoparticles were single face-centered cubic crystals with a preference for growth along the Ag axis.

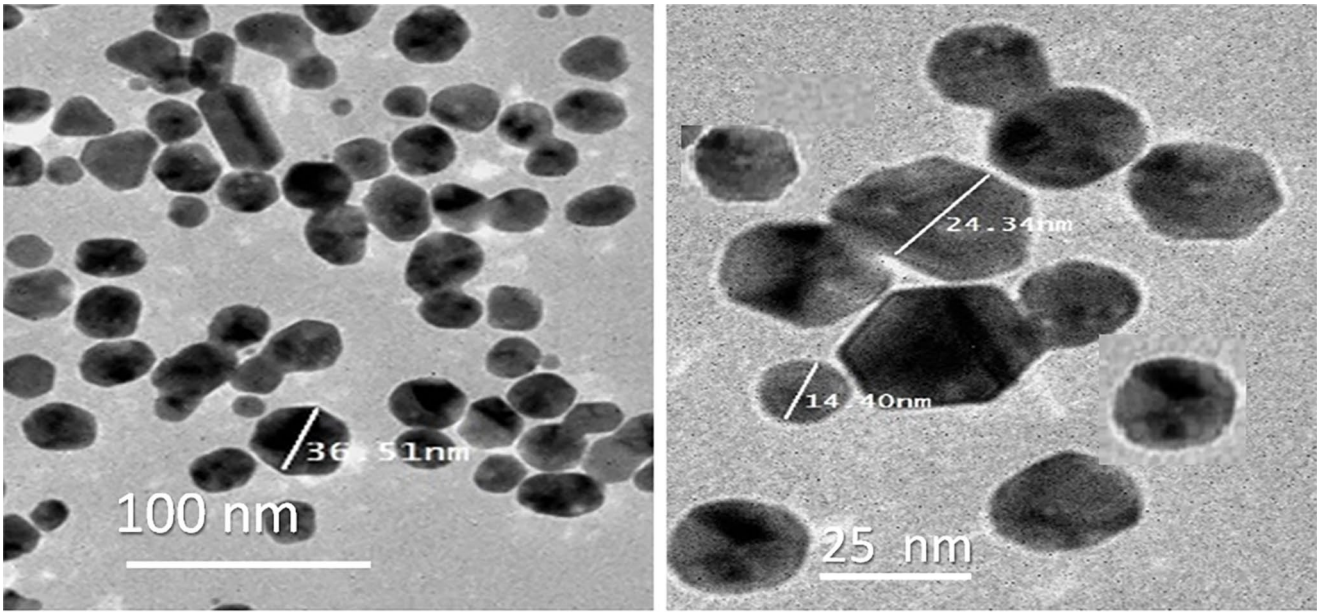


**Figure 3.** Crystalline clusters of silver nanoparticles.

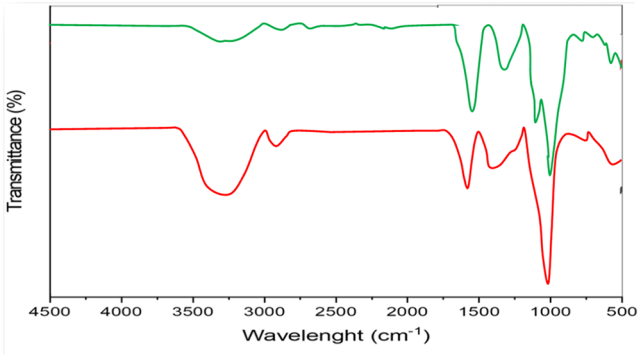


**Figure 4.** FTIR spectra of cinnamon extract (Green) and C-Ag-NPs (red).

## FTIR analysis

Figure 4 shows the FTIR spectra of the cinnamon plant extract and C-Ag-NPs. The peaks in both samples that appeared at 1595 $cm^{-1}$ were due to the stretching vibrations of the C–C bonds of the aromatic rings and the higher intensity attributes to the surface OH stretching.[37] The band around 1006 $cm^{-1}$ was very prominent in the C-Ag-NPs mixture, which indicated the presence of $Ag^+$ ions, which might have formed due to the reduction of $AgNO_3$.[38] The peaks in the 540–760 $cm^{-1}$ region were caused by the C–H bending vibrations and Ag–O stretching.[39] A small shift in the C=O stretching vibration band from 3310 $cm^{-1}$ to a lower wave number indicated a strong interaction between the capping agent and the C-Ag-NPs, which was due to the presence of flavonoids in the plant extracts.[11,40] The presence of flavonoids may have mainly been responsible for the efficient capping and stabilization of the C-Ag-NPs. Thus, the results of the FTIR studies indicated that the cinnamon extract could more effectively completely reduce the silver nitrate and stabilize the nanoparticle through its flavonoids content.

## The effect of CAE and C-Ag-NPs on hematological parameters of normal and diabetic rats

The data in Table 1 showed that no significant ($P < 0.05$) changes existed in the WBC, HGB, HCT, MCV, MCH, MCHC, MPV, and PDW values of the normal rats that ingested the CAE or C-Ag-NPs at either low or high dosages (G2–G5) compared with the normal control rats (G1). Compared with the normal control rats (G1), the STZ-induced rats (G6) experienced a significant increase in their WBCs and significant reduction in their HGB, RBCs, and MCV, whereas no significant change ($P < 0.05$) in the MCH, MCHC, MPV, or PDW values was observed. Conversely, the ingestion of the CAE or C-Ag-NPs in the diabetic rats (G7–G10) significantly ($P < 0.05$) decreased the WBCs and increased the HGB, RBC, and MCV values, whereas the MCH, MCHC, MPV, and PDW values were indifferent. In the diabetic rats, high doses of the CAE (100 mg/kg) or C-Ag-NPs (50.0 mg/kg) were more effective than low doses. A high CAE dose decreased the WBCs by 33.1%, whereas it increased the HGB, RBCs, and HCB by 11.2, 44.9, and 35.4%, respectively. As compared with the diabetic control rats (G6), high doses of C-Ag-NPs decreased the WBCs by 44.9% and increased the HGB, RBCs, and HCB by 25.8, 78.8, and 33.0%, respectively. In the diabetic rats that ingested high doses of the CAE (G8) or C-Ag-NPs (G10), the WBCs, HGB, RBCs, HCT, MCV, MCH, MCHC, MPV, and PDW values did not considerably differ from that of the normal control rats (G1).

## Effect of CAE and C-Ag-NPs on TBW and BWG in normal and diabetic rats

The data in Table 2 show that the TBW and BWG of the normal and diabetic rats that ingested the CAE (50.0 and 100.0 mg CAE/kg TBW) or C-Ag-NPs (25.0 and 50.0 mg C-Ag-NPs/kg TBW) increased compared with those of the control rats.

**Table 1.** The effect of CAE and C-Ag-NPs on hematological parameters of normal and STZ diabetic male albino rats.

| | WBC ($\times 10^9$/L) | HGB g/d | RBC ($\times 10^{12}$/L) | HCT % | MCV fl | MCH pg | MCHC g/dL | MPV fl | PDW |
|---|---|---|---|---|---|---|---|---|---|
| G1 | $10.3^a \pm 1.1$ | $12.1^a \pm 1.3$ | $8.8^a \pm 1.6$ | $45.3^a \pm 2.1$ | $61.0^a \pm 1.0$ | $18.1^a \pm 1.3$ | $33.2^a \pm 0.8$ | $7.2^a \pm 0.4$ | $16.6^a \pm 0.7$ |
| G2 | $9.2^a \pm 1.2$ | $12.5^a \pm 1.3$ | $8.1^a \pm 0.3$ | $43.2^a \pm 3.1$ | $58.9^a \pm 2.1$ | $19.8^a \pm 1.1$ | $31.2^a \pm 0.9$ | $6.8^a \pm 0.3$ | $16.2^a \pm 0.6$ |
| G3 | $10.7^a \pm 1.1$ | $13.5^a \pm 1.2$ | $8.9^a \pm 0.4$ | $45.8^a \pm 3.8$ | $62.1^a \pm 1.7$ | $18.8^a \pm 2.1$ | $32.5^a \pm 1.1$ | $7.2^a \pm 0.5$ | $16.3^a \pm 0.5$ |
| G4 | $9.2^a \pm 0.8$ | $13.6^a \pm 1.3$ | $8.8^a \pm 0.9$ | $46.3^a \pm 2.9$ | $62.4^a \pm 2.1$ | $18.9^a \pm 3.0$ | $32.1^a \pm 2.1$ | $7.8^a \pm 0.3$ | $16.2^a \pm 0.4$ |
| G5 | $10.3^a \pm 1.1$ | $14.1^b \pm 1.4$ | $9.8^a \pm 0.5$ | $47.7^a \pm 3.1$ | $61.8^a \pm 3.2$ | $19.1^a \pm 1.7$ | $31.8^a \pm 0.9$ | $7.1^a \pm 0.2$ | $15.9^a \pm 0.3$ |
| G6 | $16.9^b \pm 1.4$ | $8.9^c \pm 0.9$ | $4.9^b \pm 1.1$ | $28.5^b \pm 2.3$ | $60.2^a \pm 2.4$ | $17.9^a \pm 2.1$ | $31.1^a \pm 2.1$ | $7.8^a \pm 0.3$ | $16.5^a \pm 0.4$ |
| G7 | $14.8^b \pm 1.2$ | $9.1^c \pm 0.7$ | $6.8^b \pm 0.8$ | $34.2^c \pm 2.3$ | $61.7^a \pm 3.1$ | $18.2^a \pm 1.1$ | $31.8^a \pm 1.7$ | $7.4^a \pm 0.4$ | $15.8^a \pm 0.1$ |
| G8 | $11.3^a \pm 1.1$ | $10.9^a \pm 0.9$ | $8.5^a \pm 0.4$ | $44.6^a \pm 2.2$ | $62.1^a \pm 1.9$ | $19.1^a \pm 2.3$ | $32.1^a \pm 1.2$ | $6.9^a \pm 0.2$ | $16.3^a \pm 0.3$ |
| G9 | $11.6^a \pm 1.2$ | $9.8^c \pm 1.2$ | $7.3^c \pm 0.3$ | $38.9^c \pm 3.2$ | $62.3^a \pm 1.3$ | $19.1^a \pm 1.1$ | $32.1^a \pm 2.0$ | $7.7^a \pm 0.3$ | $16.4^a \pm 0.3$ |
| G10 | $9.3^a \pm 1.1$ | $11.2^a \pm 1.1$ | $9.2^a \pm 0.6$ | $45.6^a \pm 3.4$ | $63.1^a \pm 3.2$ | $19.7^a \pm 1.2$ | $32.8^a \pm 1.1$ | $7.2^a \pm 0.2$ | $16.2^a \pm 0.4$ |

CAE: cinnamon aqueous extract; C-Ag-NP: cinnamon silver nanoparticles; WBC: white blood cells; HGB: hemoglobin concentration; RBC: red blood cells; HCT: hematocrit; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MPV: mean platelet volume; PDW: platelet distribution width. Values are expressed as mean ± SD ($n = 10$); Superscript terms, a, b, c, d, indicate $P < 0.05$ versus various groups present within the same column. The groups are mentioned in the method section.

**Table 2.** Effect of CAE and C-Ag-NPs on TBW and BWG in normal and STZ diabetic rats.

| | Initial BW | TBW week 1 | TBW week 2 | TBW week 3 | TBW week 4 | BWG/30 days | BWG/day |
|---|---|---|---|---|---|---|---|
| G1 | $207.50 \pm 4.54$ | $222.50 \pm 4.65$ | $230.25 \pm 3.76$ | $249.65 \pm 4.33$ | 256.654.11 | $49.15^a \pm 0.11$ | $1.64 \pm 0.10$ |
| G2 | $210.75 \pm 3.87$ | $225.75 \pm 3.65$ | $239.25 \pm 4.02$ | $253.32 \pm 3.54$ | $269.11 \pm 3.56$ | $58.36^b \pm 0.12$ | $1.95 \pm 0.09$ |
| G3 | $209.50 \pm 5.77$ | $233.50 \pm 4.71$ | $248.25 \pm 3.54$ | $265.65 \pm 4.32$ | $275.21 \pm 4.11$ | $69.71^c \pm 0.09$ | $2.32 \pm 0.06$ |
| G4 | $210.50 \pm 3.98$ | $236.75 \pm 3.76$ | $248.50 \pm 4.23$ | $261.45 \pm 3.76$ | $275.89 \pm 4.56$ | $61.39^b \pm 0.04$ | $2.04 \pm 0.07$ |
| G5 | $208.00 \pm 4.65$ | $238.75 \pm 2.79$ | $253.00 \pm 3.11$ | $261.50 \pm 4.98$ | $279.32 \pm 3.55$ | $71.32^d \pm 0.03$ | $2.34 \pm 0.02$ |
| G6 | $212.67 \pm 3.54$ | $188.33 \pm 6.87$ | $165.83 \pm 4.09$ | $143.98 \pm 2.65$ | $140.98 \pm 4.43$ | $-71.69^e \pm 0.00$ | $-2.39 \pm 0.01$ |
| G7 | $211.00 \pm 2.65$ | $214.00 \pm 4.98$ | $198.00 \pm 2.98$ | $200.32 \pm 5.43$ | $202.33 \pm 2.44$ | $-8.67^f \pm 0.01$ | $-0.28 \pm 0.00$ |
| G8 | $209.00 \pm 4.87$ | $209.00 \pm 3.87$ | $200.50 \pm 3.89$ | $200.10 \pm 4.54$ | $204.23 \pm 3.44$ | $-4.77^g \pm 0.01$ | $-0.16 \pm 0.00$ |
| G9 | $208.00 \pm 4.98$ | $201.09 \pm 4.11$ | $195.00 \pm 4.11$ | $201.65 \pm 3.98$ | $205.43 \pm 4.22$ | $-2.57^h \pm 0.01$ | $-0.09 \pm 0.00$ |
| G10 | $208.94 \pm 3.76$ | $199.00 \pm 4.21$ | $200.00 \pm 3.23$ | $203.45 \pm 4.88$ | $209.99 \pm 4.66$ | $1.05^k \pm 0.00$ | $0.04 \pm 0.00$ |

CAE: cinnamon aqueous extract; C-Ag-NP: cinnamon silver nanoparticles; TBW: total body weight; BWG: body weight gain; STZ: streptozotocin; BW: body weight. Values are expressed as mean ± SD ($n = 10$); Superscript terms, a, b, c, d, e, f, g, h, k, indicate $P < 0.05$ versus various groups present within the same column. The groups are mentioned in the method section.

All the normal rats (G2–G5) had a considerably higher BWG compared with the normal control rats (G1) after 30 days of the experiment. When the rats ingested higher doses of the CAE (G3) or C-Ag-NPs (G5), their BWG increased significantly compared with the rats that ingested low doses (G2 and G4, respectively) or the rats in the normal control group (G1). The BWG was 69.71 and 70.32 g/30 days in the G3 and G5 rats, respectively, or 2.32 and 2.34 g/day in the G2 and G4 rats, respectively. The CAE or C-Ag-NPs increased the health and growth rate of the normal rats. The G6 rats experienced a decreased TBW of 71.69 g/30 days or 2.39 g/day during this experiment. The weight loss in the diabetic G7 and G8 rats that ingested the CAE at either high or low doses or low doses of the C-Ag-NPs (G9) was 8.67, 4.77, and 2.57 g/30 days, respectively. The G10 rats that ingested 50.0 mg/kg TBW of the C-Ag-NPs exhibited a slight increase in their TBW gains (1.05 g/30 days). In the diabetic rats, ingesting the CAE or C-Ag-NPs decreased the TBW losses and enhanced their health conditions during the experimental period.

## Effect of CAE and C-Ag-NPs on blood glucose of normal and diabetic rats

Table 3 shows the effects of the CAE and C-Ag-NPs on the blood glucose profiles of the normal (G1–G5) and diabetic (G6–G10) rats at different time intervals, including at the start of the experiment (FBG0), and after 3 (FBG1), 10 (FBG2), 20 (FBG3), and 30 days (FBG4) of STZ induction. The ingestion of a low or high dose of the CAE or C-Ag-NPs by the normal rats did not affect their blood sugar levels when compared with the control rats (G1). The glucose profiles of the rats from Groups 1–5 were nearly the same. Moreover, the STZ treatments (G6–G10) significantly increased the blood glucose levels ($P < 0.05$) compared with the corresponding normal rats (Groups 1–5). Initially, the hyperglycemia level in the diabetic control group (G6) was 280.87 mg/dL, but by the 10th day, it was 288.87 mg/dL, and by the 30th day, it was 278.21 mg/dL. The rats with diabetes that ingested either the CAE or C-Ag-NPs experienced a significant ($P < 0.05$) and important drop in their blood glucose levels (G7–G10). The values significantly ($P \leq 0.05$) decreased from $270.00 \pm 6.87$ to $125.44 \pm 2.12$ mg/dL after 30 days of the CAE treatment with 100.0 mg/kg b. wt. (G8) and from $276.67 \pm 6.98$ to $104.98 \pm 1.33$ mg/dL after 30 days of the C-Ag-NPs treatment with 50.0 mg/kg (G8). The rats exposed to cinnamon showed this effect at an early stage. High dosages of the CAE or C-Ag-NPs were more effective than low dosages at reducing blood glucose levels in diabetic rats ($P < 0.05$), and C-Ag-NPs had more pronounced effects as hypoglycemic agents than the CAE.

**Table 3.** Effect of CAE and C-Ag-NPs on FBG in normal and diabetic rats.

| | FBG0 | FBS0 after 72 h of STZ injection | FBG1 | FBG2 | FBG3 | FBG4 |
|---|---|---|---|---|---|---|
| G1 | $90.50^{a} \pm 2.11$ | --------- | $90.76^{a} \pm 4.51$ | $88.75^{a} \pm 1.66$ | $88.51^{a} \pm 1.55$ | $90.55^{a} \pm 1.97$ |
| G2 | $89.75^{a} \pm 1.43$ | --------- | $90.43^{a} \pm 3.33$ | $88.00^{a} \pm 1.87$ | $93.82^{a} \pm 1.29$ | $89.54^{a} \pm 2.13$ |
| G3 | $88.50^{a} \pm 2.32$ | ---------- | $87.54^{a} \pm 4.32$ | $85.00^{a} \pm 2.11$ | $89.99^{a} \pm 0.99$ | $88.67^{a} \pm 1.90$ |
| G4 | $88.50^{a} \pm 3.21$ | ---------- | $87.65^{a} \pm 4.76$ | $90.25^{a} \pm 1.97$ | $88.92^{a} \pm 1.23$ | $87.98^{a} \pm 2.11$ |
| G5 | $87.50^{a} \pm 1.54$ | ---------- | $86.54^{a} \pm 4.33$ | $87.25^{a} \pm 1.87$ | $86.88^{a} \pm 1.33$ | $87.76^{a} \pm 1.66$ |
| G6 | $90.50^{a} \pm 5.87$ | $280.87^{b} \pm 7.76$ | $288.87^{b} \pm 3.54$ | $299.65^{b} \pm 8.65$ | $289.95^{b} \pm 5.43$ | $278.21^{b} \pm 5.76$ |
| G7 | $88.32^{a} \pm 4.16$ | $263.25^{b} \pm 8.65$ | $275.00^{b} \pm 4.76$ | $250.25^{c} \pm 4.43$ | $189.86^{c} \pm 4.31$ | $139.98^{c} \pm 4.76$ |
| G8 | $91.60^{a} \pm 3.54$ | $270.00^{b} \pm 6.87$ | $252.76^{c} \pm 2.54$ | $200.00^{d} \pm 3.76$ | $175.91^{c} \pm 4.87$ | $125.44^{d} \pm 2.12$ |
| G9 | $89.60^{a} \pm 4.11$ | $281.67^{b} \pm 8.76$ | $251.43^{c} \pm 4.11$ | $205.67^{d} \pm 3.65$ | $187.33^{c} \pm 3.54$ | $136.76^{c} \pm 1.98$ |
| G10 | $88.40^{a} \pm 2.32$ | $276.67^{b} \pm 6.98$ | $205.43^{d} \pm 4.34$ | $151.67^{e} \pm 2.76$ | $132.11^{d} \pm 3.44$ | $104.98^{e} \pm 1.33$ |

CAE: cinnamon aqueous extract; C-Ag-NP: cinnamon silver nanoparticles; FBG: fasting blood glucose; STZ: streptozotocin; FBS: fasting blood sugar.
Values are expressed as mean ± SD ($n = 3$); Superscript terms, a, b, c, d, e, indicate $P < 0.05$ versus various groups present within the same column. The groups are mentioned in the method section. Where, the values of fbg0, FBG1, FBG2, FBG3, and FBG4 indicate that the value taken at starting of the experiment, and after 3, 10, 20 and 30 days of STZ induction, respectively.

### Influence of CAE and C-Ag-NPs on lipid profile of normal and diabetic rats

Table 4 shows how the CAE and *C-Ag-NPs* affected the lipid profiles (TC, TGs, LDL-C, and HDL-C) in normal and diabetic rats. In the normal rat groups (G2–G5), ingesting the CAE or C-Ag-NPs at low or high doses resulted in no considerable changes in the lipid profiles compared with the normal control rats (G1). However, the induction of diabetes by STZ (G6–G10) significantly increased the plasma lipid concentrations ($P < 0.05$). Compared with the corresponding normal rats (G1–G5), the diabetic rats (G6–G10) had considerably higher TC, TG, LDL-C, and HDL-C levels. Diabetes tends to lower good cholesterol levels (HDL-C) and rise TG and bad cholesterol (LDL-C), which increase the risk for heart disease and stroke. This condition is called diabetic dyslipidemia. The ingestion of the CAE or C-Ag-NPs at low or high dosages in the diabetic rats (G7–G10) significantly ($P < 0.05$) reduced the TC, TG, and LDL-C compared with the diabetic control rats (G6). However, the data showed that the HDL-C did not undergo any considerable changes. The CAE or C-Ag-NPs at high doses had more profound effects on the lipid profiles than at low doses. The TC, TG, and LDL-C values in the diabetic control rats (G6) were 179.34 ± 3.11, 159.87 ± 4.32, and 80.65 ± 4.65, respectively, and were considerably reduced to 137.11 ± 3.65, 111.87 ± 3.65, 50.61 ± 3.43, respectively, when the diabetic rats ingested 100.0 mg of the CAE/kg. b.wt.; these values then decreased to 115.87 ± 3.43, 107.89 ± 2.99, and 34.13 ± 2.76, respectively, when the diabetic rats ingested 50.0 mg of the CNPs/kg b.wt. In the diabetic rats, ingesting 100.0 mg of CAE/hg. b.wt. decreased the bad cholesterol (LDL-C) by 37.2%, whereas ingesting 50.0 mg of CNPs/kg. b.wt. lowered the LDL-C by 57.7% in comparison with the diabetic controls (G6). The study by El–Desoky et al.[13] suggested that cinnamon extract has an insulin potentiating factor (IPF) which potentiates the effect of insulin in serum via increasing the pancreatic secretion of insulin from the existing β cells or its release from the unbound form. The antidiabetic activity of cinnamon extract could be associated with one or more of its components (cinnamaldehyde, cinnamic acid, tannin, and water-soluble methylhydroxychalcone polymer).

### Influence of CAE and C-Ag-NPs on liver function enzymes of normal and diabetic rats

A comparison of the serum ALT, AST, ALP, and GGT levels in the normal and diabetic rats that ingested the CAE and C-Ag-NPs is shown in Table 5. In the normal rats that ingested the CAE or C-Ag-NPs at low or high dosages (G2–G5), no significant changes in enzyme activity occurred, and all the enzyme activity values were similar to those of the normal control rats (G1). The activity of the liver biomarker enzymes (ALT, AST, ALP, and GGT) significantly increased ($P < 0.05$) in the STZ diabetic rats (G6) and reached 112.63 ± 9.66, 135.63 ± 8.94, 147.72 ± 9.54, and 25.83 ± 2.34 U/L, respectively, compared with that of the control rats (G1). The ingestion of the CAE or C-Ag-NPs in the diabetic rats (G7–G10) significantly ($P < 0.05$) decreased the activities of the liver function enzyme compared with the diabetic control rats (G6). The high dosages of the CAE (100.0 mg/kg. b.wt.) and C-Ag-NPs (50.0 mg/kg. b.wt.) resulted in a significant ($P < 0.05$) reduction in all the enzyme activities, whereas low dosages did not. When the diabetic rats ingested a high dosage of C-Ag-NPs (50.0 mg/kg. b.wt.) (G10), the enzyme activity values decreased by 45.9, 49.2, 47.2, and 68.6%, respectively, whereas the ingestion of 100.0 mg CAE/kg. b.wt. (G8) decreased the enzyme activity values by 20.1, 32.3, 29.1, and 50.2%, respectively, compared with those of the diabetic control rats (G6). All the enzyme activities in the diabetic rats in G7–G10 were still significantly higher than those of the corresponding normal control rats in G2–G5, except the activity of the GGT enzyme in the G10 rats who ingested 50 mg/kg TBW of the C-Ag-NPs returned to a normal value that was similar to that found in the normal control rats.

### Influence of CAE and C-Ag-NPs on antioxidant enzyme activities

A comparison of the antioxidant enzyme biomarkers SOD, CAT, and GPx in the serum of the normal and diabetic rats that ingested the CAE (50.0 mg and 100.0 mg/kg TBW) and C-Ag-NPs (25.0 and 50.0 mg/kg TBW) is presented in Table 6. Neither low nor high doses of the CAE or C-Ag-NPs considerably affected the antioxidant enzyme activities in the normal rats (G2–G5) when compared with the control rats

**Table 4.** Effect of CAE and C-Ag-NPs on blood lipid profile in normal and diabetic rats.

| Parameters (mg/dL) | G1 | G2 | G3 | G4 | G5 | G6 | G7 | G8 | G9 | G10 |
|---|---|---|---|---|---|---|---|---|---|---|
| TG | $66.32^{a} \pm 3.04$ | $65.51^{a} \pm 2.32$ | $64.76^{a} \pm 1.33$ | $65.93^{a} \pm 1.99$ | $63.83^{a} \pm 1.54$ | $159.87^{b} \pm 4.32$ | $130.87^{c} \pm 4.65$ | $111.87^{d} \pm 3.65$ | $130.45^{c} \pm 3.54$ | $107.89^{e} \pm 2.99$ |
| TC | $73.81^{a} \pm 3.11$ | $74.67^{a} \pm 1.87$ | $73.94^{a} \pm 1.87$ | $75.98^{a} \pm 1.32$ | $73.31^{a} \pm 1.89$ | $179.34^{b} \pm 3.11$ | $158.93^{c} \pm 4.11$ | $137.11^{d} \pm 3.65$ | $158.91^{c} \pm 3.45$ | $115.87^{e} \pm 3.43$ |
| LDL-C | $26.93^{a} \pm 3.43$ | $26.98^{a} \pm 2.12$ | $24.87^{a} \pm 2.54$ | $24.91^{a} \pm 3.01$ | $22.59^{a} \pm 3.11$ | $80.65^{b} \pm 4.65$ | $69.38^{c} \pm 2.21$ | $50.61^{d} \pm 3.43$ | $65.74^{c} \pm 2.98$ | $34.13^{e} \pm 2.76$ |
| HDL-C | $39.92^{a} \pm 2.15$ | $40.11^{a} \pm 1.43$ | $41.55^{a} \pm 2.12$ | $42.12^{a} \pm 2.32$ | $44.19^{a} \pm 1.65$ | $69.77^{b} \pm 1.54$ | $69.81^{b} \pm 3.11$ | $73.39^{b} \pm 2.55$ | $70.51^{b} \pm 2.87$ | $78.45^{c} \pm 2.67$ |

TG: triglycerides; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.
Superscript terms, a, b, c, d, e, indicate $P < 0.05$ versus various groups within the same row. The groups are mentioned in the method section.

(G1). Compared with the corresponding normal rats (G1–G5), the diabetic rats (G6–G10) with STZ had significantly lower antioxidant enzyme activities ($P < 0.05$). Compared with the diabetic control rats (G6), consuming the CAE or C-Ag-NPs either at low or high doses (G7–G10) significantly ($P < 0.05$) increased the antioxidant enzyme activity. The consumption of high doses of the CAE or C-Ag-NPs significantly increased the SOD, CAT, and GPx activities by 15.0%, 10.8%, and 7.8% and 38.1%, 37.1%, 10.8%, respectively, in the diabetic rats (G8 and G10) compared with the diabetic control rats (G6). Both the CAE and C-Ag-NPs were highly effective at increasing the antioxidant enzyme activities in the diabetic rats, whereas the C-Ag-NPs were highly potent compared with the CAE.

## Discussion

The most common endocrine disease is DM, which is caused by an insufficient supply of insulin and leads to hyperglycemia and chronic complications. Diabetes is frequently associated with hyperglycemia, polyphagia, polydipsia, and weight loss. Foods, spices, and other natural products that have an IPF are important to enhance glucose metabolism in diabetes, and using these products is a more appropriate approach to treat diabetes in terms of applicability and cost for diabetes in developing countries.[13] Several hypoglycemic herbs have been used for non-prescription diabetes treatments. Foods containing cinnamon exhibit biological effects against DM and its complications. Consequently, they should be enhanced to act against diabetes more effectively and to be more bioavailable to the targeted organs and systems. Therefore, cinnamon extract was used to synthesize green silver nanoparticles, which were thought to be more effective and freer of side effects than the original material. Hence, we aimed to study the physical and chemical properties of composite nanoparticles and evaluate their biological ecofriendliness when controlling hyperglycemia in STZ-induced diabetic rats. The formation of cinnamon silver nanoparticles (C-Ag-NPs) was monitored by observing the color change and using the UV–vis spectrum. Light is efficiently absorbed and scattered by silver nanoparticles. In response to light at specific wavelengths, the conduction electrons on the metal surface undergo a collective oscillation, which results in a strong interaction with light. The SPR causes silver nanoparticles to have higher absorption and scattering intensities than identically sized non-plasmonic nanoparticles.[21,41] After 1 h, the reaction mixture turned yellowish brown and then dark brown after 8 h. This color change was caused by the reduction of $Ag^{+}$ to $Ag^{0}$, which excited the SPR. As shown in Figure 2, the silver nanoparticles solution showed a single sharp SPR band at 410 nm (Figure 2). A silver solution is characterized by a narrow plasmon absorption band between 300 and 570 nm. A distinct visible peak was observed at 410 nm, which indicated a silver reduction. These results were in accordance with the data obtained by different researcher, who monitored the reduction of pure $Ag^{+}$ ions in an $AgNO_3$ mixture with cinnamon extract by measuring the UV–vis spectrum.[37] The surface plasmon absorption band of the cinnamon AgNPs reached a maximum of 446 nm, and this coincided with the silver plasmon absorption band (325–525 nm),

**Table 5.** Effect of CAE and C-Ag-NPs on liver function biomarkers in normal and diabetic rats.

| | ALT (U/L) | AST (U/L) | ALP (U/L) | GGT (U/L) |
|---|---|---|---|---|
| Group 1 | $26.33^{a} \pm 3.65$ | $49.69^{a} \pm 5.52$ | $89.56^{a} \pm 5.45$ | $7.13^{a} \pm 0.69$ |
| Group 2 | $27.99^{a} \pm 2.12$ | $48.78^{a} \pm 3.87$ | $88.94^{a} \pm 3.43$ | $7.11^{a} \pm 0.67$ |
| Group 3 | $29.98^{a} \pm 3.55$ | $49.66^{a} \pm 4.76$ | $90.39^{a} \pm 4.43$ | $7.36^{a} \pm 0.92$ |
| Group 4 | $27.62^{a} \pm 7.44$ | $48.21^{b} \pm 2.23$ | $90.13^{a} \pm 4.66$ | $8.64^{a} \pm 0.96$ |
| Group 5 | $30.98^{a} \pm 2.12$ | $50.88^{b} \pm 2.54$ | $91.99^{a} \pm 3.98$ | $9.01^{a} \pm 0.41$ |
| Group 6 | $112.63^{b} \pm 9.66$ | $135.63^{c} \pm 8.94$ | $147.72^{b} \pm 9.54$ | $25.83^{b} \pm 2.34$ |
| Group 7 | $102.43^{c} \pm 6.21$ | $112.76^{d} \pm 5.21$ | $115.98^{c} \pm 6.11$ | $15.98^{c} \pm 1.66$ |
| Group 8 | $89.97^{d} \pm 4.65$ | $91.87^{e} \pm 5.98$ | $104.76^{d} \pm 4.77$ | $12.87^{d} \pm 1.98$ |
| Group 9 | $78.76^{e} \pm 3.32$ | $95.76^{e} \pm 5.65$ | $100.65^{d} \pm 5.54$ | $11.76^{d} \pm 1.22$ |
| Group 10 | $60.98f \pm 3.76$ | $68.9f \pm 2.76$ | $98.94^{d} \pm 4.89$ | $8.11^{a} \pm 1.01$ |

CAE: cinnamon aqueous extract; C-Ag-NP: cinnamon silver nanoparticles; U/L: units per liter; GGT: gamma-glutamyl transferase; ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase.
Values are expressed as mean ± SD ($n = 3$); Superscript terms, a, b, c, d, e, indicate $P < 0.05$ versus various groups present within the same column. The groups are mentioned in the method section.

**Table 6.** Effect of CAE and C-Ag-NPs on antioxidant enzyme biomarkers in STZ diabetic rats.

| | SOD (U/L) | CAT (U/L) | GPx (U/L) |
|---|---|---|---|
| Group 1 | $250.23 \pm 8.22^{a}$ | $4.01 \pm 0.46^{a}$ | $921.26 \pm 13.25^{a}$ |
| Group 2 | $248.65 \pm 6.87^{a}$ | $4.21 \pm 0.11^{a}$ | $922.87 \pm 15.23^{a}$ |
| Group 3 | $249.33 \pm 9.28^{a}$ | $4.02 \pm 0.93^{a}$ | $916.62 \pm 14.75^{a}$ |
| Group 4 | $251.32 \pm 8.94^{a}$ | $4.29 \pm 0.72^{a}$ | $918.72 \pm 12.61^{a}$ |
| Group 5 | $252.54 \pm 8.98^{a}$ | $4.76 \pm 0.21^{c}$ | $911.87 \pm 13.98^{b}$ |
| Group 6 | $169.32 \pm 9.62^{c}$ | $2.53 \pm 0.56^{d}$ | $699.32 \pm 15.40^{d}$ |
| Group 7 | $185.76 \pm 9.54^{d}$ | $3.24 \pm 0.43^{e}$ | $723.76 \pm 12.98^{e}$ |
| Group 8 | $194.66 \pm 10.65^{e}$ | $3.91 \pm 0.54^{e}$ | $753.54 \pm 13.54^{f}$ |
| Group 9 | $201.54 \pm 10.67^{e}$ | $3.99 \pm 0.54^{a}$ | $756.87 \pm 13.65^{f}$ |
| Group 10 | $233.75 \pm 11.71^{f}$ | $4.02 \pm 0.76^{a}$ | $774.65 \pm 14.87^{g}$ |

CAE: cinnamon aqueous extract; C-Ag-NP: cinnamon silver nanoparticles; STZ: streptozotocin; SOD: superoxide dismutase; U/L: units per liter; CAT: catalase.
Term: Values are expressed as mean ± SD ($n = 3$); Superscript terms, a, b, c, d, e, f, g indicate $P < 0.05$ versus various groups present within the same column. The groups are mentioned in the method section.

which indicates the presence of silver nanoparticles. A TEM image of the silver nanoparticles solution is shown in Figure 3. The findings indicated that the silver nanoparticles were adsorbed and deposited onto polydisperse particles that were roughly sphere-shaped. The nanoparticles that emerged in the images had a variety of irregular shapes, including spheres, triangles, and other irregular shapes. The typical electron diffraction pattern (Figure 3) revealed that the spherical nanoparticles had a single face-centered cubic crystalline structure. The C-Ag-NPs ranged in size from 6.0 to 37.0 nm. In addition, Figure 4 shows the FTIR spectra of the cinnamon plant extract system after the $AgNO_3$ was reduced. The bands in this figure indicate a strong interaction between the capping agent and silver nanoparticles. Flavonoids and terpenoids in plant extracts are mainly responsible for capping the nanoparticles.[38,39]

The CAE or C-Ag-NPs ingested by the normal rats (G2–G5) did not considerably affect their blood count (BC) compared with the G1 rats. In contrast, the WBC levels in the diabetic rats treated with the CAE (G7 and G8) or C-Ag-NPs (G9 and G10) were significantly lower ($P < 0.05$) than those of the G6 rats. Likewise, higher concentrations of the CAE in the G8 rats or C-Ag-NPs in the G10 rats were more effective than the lower concentrations. In addition, the C-Ag-NPs were more effective than the CAEs. This demonstrates the effectiveness of the above treatments at reducing the hematological abuse within the diabetic rats' defense system. A significant increase in the RBC, HGB, and HCT levels was observed in the STZ diabetic rats that ingested the CAE or C-Ag-NPs compared with the G6 rats (Table 2).

In the diabetic rats that were not treated (G6), these effects could have been caused by anemia or glycosylation. The metabolism of bone marrow, kidneys, and hemoglobin may not be adversely affected by cinnamon extract or C-Ag-NPs because only substances that significantly alter red blood cell values and the associated parameters will affect the bone marrow, kidneys, and HGB metabolism.[42] Because an increase in the MCV and MCH values is indicative of macrocytic anemia, the non-considerable change in the MCV and MCH values indicates the absence of macrocytic anemia. The MCHC values were not changed significantly by the cinnamon extract or C-Ag-NPs, which suggests the absence of hereditary spherocytosis because MCHC values are known to be elevated in this disorder.[42] The other hematological parameters (RDW-CV, RDW-SD, PLT, MPV, PWD, and PCT) were not considerably different between the groups, which aligns with the reported results.[42,43] The results of this study showed that the ingestion of the CAE or C-Ag-NPs in normal rats (G2–G5) resulted in no significant changes in the TBW or BWG compared with the G1 rats, whereas in the STZ diabetic rats (G6), the TBW and BWG were considerably decreased compared with the normal control rats (G1).

The CAE or C-Ag-NPs ingested by the STZ diabetic rats (G7–G10) resulted in significant ($P < 0.05$) increases in their TBW compared with the diabetic control rats (G6). The higher bioavailability and solubility of the C-Ag-NPs in water media may explain their effectiveness over the cinnamon extract.[14] Decreasing the TBW of the diabetic rats was possible by catabolizing fats and proteins. A characteristic condition of diabetes is a defect in the glucose metabolism and excessive breakdown of tissue proteins.[13] Administering cinnamon resulted in a remarkable recovery of the TBW. This may have occurred because cinnamon controls hyperglycemia and enhances insulin secretion, which both decrease protein degradation. In normal rats (G2–G5), the CAE or CNP consumption had no considerable effect on the serum

glucose levels compared with the untreated control rats (G1). When the cinnamon extract or C-Ag-NPs were ingested by the STZ diabetic rats, the serum glucose level was significantly reduced ($P < 0.05$) compared with the untreated diabetic rats (G6). As well, the C-Ag-NPs more effectively gradually lowered the serum glucose than the cinnamon extract. According to Hussein and his coworkers,[14] nanocinnamon capsules are much more soluble and bioavailable than cinnamon powder extracts. In addition to facilitating the absorption of water-soluble nutrients, bile salts facilitate the absorption of lipophilic vitamins, lipids, fatty acids, and cholesterol in the same way that nanomicelles created from cinnamon do. At the dosages used, the serum glucose levels in the CAE- or C-Ag-NPs-treated diabetic rats did not reach normal levels until 30 days after the treatment. With a similar study by El–Desoky et al.,[13] our group found that cinnamon at 250 mg/kg supplemented into the diets of alloxan diabetic rats caused an increase in their TBW and decrease in their blood glucose levels. According to Governa et al.,[44] cinnamon's antihyperglycemic effects are attributed to its role as an insulin secretagogue, which stimulates insulin release and activates the enzymes that are involved in glucose metabolism, glycolysis, and gluconeogenesis. In addition, cinnamon enhances glucose uptake by the cells, which contributes to its hypoglycemic effects, and decreases plasma glucose levels in STZ-induced diabetic rats.[45] It has been found that the CAE contained an IPF that potentiated insulin's effect in the serum by increasing insulin release from the pancreatic cells or from unbound forms. Therefore, CAE may have antihyperglycemic properties due to one or more of its active components. Moreover, flavonoids also regenerated damaged cells in alloxan-induced rats and are known to act as insulin secretagogues.[46]

Cinnamon oil administered to diabetic rats at 100 mg/kg resulted in positive effects on the blood glucose and lipids, and enhanced the function of pancreatic islets by regenerating damaged pancreatic β-cells in alloxan-induced diabetic rats.[47] In comparison with the treated normal control (G1), the CAE or CNP administration in normal rats (G2–G5) did not considerably change their lipid profiles (TC, TG, LDL-C, and HDL-C). In contrast, the STZ diabetic rats (G6) had significantly ($P < 0.05$) higher plasma lipids (TC, TG, LDL-C, and HDL-C) compared with the controls (G1). According to the report by Blevins et al.,[48] diabetes is characterized by abnormally high plasma lipid concentrations that are related to an increase in the mobilization of free fatty acids from peripheral depots as insulin inhibits hormone-sensitive lipase. Cinnamate reduced cholesterol levels in rats by inhibiting HMG Co-A reductase enzyme activity and suppressing lipid peroxidation by enhancing the hepatic antioxidative enzyme activity. The STZ diabetic rats (G7–G10) that ingested the CAE or C-Ag-NPs experienced significant ($P < 0.05$) decreases in their TG, TC, and LDL-C levels. In contrast, their HDL-C levels were significantly higher than those in the untreated diabetic rats (G6).

The C-Ag-NPs had a greater impact on the lipid profiles than the CAE. Hussein[14] explained that cinnamon does not mix well with water, so absorbing cinnamon in one's mouth is difficult. Nanocinnamon is far more effective when ingested than ground cinnamon. The results clearly demonstrated that the CAE or C-Ag-NPs had a positive effect on the lipid profiles as they are hypoglycemic and hypolipidemic and may prevent cardiovascular diseases. According to the increase in the plasma TC, TG, LDL-C, and atherogenic index levels, accompanied by a decrease in the HDL-C concentration, increase cardiovascular disease risk factors.[48] Qin et al.[49] reported that CAE decreased the TG and TC levels in STZ diabetic rats after three weeks of administration. In the normal rats (G2–G5), the CAE or C-Ag-NPs showed no significant effect on the AST, ALT, ALP, and GGT activities compared with the control rats (G1). Ingesting the CAE or C-Ag-NPs considerably decreased the activities of these enzymes in the ZTS diabetic rats (G7–G10) compared with the diabetic control rats (G6). However, the C-Ag-NPs were highly active at reducing the activity of the liver biomarker enzymes, more than the CAE, which may have been due to its higher bioavailability and solubility compared with the CAE. Based on these results, cinnamon, specifically C-Ag-NPs, may be able to reduce hepatic damage.[50] Large bile duct obstructions, intrahepatic cholestasis, and liver infiltrating diseases increased the ALP levels in the plasma. Increasing ALP levels are associated with damaged hepatic cells because alkaline phosphatase is in the cytoplasm and is released into circulation after a cellular injury. Several scholars have linked DM to oxidative stress, which can result from a reduction in one's antioxidant defense, an increase in free radical production, or both.[51] Modulating insulin resistance and oxidative stress are important therapeutic strategies for this disease. Several biomarkers can be used to evaluate oxidative stress. Because they are protective enzymes that act against free radical formation in tissues, we measured the activity of SOD, CAT, and GPx for this study. The antioxidative enzymes SOD, CAT, and GPx were not considerably altered after the CAE or CNP consumption in the normal rats (G2–G5) compared with the untreated control rats (G1). The STZ-induced diabetic rats experienced a significant reduction in their serum SOD, CAT, and GPx levels. After four weeks, the cinnamon extract and C-Ag-NPs significantly ($P < 0.05$) increased the serum SOD, CAT, and GPx levels to levels that were near that of the control rats (G1). These data align with the results by El–Baz et al.,[11] whereby we found a significant increase in the antioxidative enzymes (SOD, CAT, GPx, and GST) in Hep-G2 cancer and Bj-1 normal cells after the rats were treated with cinnamon extract or nanoparticles. They further suggest that cinnamon nanoparticles have a powerful antioxidant effect and the ability to reduce oxidative stress levels in the cells because they are more soluble and bioavailable. The C-Ag-NPs were found to sustain hyperglycemia reductions, decrease the risk of developing microvascular and hepatic diseases, and reduce related complications in diabetic patients, and stronger results were found when the C-Ag-NPs were used than the cinnamon extract itself. Both the CAE and C-Ag-NPs decreased the lipid peroxidation and normalized the antioxidant systems. In addition, the C-Ag-NPs increased the activity of the antioxidative enzymes more than the CAE. The reason that the C-Ag-NPs showed a greater effect than the CAE might have been due to their higher bioavailability and solubility in water.

## AUTHORS' CONTRIBUTIONS

YGEB, AM, and MAA involved in conceptualization. YGEB and MAA participated in methodology. AM and YGEB performed validation. GEED and SMW participated in data curation. AI involved in writing – original draft preparation. GEED, SMW, and AI involved in writing – review and editing. GEED participated in project administration. GEED and SMW contributed in funding acquisition. All authors have read and agreed to the published version of the article.

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