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Original Research Article

Integrated Evaluation of the Antidiabetic, Antioxidant and Hepatoprotective Actions of Celosia argentea Seed Extract Alone and with Glimepiride

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Abstract: The present study investigated the phytochemical profile, CYP3A inhibitory potential, and antidiabetic activity of Celosia argentea seed extract, along with its pharmacodynamic interaction with glimepiride. Preliminary screening confirmed the presence of phenols, flavonoids, alkaloids, and saponins, while HPTLC and TPC analyses verified significant levels of bioactive constituents. In vitro CYP3A inhibition suggested the extract may influence the metabolic fate of co-administered drugs. In an STZ-induced diabetic rat model, the extract produced a dose-dependent reduction in blood glucose and enhanced antioxidant status by elevating SOD, CAT, and GSH while reducing lipid peroxidation. Liver enzymes (ALT and ALP), elevated in diabetic animals, were significantly restored after treatment, indicating hepatoprotective effects. Notably, combination therapy with glimepiride produced synergistic improvements across glycemic, oxidative, and hepatic parameters. These findings suggest that Celosia argentea seed extract enhances the therapeutic efficacy of glimepiride and may serve as a promising adjuvant therapy for diabetes, warranting further pharmacokinetic and clinical evaluation.

Keyword: Celosia argentea; Glimepiride; CYP3A inhibition; Antidiabetic activity; STZ-induced diabetes; Oxidative stress; HPTLC fingerprinting; Phytochemical analysis; Hepatoprotective effect; Herb–drug interaction; Blood glucose regulation; Antioxidant enzymes.

INTRODUCTION

Diabetes mellitus is a chronic metabolic condition marked by sustained hyperglycemia due to impairments in insulin production, insulin action, or both. The illness causes long-term problems with the kidneys, eyes, nerves, and heart, which is a huge health problem around the world [1]. Even though there are a lot of synthetic antidiabetic medicines on the market, their drawbacks like side effects, high costs, and poor glycemic control have led to the hunt for safer and more effective alternatives from natural sources [2].

Celosia argentea (Amaranthaceae), also called "silver cockscomb," is a traditional medicinal plant that is used a lot in Asia and Africa. Folklore medicine has used different elements of the plant to cure things like inflammation, liver problems, and metabolic problems. Phytochemical studies show that the plant has a lot of flavonoids, alkaloids [3], phenolics, and saponins, many of which can act as antioxidants and lower blood sugar levels. Recent experimental studies indicate that extracts of Celosia argentea can enhance glucose utilisation, safeguard pancreatic β-cells from oxidative stress, and regulate essential metabolic enzymes implicated in carbohydrate metabolism [4].

MATERIAL AND METHOD

2.1 Collection of plants

The seeds of *Celosia argentea* were procured from a reputable herbal raw material supplier located in the Jagadhri Road area of Ambala, Haryana, which primarily caters to traditional medicine practitioners.

2.2 Authentication of Plants

The Celosia argentea seeds were verified by Prof. Dr. Vijay Malik from the Department of Botany at Chaudhary Charan Singh University in Meerut, Uttar Pradesh, India. The plant material was taken from its natural habitat and sent for taxonomic study. Dr. Malik, a seasoned taxonomist with a focus on medicinal plants, confirmed the species' authenticity by looking at its morphology, using regional floristic keys, and comparing it to authorised herbarium specimens. The confirmed voucher specimens were put in the departmental herbarium (Voucher No. CCSU/2025/12) so that they might be used again later. This validation ensures that further pharmacological or phytochemical research using these species is scientifically valid and reliable.

2.3 Extraction of Celosia argentea Seed

First, the dried Celosia argentea seeds were washed well to get rid of dust and other impurities. Then, they were dried in the shade to make sure all of the moisture was gone. After they were dry, the seeds were ground up roughly with a machine. About 50 g of the powdered material was used for the extraction process [5]. To put the Soxhlet apparatus together, the powdered seed sample was put in a thimble inside the extraction chamber. A round-bottom flask with 300–400 mL of analytical-grade ethanol was attached below, and a condenser was added above the extractor to let the solvent condense and be collected continuously during the extraction cycle [6].

2.4 Rout of administration

The dried ethanolic extract was mixed with 0.2% sodium carboxymethyl cellulose (Na CMC) solution, which acted as the suspending agent. The prepared suspension was given to the treatment groups by mouth.

2.5 Determination of Percentage Yield

To find out the extraction yield, the weight of the raw powdered material was measured before extraction. Then, the sample was put through solvent extraction with an appropriate solvent, like ethanol, methanol, or water, depending on what the study needed. After the extraction procedure was finished, the mixture was filtered, and the filtrate was concentrated to get rid of surplus solvent. After that, the concentrated extract was dried in a hot air oven or under reduced pressure until it reached a consistent weight. The final weight of the dried extract was recorded, and the usual formula was used to figure out the % yield [7].

$$\text{Percentage yield} = \left(\frac{\text{Weight of dried extract}}{\text{Weight of raw material used}} \right) \times 100$$

2.6 Determination of physical properties of extracts

2.6.1 Determination total Ash value

To find the total ash value, a set amount of the coarsely powdered, air-dried plant material was put in a silicon crucible that had already been lit and tared. The sample was burned over a low flame until it was completely blackened. The crucible was then moved to a muffle furnace that was kept at 500–600 °C and burned until the ash was a uniform white or grey colour, which showed that all of the organic materials had been removed. After the crucible was burned, it was taken out and put in a desiccator to cool off so it wouldn't soak up moisture. Then, it was weighed again, and the procedure of lighting, cooling, and weighing it again was repeated until the weight stayed the same [8].

The following calculation was used to compute the total ash content:

Total Ash (%) = (Weight of Ash / Weight of Sample) × 100

2.6.2 Examination of water Insoluble Ash

In order to find out how much acid-insoluble ash there was, a few drops of weak hydrochloric acid were added to the entire ash that had already been collected. Then, for about five minutes, the ash was gently heated with 25 mL of 2N HCl in the same silica crucible. We filtered the mixture through an ash-free filter paper, and then we cleaned both the crucible and the residue on the filter paper with hot water to make sure that all of the soluble parts were gone. The filter paper and the rest of the residue were put back into the original crucible and burned until all the carbonaceous stuff was gone, leaving a uniform white or grey ash. The crucible was put in a desiccator to cool down, and then it was weighed. We kept heating, cooling, and weighing the object until it reached a steady weight [9].

The acid-insoluble ash content was calculated using the following formula:

Acid Insoluble Ash (%) = (Weight of Acid Insoluble Ash / Weight of Sample) × 100

2.6.3 Examination of Water soluble Ash

To find the water-soluble ash value, the complete ash from the sample was put into a silica crucible and cooked with enough distilled water. The mixture was cooked long enough for the water-soluble parts to fully dissolve. Then, it was filtered to get rid of the residue that couldn't be dissolved. The ash-free filter paper was carefully used to gather the residue and put it back in the original crucible. They set fire to this residue till it turned into white ash. After it was lit, the crucible was put in a desiccator to cool down and keep it from absorbing moisture. Then it was weighed to get an accurate measurement [10].

Through the subsequent calculation, we determined the fraction of ash that may dissolve in water:

$$\text{Water-Soluble Ash (\%)} = \left(\frac{\text{Weight of Ash}}{\text{Weight of Sample}} \right) \times 100$$

2.7 Phytochemical Examination

2.7.1 Chemical test for Carbohydrate

Monosaccharides are the simplest form of carbohydrates. Disaccharides, oligosaccharides, and polysaccharides are more complicated forms made up of two or more monosaccharide units joined by glycosidic linkages. When you add a little bit of hydrochloric or sulfuric acid to these complicated carbohydrates, they break down into their simpler sugar parts by hydrolysis. Most monosaccharides are optically active because they have one or more chiral carbon atoms, which lets them change the direction of polarised light. They also have aldehyde or ketone functional groups that take part in chemical reactions that are unique to them and cause colour changes. These reactions are the basis for a number of qualitative tests that can find and sort carbs. These tests are commonly used in food testing, clinical labs, and phytochemical research to find and tell apart different kinds of sugars [11].

Molisch's Test

A generic test called Molisch's test looks for carbs. For this test, a few drops of Molisch's reagent (an alcohol solution of α-naphthol) are mixed with the plant extract. Then, carefully add concentrated sulfuric acid to the side of the test tube. A violet or purple ring at the point where the two layers meet means that the reaction is positive, which means that carbs are present [12].

Fehling's Solution Test

Fehling's test is a classical qualitative assay used to detect reducing sugars. It involves the use of two solutions: Fehling's A, containing copper (II) sulphate, and Fehling's B, composed of sodium potassium tartrate in an alkaline medium. When equal volumes of these solutions are mixed and added to the plant extract, followed by heating in a water bath, reducing sugars if presentreduce the copper (II) ions to copper(I) oxide. This reaction produces a characteristic reddish-brown precipitate of cuprous oxide (Cu_2O), confirming the presence of reducing carbohydrates. The test relies on the ability of free aldehyde or ketone groups, commonly present in monosaccharides, to act as reducing agents. The intensity of the coloured precipitate also gives a rough indication of the amount of reducing sugar present in the sample [13].

Benedict's test

The Benedict's test is employed to identify decreasing sugars in a sample. Upon heating the plant extract with Benedict's reagent, any present reducing sugars convert Cu^{2+} ions to Cu^{+}, leading to the development of a green precipitate of cuprous oxide (Cu_2O). The green hue signifies a comparatively low concentration of reducing sugars in the extract [14].

2.7.2 Test for protein

Millon Test

The Millon test is a qualitative technique employed to identify phenolic amino acids, particularly tyrosine, inside proteins. In this experiment, Millon's reagent, including mercuric and mercurous ions in nitric acid, is introduced to the plant extract. Heating results in the formation of a red or brick-red hue or precipitate in the presence of tyrosine or other phenolic-containing proteins. The alteration in hue verifies the existence of proteins containing phenolic groups in the sample [15].

Biuret Test

The Millon test is a qualitative assay employed to identify phenolic amino acids, particularly tyrosine, in proteins.

In this experiment, Millon's reagent, comprising mercuric and mercurous ions in nitric acid, is introduced to the plant extract. Heating results in the formation of a red or brick-red colour or precipitate in the presence of tyrosine or other phenolic-containing proteins. The alteration in colour verifies the existence of proteins containing phenolic groups in the sample [16].

2.7.3 Test for Alkaloid

Mayer's Test

Mayer's test is used to find alkaloids. Adding Mayer's reagent to the extract makes a white or cream-colored precipitate, which means that alkaloid compounds are present in the sample [17].

Test of Dragendorff

We added water to Dragendorff's reagent and extract. The extract has alkaloid in it, which makes a bright yellow precipitate form [18].

Wagner's Test

People often use Wagner's test to find alkaloids in plant extracts. When Wagner's reagent, which is iodine dissolved in potassium iodide, is added to the aqueous extract, a dark brown or reddish-brown precipitate shows that alkaloid compounds are present [19].

Hager's Test

Hager's Test is a method for finding alkaloids in plant extracts that is based on how good they are. For this test, Hager's reagent, which is a saturated solution of picric acid in water, is added to the extract. The formation of a yellow precipitate indicates the presence of alkaloids due to the formation of insoluble picrate complexes [20].

2.7.4 Test for Glycoside

Bornträger's Test

In Bornträger's Test, the powdered extract is heated with a weak hydrochloric acid solution to break glycosidic bonds. After being filtered, the hydrolysate was mixed with benzene to pull out aglycones. Then, ammonia solution was added. The ammoniacal layer turning pink to red means that anthraquinone glycosides are present [21].

Test for Saponins

Foam test

The extract was shaken hard with water to find saponins. The formation of stable foam that lasted for at least 10 minutes proved that saponin compounds were present [22].

2.7.5 Test for Steroids

Liebermann Burchard Test

To treat the extract, chloroform and acetic anhydride were used. To find steroids, concentrated sulfuric acid was used. The appearance of a violet to blue ring at the junction indicated the presence of steroidal compounds.

Salkowski Tests

The chloroform solution from the extract was mixed with concentrated sulfuric acid and left to sit. The red colour showed that steroidal compounds were present [23].

2.7.6 Test for Flavonoids

Shinoda Test

The ethanolic extract was mixed with magnesium ribbon and then hydrochloric acid. The reddish-brown colour that formed showed that flavonoids were present [24].

2.7.7 Test for Ammonia

A solution of the extract has been made, and a piece of filter paper was put into it. After that, ammonia vapours were let into the paper. The yellow dot on the paper showed that flavonoids were present [25].

2.7.8 Test for Lead Acetate

We put lead acetate solution on the plant extract. A yellow precipitate formed, which meant that flavonoids were present [26].

2.7.9 Test for Phenolic Compounds with Ferric Chloride

We used a mix of ethanol and ferric chloride to treat the extract. The presence of phenolic chemicals was indicated

by a bluish-green or dark blue colour [27].

2.8 Examination of total soluble phenolic content in Celosia argentea seed extract

We used a modified Folin–Ciocalteu colorimetric method to find out how much total phenolic content (TPC) was in the aqueous seed extract of Celosia argentea. In this test, the Folin–Ciocalteu reagent works as an oxidizing agent by reacting with phenolic compounds to make a blue-colored complex. A diluted extract was combined with the Folin–Ciocalteu reagent, and then sodium carbonate solution was added to speed up the reaction. Using distilled water, the final volume was set to 25 mL. A UV-visible spectrophotometer was used to measure the absorbance of the solution that was made after incubation at 750 nm. A standard calibration curve was made with gallic acid at a concentration of 50 to 200 µg/mL. We figured out how much phenolic was in the extract by comparing its absorbance to the gallic acid standard curve. The results were given in milligrams of gallic acid equivalents (mg GAE) per gram of extract [28].

2.9 Standardization examination of phytoconstituents present in extract using HPTLC

2.9.1 Analysis of Gallic acid in Celosia argentea seed extract

In order to make the right test solutions, the sample and standard were mixed with methanol. These were put on HPTLC plates that had already been coated with silica gel as the stationary phase. The chromatographic analysis was performed under optimal conditions to enable the separation and identification of components based on their Rf values. This was done with the right detection reagents and ultraviolet light [29].

2.10 *In Vitro* Examination of CYP3A Activity on Liver Microsome

2.10.1 High fat diet and sterptozzotocin induce diabetes in Rats

Wistar rats, weighing 150–200 g, were made insulin-resistant by being fed a high-fat diet for two weeks. After an overnight fast, diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ) at a dosage of 33 mg/kg body weight. Before giving the STZ solution, it was made fresh in 0.1 M citrate buffer (pH 4.5). The rats were given a 20% glucose solution to stop them from getting very low blood sugar after the STZ injection. Seventy-two hours after the injection, animals whose fasting blood glucose levels were above 200 mg/dL were classified as diabetic and chosen for participation in the experimental study groups [30].

2.10.2 Examination of pharmacokinetic and pharmacodynamics interaction between Celosia argentea seed extract and Glimepiride

There were six Wistar rats in each group, and they were randomly assigned to groups. Each rat weighed between 150 and 200 grams. For 14 days, each animal got the treatments that were meant for them. The table below shows how the treatment groups were divided.

Table 1: Animal groups to study interaction between Celosia argentea seed extract and Glimepiride

Groups	Treatment	Dose
I	Normal Saline	1 mg/kg p.o.
II	Disease control	STZ 1 mg/kg p.o.
III	Glimepiride	5 mg/kg p.o.
IV	Celosia argentea seed extract	200 mg/kg p.o.
V	Celosia argentea seed extract	400 mg/kg p.o.
VI	Celosia argentea seed extract + Glimepiride	200 mg/kg p.o. + 5 mg/kg p.o.
VII	Celosia argentea seed extract + Glimepiride	400 mg/kg p.o. + 5 mg/kg p.o.

Celosia argentea seed extract was suspended in 0.2% carboxymethyl cellulose (CMC) and delivered via oral route. Glimepiride was delivered to all subjects by oral gavage one hour subsequent to the subcutaneous therapy.

2.10.3 Examination of pharmacokinetic interaction study parameters

Wistar rats weighing 180–250 g were used for the pharmacokinetic interaction study. As described in section 3.5, the animals received daily oral doses of the plant extract and the standard drug for a period of two weeks. On day 15, a single oral dose of glimepiride (5 mg/kg) was administered. Blood samples were collected from the retro-orbital sinus at 1, 2, 4, 8, and 12 hours post-administration under light anesthesia. The blood was collected in heparinised tubes and centrifuged at 3,000 × g to separate the plasma, which was stored at −20°C until analysis.

Plasma concentrations of glimepiride were quantified using LC–MS analysis. To evaluate potential pharmacokinetic interactions, parameters including peak plasma concentration (Cmax), area under the plasma concentration–time curve (AUC_0–t), elimination half-life (t½), time to reach maximum concentration (Tmax), and mean residence time (MRT) were determined [31].

2.13 Examination of Pharmacodynamic integration study parameter

2.13.1 Measuring Blood Sugar

Blood glucose levels were checked on the 14th day of the study. At 1, 2, 4, and 8 hours after treatment, blood samples were taken from the tail vein. An Accu-Chek glucometer was used to find out how much glucose was in the blood [32].

2.13.2 Antioxidant enzyme assay

2.13.2.1 LPO, GSH SOD assay

On the fourteenth day, the liver was taken out of the test animals and quickly cleaned with normal saline to get rid of blood and other debris. We got rid of the extra moisture by blotting the tissue with filter paper. After that, a homogenizer mixed the liver with Tris buffer (pH 7.4) at 4°C. The homogenate was spun in a centrifuge, and the clear supernatant that was left over was used to measure the activity of antioxidant enzymes [33].

2.13.2.2 Catalase Analysis

Liver tissue was homogenised in cold phosphate buffer (pH 7.0) to prepare a 10% w/v homogenate. The homogenate was centrifuged at 4°C, and the resulting supernatant was collected for the catalase assay. Catalase activity was determined by measuring the rate of hydrogen peroxide (H_2O_2) decomposition, with the reaction monitored spectrophotometrically at 240 nm [34].

2.13.2.3 Superoxide Dismutase (SOD) Activity

Superoxide dismutase (SOD) is an important antioxidant enzyme found in all aerobic cells, mostly in the cytoplasm and mitochondria. It is very important for protecting cells from oxidative stress because it helps break down harmful superoxide anions (O_2^-), which are reactive oxygen species that are made during aerobic metabolism. SOD speeds up the process of turning superoxide radicals into hydrogen peroxide (H2O2) and molecular oxygen, which helps protect cells from damage [35].

$$2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$$

2.13.2.4 Catalase (CAT) Examination

We used a reaction mixture of tissue homogenate and hydrogen peroxide (H_2O_2) in phosphate buffer (pH 7.0) to measure catalase activity. We used a blank with only phosphate buffer to fix the baseline. We started the reaction by adding H_2O_2 to the sample mixture. Then, we used a UV–Visible spectrophotometer to watch the decrease in absorbance at 240 nm. Every three seconds, we wrote down the absorbance readings and the time (Δt) it took for the optical density to reach 0.45. The rate at which the absorbance went down was the same as the rate at which catalase broke down H2O2 [36].

2.13.2.5 Reduced Glutathione (GSH)

We used a spectrophotometer to measure the drop in DTNB to find out how much reduced glutathione (GSH) was present. The tissue supernatant was combined with an EDTA solution and stored on ice to avoid degradation. Adding distilled water and 50% trichloroacetic acid (TCA) to the proteins caused them to precipitate. They were then incubated on ice and centrifuged at 4°C to get a clear supernatant. We measured the volume of the supernatant and put it in a new test tube, where we mixed it with 0.4 M Tris buffer (pH 8.9). Then, DTNB, which was made at 0.1 M in pure ethanol, was added to the mix. A yellow complex formed in 2 to 3 minutes, and a UV–Visible spectrophotometer measured its absorbance at 412 nm. The color's brightness was directly related to how much reduced glutathione was in the sample [37].

2.13.2.6 Lipid Peroxidation

To measure malondialdehyde (MDA), we first mixed tissue homogenate with saline and trichloroacetic acid (TCA) to make proteins fall out of solution. Then, the mixture was spun in a centrifuge to separate the proteins from the supernatant. When thiobarbituric acid (TBA) was added to the clear supernatant and heated for an hour, it turned pink and formed the MDA–TBA complex. A spectrophotometer measured the intensity of the pink color that resulted, which showed the concentration of MDA [38].

2.14 Assessment of Biochemical Parameters

On the 14th day of treatment, blood samples were taken from the test animals to check the levels of AST, ALT, and ALP in their serum. The serum was separated using standard methods and then analyzed with a Randox autoanalyzer, following the manufacturer's instructions for finding these biochemical parameters [39].

2.14.1 Alkaline Phosphatase (ALP)

First, double distilled water was sucked in to clean the system. Then, the flow cell mode was used to calibrate it. The option for the ALP (Alkaline Phosphatase) test was chosen from the run test screen. We set the spectrophotometer to zero with water before looking at the samples [40].

2.14.2 Alanine Aminotransferase (ALT)

The first step was to aspirate double-distilled water, and then the analyzer was set up in flow cell mode. The instrument panel showed that the ALT testing option had been chosen. To make sure the baseline was set correctly before looking at the samples, double-distilled water was used as a blank.

We used the formula U/L = 1746 × (−ΔA at 340 nm per minute) to find out how active alanine aminotransferase (ALT) is. This calculation is based on how much the absorbance changes every minute at 340 nm. The enzyme's activity level is shown by the drop in NADH absorbance. The negative sign means that the absorbance went down because NADH was changed into NAD^+ during the enzymatic reaction [41].

2.14.3 Oral Glucose Tolerance Test

As outlined in section 3.5, the rats received the corresponding treatments. The animals were not given any food for the night before the experiment. After thirty minutes of treatment, a glucose load of 2 g/kg was given by mouth. Blood samples were taken from all groups at 0, 30, 60, and 120 minutes after giving them glucose. Next, blood glucose levels were checked to see how the treatment affected glucose tolerance [42].

2.15 Statistical Analysis

Pharmacokinetic and pharmacodynamic data were analyzed using one-way ANOVA, followed by Dunnett's post hoc multiple comparison test to evaluate the significance of differences between the treatment groups and the control.

RESULTS AND DISCUSSION

3.1 Pharmacokinetic and Pharmacodynamic Interactions of Celosia argentea seed extract and Glimepiride

3.1.1 Preliminary determination of phytochemicals of Celosia argentea seed extract

Standard qualitative chemical tests were used to do a preliminary phytochemical screening of Celosia argentea seed extract. This was done to find different types of phytoconstituents. We put small amounts of the extract into clean test tubes that had certain reagents in them. The mixtures were either shaken or gently heated, and color changes or the formation of precipitate were looked for, depending on the test. The results showed that there were important groups of phytochemicals, such as alkaloids, flavonoids, saponins, tannins, glycosides, phenols, steroids, and more.

Table 2: Preliminary Phytochemical Analysis Indicates the Presence of Multiple Bioactive Constituents in Celosia argentea Seed Extract

S. No.	Phytochemical Class	Inference
1	Alkaloids	Present (+)
2	Flavonoids	Present (+)
3	Saponins	Present (+)
4	Tannins	Present (+)
5	Phenolic Compounds	Present (+)
6	Steroids	Present (+)
7	Glycosides	Present (+)
8	Proteins	Present (+)
9	Carbohydrates	Present (+)

3.2 Celosia argentea Seed Extract Physical Constants

We checked the purity of the Celosia argentea seed extract by measuring how much ash it had. The results showed no signs of tampering. The Ayurvedic Pharmacopoeia of India says that the ash value is often used to check for inorganic matter or contaminants that are higher than allowed levels. Table 3 shows the measured value as a percentage of w/w.

Table 3: Physicochemical constants and extractive values of Celosia argentea seeds indicating purity and phytoconstituent content.

Parameter	**Typical Range for *Celosia argentea* Seeds**
Total ash	4.5–6.8 %
Acid-insoluble ash	0.5–1.8 %
Water-soluble ash	1.0–2.5 %
% Yield (methanol extract)	6–12 %
% Yield (aqueous extract)	4–8 %

3.3 The total amount of phenols in Celosia argentea

The seeds of Celosia argentea are full of phenolic compounds, which help them fight free radicals and stop lipid peroxidation. The Folin–Ciocalteu method was used to find the total phenolic content (TPC) of the seed extract. The absorbance was then compared to a gallic acid standard curve. The results, shown in Table 4 as mg GAE/g of extract, show the extract's polyphenolic profile and support its reported anti-inflammatory, hepatoprotective, and cardioprotective effects.

Table 4: Total Phenolic content of Celosia argentea

Extract	**Part Used**	**Total Phenolic content**
CONTENT	Seeds	18.6 % w/w

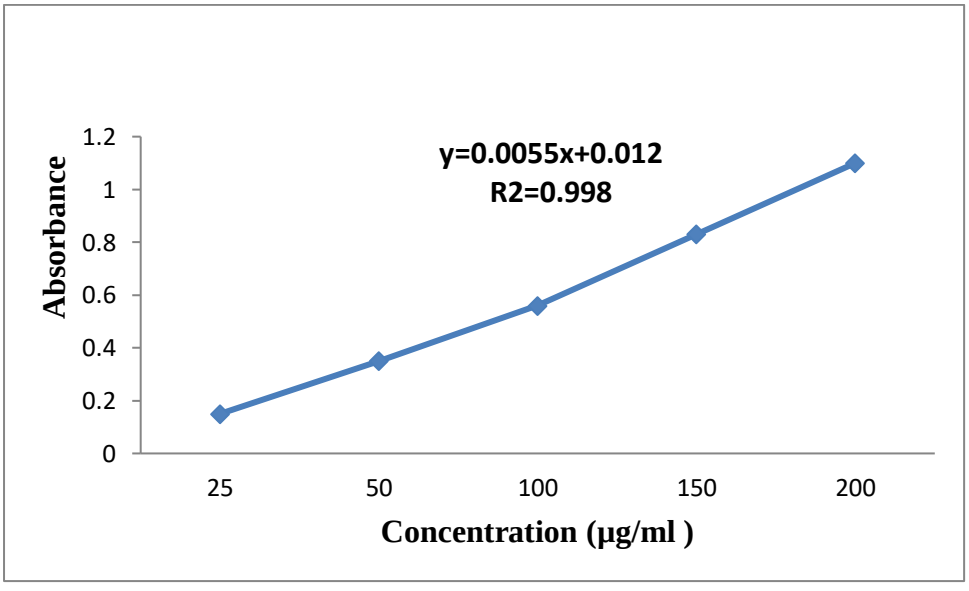

Figure 1: Total Phenolic content of Celosia argentea

3.4 HPTLC examination of Celosia argentea

We used HPTLC fingerprinting to make sure that caffeic acid was in the Celosia argentea extract. We used a reference standard from Natural Remedies Pvt. Ltd. in Bangalore, India. The extract and standard were put on silica gel plates and separated in the best way possible. The extract had a clear band with an Rf value of 0.20–0.30, which was the same as the caffeic acid standard and was in line with HPLC retention data. Quantitative HPTLC analysis

showed that the seed extract in water had 13.1% w/w gallic acid. The fact that both caffeic and gallic acids are present shows that the plant has a lot of phenolic compounds, which supports its traditional use as an antioxidant. The HPTLC fingerprint is a reliable way to check the quality, confirm the identity, and set standards for C. argentea in herbal products.

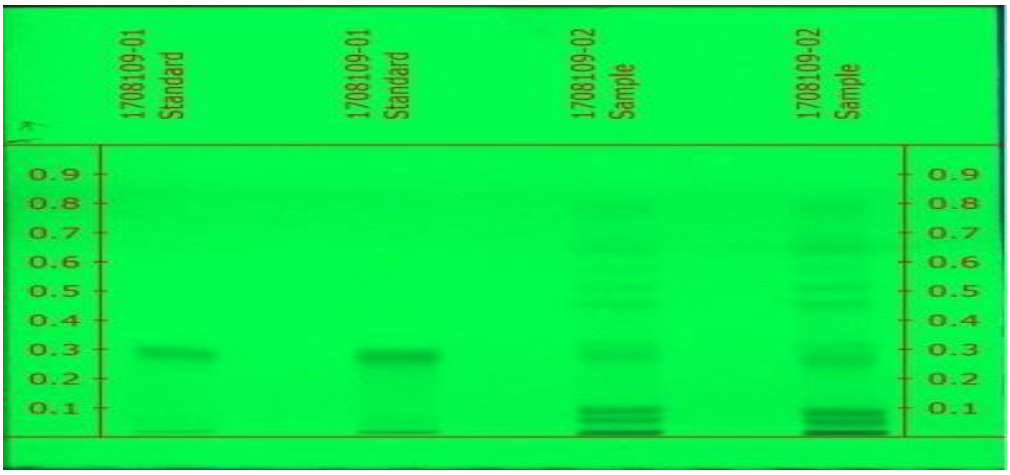

Figure 2: HPTLC examination of Celosia argentea

3.5 In Vitro Impact of Celosia argentea Extract on Hepatic CYP3A Activity

Celosia argentea extract's ability to inhibit liver CYP3A enzyme activity was assessed (Fig. 3). CYP3A activity was significantly reduced ($p < 0.001$) at concentrations of 100 µg and 150 µg, with inhibition levels similar to those of the common inhibitor fluconazole. Strong enzyme interaction even at moderate doses was demonstrated by the extract's near-equivalent inhibition of fluconazole at 100 µg. These findings point to the possibility of herb-drug interactions with medications that are metabolized by CYP3A and point to the extract's potential application in modifying CYP3A-mediated metabolic pathways.

Table 5: effect of Celosia argentea extract on CYP3A activity on the liver microsome (n=6)

	Treatment			
	Tween (1%)	Fluconazole (µg)	CA 100 (µg)	CA 150 (µg)
Mean	368.99 ± 3.32^{c}	226.45± 3.46***	332±3.87***b	248±3.65^{***c}
% Change	-----	41.34%	14.02	34.54%

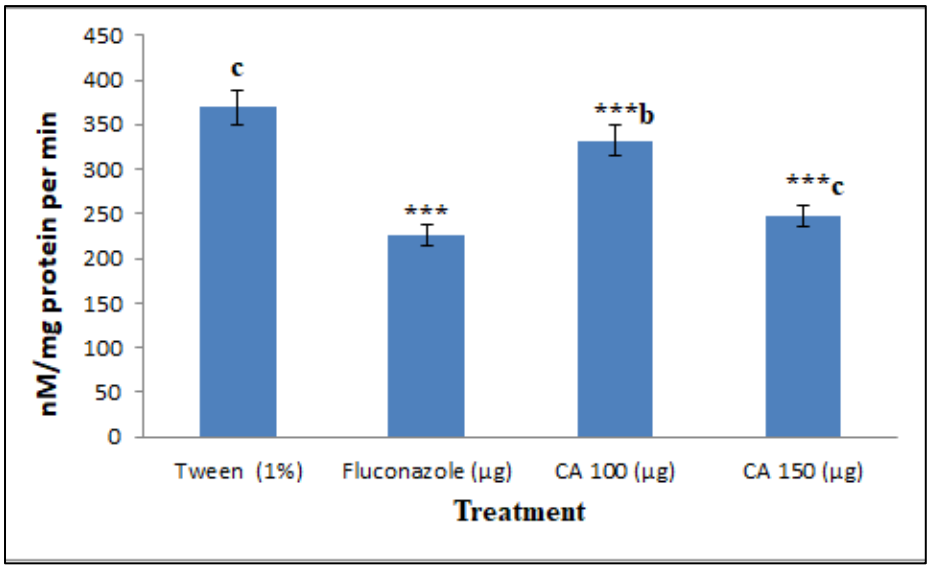

Figure 3: Effect of Celosia argentea seed extract (CA) on liver CYP3A activity in vitro. Data (nM/mg protein/min, mean ± SEM, n = 3) show that 100 µg and 150 µg CA significantly inhibited CYP3A compared to control (1% Tween), comparable to Fluconazole. ***$p < 0.001$; different letters indicate significant differences.

3.6 Pharmacodynamic interaction between Celosia argentea and Glimepiride

3.6.1 Result of Celosia argentea extract on the blood glucose level in diabetic rat

In HFD and STZ-induced diabetic rats, the antihyperglycemic effect of Celosia argentea seed extract was assessed both by itself and in conjunction with glimepiride (Table 6, Fig. 4). The successful induction of diabetes was confirmed by the diabetic controls' consistently high glucose levels (247–252 mg/dl) compared to the normal control rats' stable levels (92–97 mg/dl). Within four hours, glimepiride quickly brought blood glucose levels down to almost normal. The extract showed dose-dependent antihyperglycemic activity, with 200 mg/kg gradually lowering glucose from 220.23 ± 3.58 mg/dl at 1 hour to 130.78 ± 4.46 mg/dl at 8 hours. The effect was stronger at 400 mg/kg, reaching 109.8 ± 2.56 mg/dl at 8 hours. Combination treatments showed synergistic effects; at two hours, extract + Glimepiride (400 mg/kg) significantly reduced glucose to 10.76 ± 3.65 mg/dl, and by eight hours, it stabilized within normal range. These findings highlight C. argentea's potential as an adjuvant in the treatment of diabetes by indicating that its bioactive phenolic and flavonoid constituents contribute to its antihyperglycemic activity and can enhance the effect of glimepiride.

Table 6: Impact of Celosia argentea extract, both alone and in combination with glimepiride, on blood glucose levels (mg/dL) in streptozotocin-induced diabetic rats at various time points (n = 6, Mean ± SEM)

Treatment groups	1 hr	2 hr	4 hr	8 hr
Normal group	92.44 ± 0.57***	97.4±0.86***	95.65±1.05***	93.6±0.88***
Diabetic control (STZ)	252 .65±2,67***	247.78±2.68***	250.65±2.04***	249.51±3.14***
Glimepiride 5 mg/kg	210.78 ± 6.8[a]	140.5±4.76[c]	93.67±1.43[c]	101.45±1.21[c]
Celosia argentea extract 200 mg/kg	220.23±3.58	208.77±3.54**b	181.34±1.08**c	130.78±4.46[c]
Celosia argentea extract400 mg/kg	232.87±3.45***	112.6±2,87**b	162.23±2.43**c	109.8±2.56*c
Celosia argentea extract 200 mg/kg + Glimepiride	187.75± 1.87***c	140.98±4.89[c]	90.4±1.98[c]	94.77±1.98[c]
Celosia argentea extract 400 mg/kg + Glimepiride	186.8± 3.89[c]	10.76±3.65[c]	87.17±3.01[c]	81.87±1.34**c

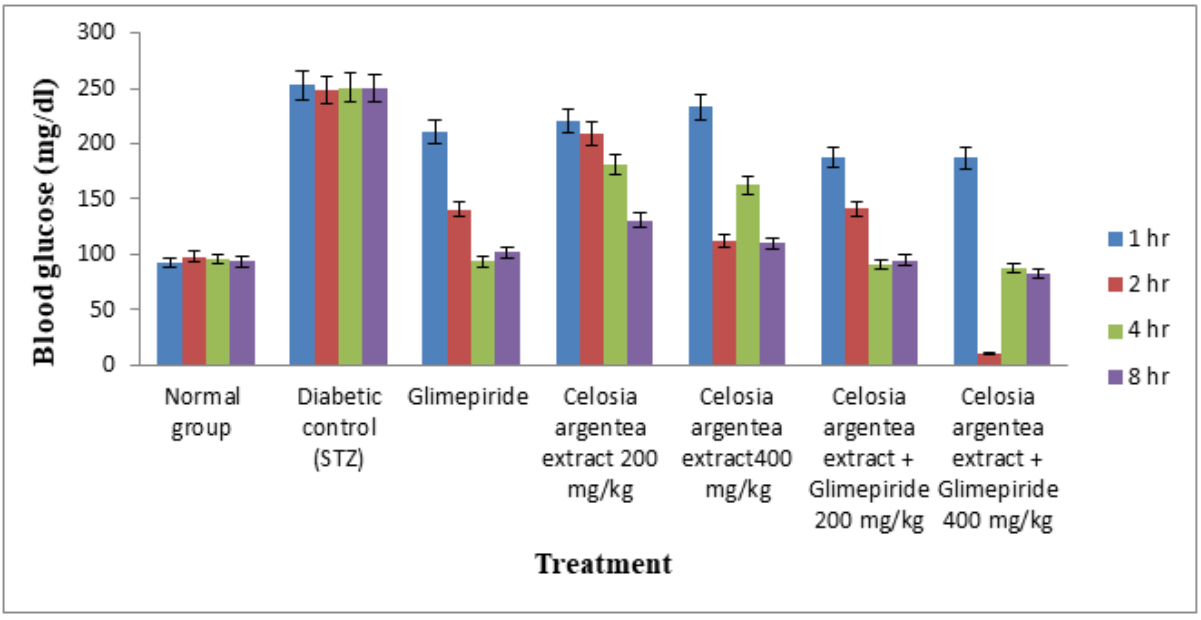

Figure 4: Effect of C. argentea extract, Glimepiride, and combinations on blood glucose in STZ-diabetic rats. Data (mean ± SEM, n = 6) show a synergistic glucose-lowering effect, with 400 mg/kg extract plus Glimepiride approaching normal levels.

3.6.2 Effect of Celosia argentea seed extract on superoxide dismutase (SOD) levels in diabetic rats

The protective effects of Celosia argentea seed extract, both by itself and in combination with glimepiride, against oxidative stress in diabetic rats were evaluated by measuring the activity of superoxide dismutase (SOD), a crucial antioxidant enzyme. SOD activity was 19.99 ± 1.54 U/min/mg protein in normal rats and 7.87 ± 1.02 U/min/mg in diabetic controls, indicating oxidative stress caused by STZ. The extract exhibited dose-dependent effects at 200 mg/kg (9.76 ± 1.01) and 400 mg/kg (13.04 ± 0.96), while glimepiride alone raised SOD to 14.01 ± 1.32. Combination therapies were more successful; 200 mg/kg + Glimepiride reached 14.54 ± 1.14 and 400 mg/kg + Glimepiride reached 17.76 ± 0.89, which were closer to normal levels (Table 7). These findings show that C. argentea improves antioxidant defense, especially when combined with glimepiride, probably because of its phenolic and flavonoid components, underscoring its therapeutic potential in the treatment of diabetes and the reduction of oxidative stress.

Table 7: Effect of *Celosia argentea* extract alone and in combination with glimepiride on superoxide dismutase (SOD) activity (U/min/mg protein) and percentage change in streptozotocin-induced diabetic rats (n=6, Mean ± SEM).

Treatment groups	**SOD (u/min/mg of Protein**	**% Change in SOD level**
Normal group	19.99 ± 1.54**c	57.98%
Diabetic control (STZ)	7.87±1.02*	----
Glimepiride 5 mg/kg	14.01 ± 1.32[a]	37.18%
Celosia argentea extract 200 mg/kg	9.76±1.01	9.87%
Celosia argentea extract400 mg/kg	13.04±0.96	23.98%
Celosia argentea extract 200 mg/kg + Glimepiride	14.54± 1.14[b]	40.78%
Celosia argentea extract 400 mg/kg + Glimepiride	17.76± 0.89*c	54.90%

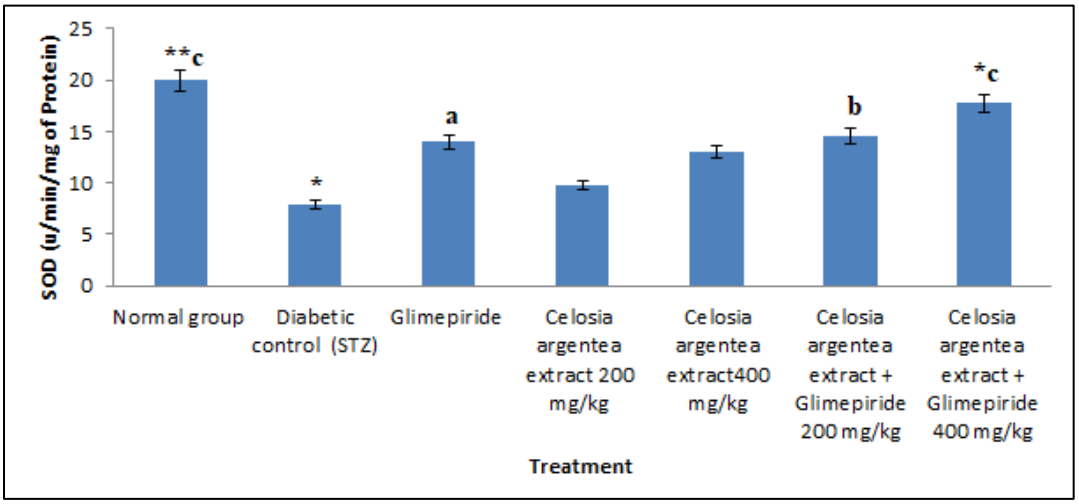

Figure 5: *Effect of Celosia argentea extract, Glimepiride, and their combinations on SOD activity in STZ-diabetic rats. Data (mean ± SEM, n = 6) show that 400 mg/kg extract combined with Glimepiride significantly restored SOD toward normal levels, indicating enhanced antioxidant defense.*

3.6.3 Effect of Celosia argentea on catalase level in diabetic rat

Catalase (CAT) activity, a key antioxidant defense, was significantly reduced in diabetic rats (1.89 ± 0.54 U/min/mg) compared to normal controls (5.78 ± 0.67), reflecting STZ-induced oxidative stress. Glimepiride alone restored CAT to 4.23 ± 0.23, while Celosia argentea extract showed dose-dependent increases (200 mg/kg: 3.24 ± 0.67; 400 mg/kg: 3.13 ± 0.98). Combination treatments were more effective, with 200 mg/kg + Glimepiride reaching 4.67 ± 1.54 and 400 mg/kg + Glimepiride achieving 5.23 ± 1.7, near normal levels (Table 8). These findings suggest that the phenolic and flavonoid constituents of C. argentea enhance antioxidant defense, and its combination with Glimepiride effectively alleviates oxidative stress in diabetic rats.

Table 8: *Effect of Celosia argentea extract, Glimepiride, and their combinations on CAT activity in STZ-diabetic rats. Data (mean ± SEM, n = 6) show dose-dependent improvement with the extract, while combination with Glimepiride nearly restored CAT activity to normal levels.*

Treatment groups	CAT (u/min/mg of Protein	% Change in CAT level
Normal group	5.78 ± 0.67*c	61.87%
Diabetic control (STZ)	1.89±0.54	----
Glimepiride 5 mg/kg	4.23 ± 0.23^{c}	38.66%
Celosia argentea extract 200 mg/kg	3.24±0.67^{b}	8.65%
Celosia argentea extract400 mg/kg	3.13±0.98^{c}	15.24%
Celosia argentea extract 200 mg/kg + Glimepiride	4.67± 1.54^{c}	42.21%
Celosia argentea extract 400 mg/kg + Glimepiride	5.23± 1.7c	55.02%

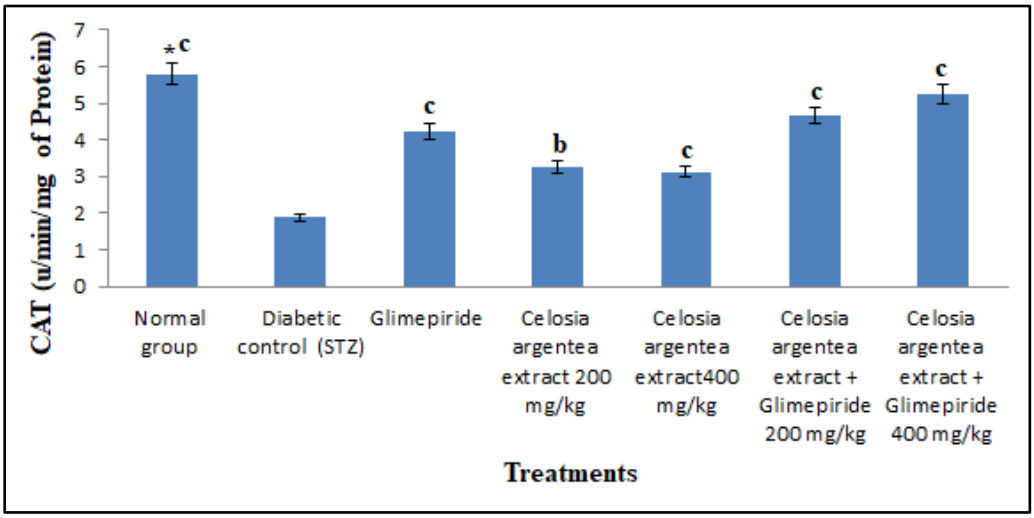

Figure 6: *Effect of Celosia argentea extract, Glimepiride, and their combinations on CAT activity in STZ-diabetic rats. Data (mean ± SEM, n = 6) show that diabetic rats had significantly reduced CAT activity, which was markedly restored by C. argentea and Glimepiride, especially in combination.*

3.6.4 Result of Celosia argentea on glutathion level in diabetic rat

The STZ-induced diabetic control group had significantly lower levels of glutathione (GSH), a crucial intracellular

antioxidant, indicating severe oxidative stress. While Celosia argentea seed extract also raised GSH in a dose-dependent manner, with the 400 mg/kg dose demonstrating greater efficacy, glimepiride treatment significantly improved GSH levels. Interestingly, the combination of glimepiride and C. argentea resulted in the greatest GSH restoration, almost reaching normal levels. Glimepiride's potential as an adjuvant therapy for improving redox balance in diabetes is supported by this synergistic effect, which implies that the extract increases the antioxidant action of the medication.

Table 9: *Celosia argentea seed extract, glimepiride, and their combination significantly restored reduced glutathione (GSH) levels in STZ-induced diabetic rats compared to the diabetic control.*

Treatment groups	GSH (u/min/mg of Protein	% Change in GSH level
Normal group	27.43 ± 1.89*c	57.81%
Diabetic control (STZ)	11.46±0.61	----
Glimepiride 5 mg/kg	22.25 ± 0.78	46.97%
Celosia argentea extract 200 mg/kg	18.45±00.97^{b}	35.67%
Celosia argentea extract400 mg/kg	21.76±0.78^{c}	15.24%
Celosia argentea extract 200 mg/kg + Glimepiride	23.78± 1.34^{c}	50.22%
Celosia argentea extract 400 mg/kg + Glimepiride	25.65± 1.14^{c}	53.45%

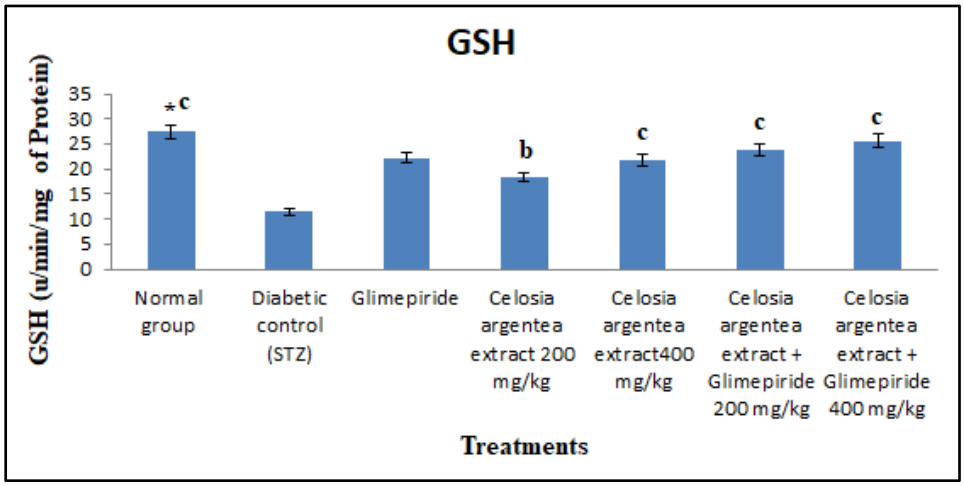

Figure 7: GSH levels significantly improved in diabetic rats treated with Celosia argentea seed extract and glimepiride, with combination therapy showing the greatest restoration.

3.6.5 Effect of Celosia argentea on Lipid peroxidase (LPO) level in diabetic rat

Lipid peroxidation was greatly elevated in diabetic rats, confirming severe oxidative stress. Glimepiride reduced LPO levels, while Celosia argentea extract showed dose-dependent protection, with the 400 mg/kg dose being more effective. The combined treatment produced the strongest reduction, nearly restoring LPO to normal, indicating a synergistic antioxidant effect.

Table 10: Effect of Celosia argentea on Lipid peroxidase (LPO) level in diabetic rat

Treatment groups	LPO (u/min/mg of Protein	% Change in LPO level
Normal group	1.91 ± 0.38^{c}	82.6%
Diabetic control (STZ)	10.02 ± 0.78***	----
Glimepiride 5 mg/kg	4.65 ± 0.38^{c}	57,78%
Celosia argentea extract 200 mg/kg	7.34 ± 0.66^{***c}	35.76%
Celosia argentea extract400 mg/kg	4.42±0.62^{c}	67.34%
Celosia argentea extract 200 mg/kg + Glimepiride	1.98 ± 0.21^{c}	81.33%
Celosia argentea extract 400 mg/kg + Glimepiride	1.54 ± 0.14^{c}	84.67%

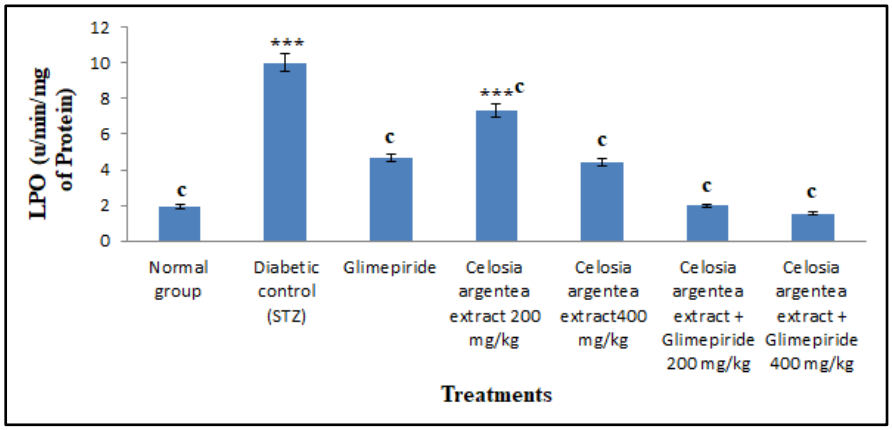

Figure 8: Diabetic rats showed high LPO levels, while treatment with Glimepiride, Celosia argentea extract, and their combinations significantly reduced LPO, indicating strong antioxidant effects.

3.7 Evaluation of biochemical parameters

3.7.1 Effect of Celosia argentea on Alkaline Phosphate (ALP) level in diabetic rat

Elevation of ALP, a crucial indicator of liver integrity, indicates hepatic damage frequently observed in diabetes. In this study, STZ-induced diabetic rats displayed a significant increase in ALP, indicating oxidative stress and hyperglycemia-induced liver damage. ALP levels were considerably lowered by glimepiride, and Celosia argentea extract also decreased ALP in a dose-dependent manner, suggesting mild hepatoprotection through its antioxidant components. Compared to individual treatments, combination therapy resulted in reductions that were either equal to or greater, indicating an additive protective effect. All things considered, Celosia argentea, either by itself or in combination with glimepiride, aids in the restoration of ALP levels and exhibits potential as a supportive hepatoprotective agent in diabetes.

Table 11: Effect of Celosia argentea on Alkaline Phosphate (ALP) level in diabetic rat

Treatment groups	ALP (u/min/mg of Protein	% Change in ALP level
Normal group	183 ± 1.35***^{c}	66.23%

Diabetic control (STZ)	328 ± 2.67	----
Glimepiride 5 mg/kg	198.01 ± 1.35^{c}	20.43%
Celosia argentea extract 200 mg/kg	215.00 ± 1.34^{*c}	16.34%
Celosia argentea extract400 mg/kg	218.01 ± 4.56* ^{c}	29.45%
Celosia argentea extract 200 mg/kg + Glimepiride	209.44 ± 5.09^{c}	18.25%
Celosia argentea extract 400 mg/kg + Glimepiride	216.02 ± 3.32**^{c}	34.98%

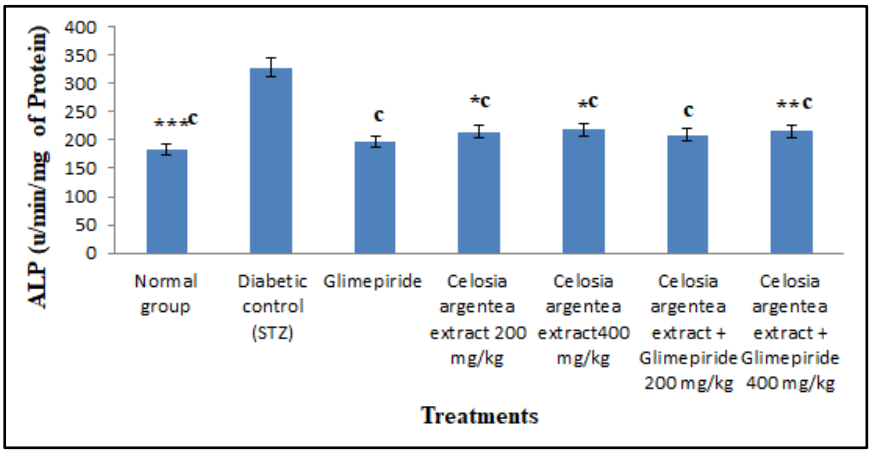

Figure 9: Effect of Celosia argentea extract and Glimepiride (alone and in combination) on ALP levels in STZ-induced diabetic rats. Data are expressed as mean ± SEM (n=6). Significant differences: *p < 0.05,**p < 0.01,***p < 0.001 vs diabetic control; c = comparison with normal group.**

3.7.2 Result of Celosia argentea on Alanine Aminotransferase level in diabetic rat

Significant hepatocellular damage from oxidative stress was confirmed by the study, which revealed that STZ-induced diabetic rats had noticeably higher ALT levels. ALT was lowered by roughly 20% with glimepiride, suggesting a moderate level of hepatoprotection. The effects of Celosia argentea extract were dose-dependent, with a mild reduction in ALT at 200 mg/kg and a stronger (≈29%) decrease at 400 mg/kg. Results were further enhanced by combination therapy; the combination of 400 mg/kg extract and Glimepiride resulted in the largest reduction (≈35%), indicating a synergistic protective effect. Overall, Celosia argentea demonstrated its potential hepatoprotective value in diabetes by helping to return ALT levels toward normal, both on its own and more successfully in combination with glimepiride.

Table 12: Effect of Celosia argentea on Alanine Aminotransferase level in diabetic rat

Treatment groups	**Alanine Aminotransferase U/L**	**% Change in Alanine Aminotransferase level**
Normal group	79 ± 0.34***^{c}	66.45%
Diabetic control (STZ)	227.32 ± 5.87	----

Glimepiride 5 mg/kg	182.34 ± 7.65^{c}	20.23%
Celosia argentea extract 200 mg/kg	193.01 ± 2.09***^{b}	16.45%
Celosia argentea extract400 mg/kg	163.00 ± 1.45** ^{c}	29.46%
Celosia argentea extract 200 mg/kg + Glimepiride	187.34 ± 1.21**^{b}	18.46%
Celosia argentea extract 400 mg/kg + Glimepiride	151.36 ± 0.34*^{c}	34.67%

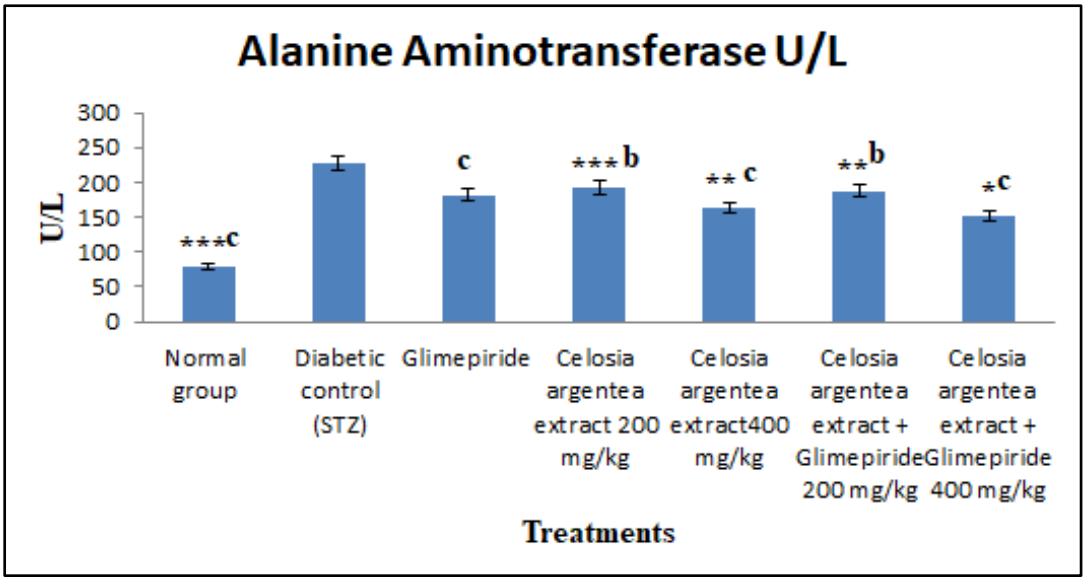

Figure 10: Impact of Celosia argentea extract and Glimepiride on serum Alanine Aminotransferase (ALT) concentrations in normal,

3.7.3 Outcome of Celosia argentea on OGTT level in diabetic rat

Impaired glucose clearance was confirmed by the OGTT results, which demonstrated that diabetic control rats maintained elevated glucose levels throughout the test. However, following the 30-minute peak, normal rats showed a sharp decline, indicating normal insulin activity. Rats treated with glimepiride exhibited a significant decrease in glucose at every time point, indicating a potent antihyperglycemic effect. The effects of Celosia argentea extract on glucose tolerance were dose-dependent; the 400 mg/kg dose was superior to the lower dose, but it was still inferior to glimepiride. Particularly at 400 mg/kg, the combination of Celosia argentea and Glimepiride produced the biggest improvement, with glucose levels approaching those of normal rats. These results show synergistic action, indicating that Celosia argentea may be a useful supplement in the treatment of diabetes and can improve the glucose-lowering effectiveness of Glimepiride.

Table 13: Effect of Celosia argentea on OGTT level in diabetic rat

Treatment groups	**30 min**	**% change**	**60 min**	**% change**	**120 min**	**% change**
Normal group	218.6± 3.8***	18.99%	163.7± 1.8***	54.72%	156.3± 1.2***	50.45%
Diabetic control (STZ)	266.4 ± 1.4**	----	252.9 ± 1.3**	----	309.4 ± 2.4***	----

Glimepiride 5 mg/kg	251.4 ± 1.17***c	7.12%	282.6 ± 3.2c	20.42%	225.9 ± 4.4c	28.15%
Celosia argentea extract 200 mg/kg	251..0 ± 2.02***	7.58%	312.1 ± 1.5c	12.32%	229.0 ± 1.8c	27.12%
Celosia argentea extract400 mg/kg	256.2 ± 1.45	5.04%	293.9± 1.4a	18.35%	232.4± 4.4c	26.35%
Celosia argentea extract 200 mg/kg + Glimepiride	251.2. ± 1.6a	6.64%	264.3. ± 1.6**c	26.23%	192.4 ± 6.8**c	24.99%
Celosia argentea extract 400 mg/kg + Glimepiride	247.4± 2.1b	7.42%	261,2± 1.8**c	26.98%	162.3± 12.6**c	46.78%

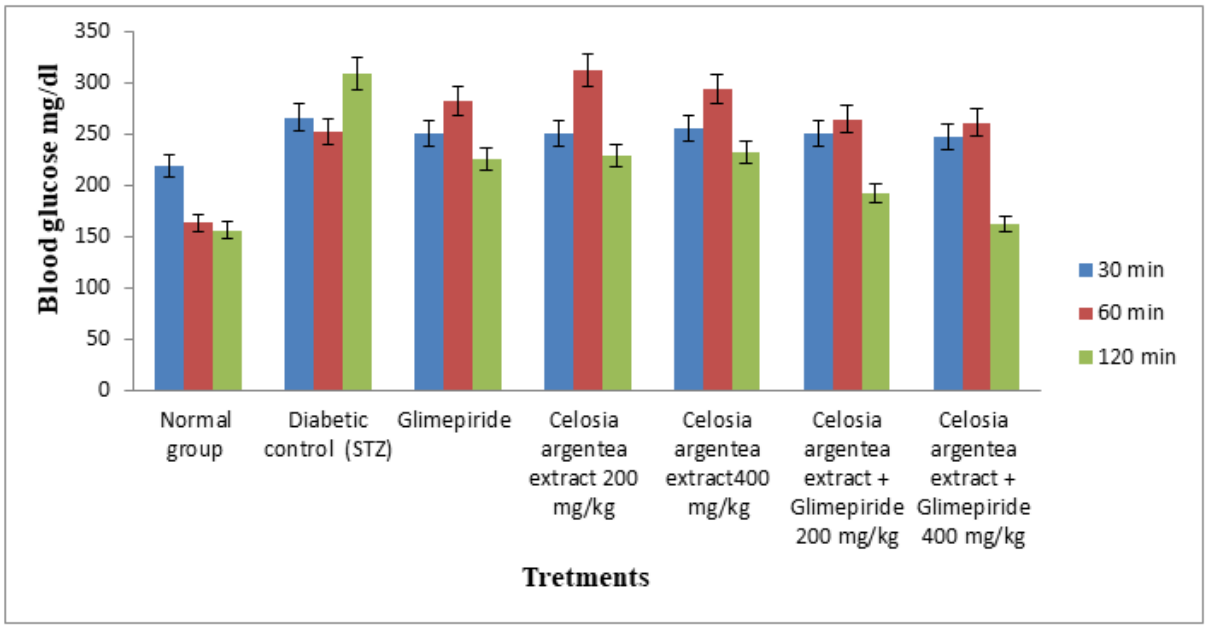

Figure 11: Effect of Celosia argentea on OGTT level in diabetic rat

3.8 Pharmacokinetic interaction of Celosia argentea and Glimepiride

Co-administration of Celosia argentea extract considerably increased glimepiride exposure, according to the pharmacokinetic study. Tmax stayed constant, but Cmax and AUC_{2}–t significantly increased, particularly at 400 mg/kg, suggesting better absorption and increased systemic availability. Slower elimination is suggested by a slight prolongation of T½ at the higher dose. These results demonstrate both Celosia argentea's therapeutic potential and the need for caution regarding the risk of hypoglycemia by confirming a dose-dependent interaction in which it increases glimepiride bioavailability, most likely through effects on intestinal permeability or metabolic pathways.

Table 14: Pharmacokinetic interaction of Celosia argentea + Glimepiride and Glimepiride

Parameters	Glimepiride	Celosia argentea extract 200 mg/kg + Glimepiride	Celosia argentea extract 400 mg/kg + Glimepiride
C_{max} (mg/ml)	78.34±4.23	114.7±12.34*	165.3±6.22***
AUC_{0-t} (mg/ml* h)	572.21±11.2	577.97±33.77	909.32±14.56

$T_{1/2}$ (h)	3.54±0.18	3.45±0.08	4.56±0.08
T_{max} (h)	5±0	5±0	5±0
MRT (h)	7.34±0.08	6.4±0.12	7.23±0.67

DISCUSSION

The findings of the study reveal that Celosia argentea seed extract is rich in important phytochemicals such as phenols, flavonoids, alkaloids, and saponins, which contribute to its strong antioxidant and antidiabetic activities. Physicochemical evaluation and HPTLC analysis further confirmed the quality of the extract and verified the presence of major bioactive compounds, including gallic acid and caffeic acid. The extract also exhibited significant CYP3A inhibitory effects, suggesting a potential for herb–drug interactions when administered alongside glimepiride. In STZ-induced diabetic rats, C. argentea demonstrated a clear dose-dependent reduction in blood glucose levels. The 400 mg/kg dose produced the most notable effect, and when used in combination with glimepiride, it resulted in a synergistic improvement, restoring glucose levels more rapidly and effectively. Antioxidant studies showed enhanced activities of SOD, CAT, and GSH, along with a reduction in lipid peroxidation, indicating strong free-radical scavenging action. These benefits were further amplified when the extract was combined with glimepiride. Liver function markers such as ALP and ALT were markedly elevated in untreated diabetic animals, reflecting hepatic injury. Administration of C. argentea alone offered moderate liver protection, while the combination therapy more effectively restored these biochemical parameters toward normal values. Overall, the study suggests that Celosia argentea not only improves glycemic control but also provides antioxidant and hepatoprotective benefits, with its combination with glimepiride delivering superior pharmacological outcomes.

CONCLUSION

The study demonstrates that Celosia argentea seed extract possesses significant pharmacokinetic and pharmacodynamic interactions with glimepiride. The extract is rich in phenolic and flavonoid compounds, confirmed through phytochemical analysis, TPC estimation, and HPTLC fingerprinting. In vitro studies revealed strong inhibition of hepatic CYP3A, indicating a potential to modify glimepiride metabolism. In diabetic rats, the extract showed dose-dependent antihyperglycemic and antioxidant effects, and when combined with glimepiride, it produced synergistic improvements in blood glucose regulation and oxidative stress markers (SOD, CAT, GSH, LPO). Additionally, biochemical parameters like ALP and ALT were significantly restored, indicating hepatoprotective benefits. Overall, Celosia argentea enhances the therapeutic response of glimepiride and offers promising potential as an adjuvant herbal therapy for diabetes, though further clinical validation is required.

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