1. Introduction

Diabetes is a set of metabolic illnesses marked by a rise in blood sugar caused by an error in insulin release or activity [1]. Insulin shortage results in a malfunction of cell metabolism, which can result in a variety of consequences, including high cholesterol levels, cardiovascular illness, kidney failure, nerve dysfunction, and eye-related issues. According to recent research, 75% of the world’s population is dependent on phytomedicines. Recently, phytoconstituents have demonstrated a remarkable ability to manage blood glucose levels and associated issues [2].

Improvements in the incidence of diabetes lead to isolation, as well as the demand for specialized, effective treatments with few adverse effects are urgent. For diabetes treatment, the majority of patented drugs are available, with more on the way. Even so, when it comes to managing the amount of glucose in the body, these commercially available drugs frequently induce concerns including obesity and hyperandro- genemia [3]. Excellent biologically active compounds can be found in medicinal plants with extensive therapeutic resources, and they are used to treat a varied range of disorders by people from all walks of life. These active substances are commonly ingested as ethnomedicine in traditional medicine. Plant-derived chemicals are used to treat diabetes because they are less harmful and less expensive than synthetic medications. Edible plant items, according to preventive health care information, provide improved protection against diseases induced by oxidative stress, such as diabetes [4]. The current research backdrop is mainly focused on using plant-based products as medications in target diseases and developing novel plant compounds to treat a variety of ailments.

C. frutescens L. (Solanaceae) is a shrubby perennial herb with green or white fruit that grows erect and is frequently used as folkloric medicine in all Kerala districts of India for antilipidemic, antiobesity, and analgesic properties. Cancer, and other respiratory tract illnesses have all been treated with it. It has also been used to cure arthritis and neuralgia as a topical anti-inflammatory. C. frutescens has various positive benefits on the cardiovascular system when taken internally. C. frutescens has been demonstrated in trials to reduce the risk of...
atherosclerosis by lowering blood cholesterol, triglyceride levels, platelet aggregation, and enhancing fibrinolytic activity, in addition to having antioxidant components. *C. frutescens* consuming cultures had a significantly decreased rate of cardiovascular disease [6]. However, bioactivity and phytoconstituents can differ greatly between organisms and biomolecule separation circumstances [7]. As a result, it is vital to check the substances employed in conventional medicine in treating diabetes and associated complications. Accordingly, the goal of this research was therefore to investigate the anti-diabetic impact of acetone extracts of *C. frutescens* fruits. This is, to the authors’ knowledge, the first complete assessment of the *C. frutescens* fruit’s antidiabetic potential.

2. Materials and Methods

2.1. Chemicals and Fruit Extract preparation

Chemicals used for animal studies were purchased from Sigma-Aldrich (India) with the highest purity and the rest of the chemicals were procured from Hi-media (Mumbai, India). The fruits of *C. frutescens* were collected from The Thrissur district of Kerala, India. The type specimen was identified and authenticated by Dr. M. Kumar, Assistant Professor, Department of Plant Biology and Biotechnology, Madras Christian College, Chennai Tamil Nadu India. The same was deposited in the herbarium of PG and Research Centre in Biotechnology, MGR College, Hosur. *C. frutescens* fruits were dried and powdered in the shade and extortionate with acetone for ten hours using a soxhlet extractor (Borosil, India) and concentrated using a rotary evaporator (Rotavapor® R-300 Buchi, India). The obtained dried mass was stored for further study at room temperature.

2.2. Experimental animal and acute toxicity test

The animals (Adult Wistar rats of either sex weighing between 150–200 gms for anti-hyperglycemic activity and male Swiss albino mice weighing between 18–25 gms for acute toxicity test) used for research were purchased from Kerala Veterinary and Animal Sciences University (KVASU), Mannuthy, Kerala, India located individually in steel cages following the light/dark cycle (12 hours each). This study’s experimental methodologies and protocols were thoroughly examined by the Institutional Animal Ethics Committee (Proposal number: NCP/IAEC/2018-19/05) and were carried out in compliance with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA, Regd no: 688/PO/Re/S/02/CPCSEA). For acute toxicity studies Swiss albino mice (18–25 g) were chosen randomly among the population for this work. CFA was given orally to the trial animals at a dosage of 2 g/kg b/w and examined for 24 hours to see whether any mortality occurred. After the CFA was fed, the dosed Swiss albino mice were inspected for 48 hours individually, with food delayed for three to four hours. Particular attention was paid during the first 4 hours for suspicious behaviours and adverse signs. The Swiss albino mice were observed twice a day (morning and evening) for a total of 14 days to determine any behavioural changes after they had survived for 48 hours. [8,9].

2.3. Diabetes induction and experimental design

The animals (adult Wistar rats) fasted overnight for the research were impregnated intraperitoneally (i.p) with a single administration (45 mg/kg) of streptozotocin to stimulate diabetes. Animals measuring 200 mg/dl or above of blood glucose were chosen for experimentation [8,9]. Animals (n = 5) were divided into five groups and treated as normal control (NC); diabetic control (DC); reference control (RC) provided with glibenclamide (5 mg/kg); diabetic Wistar rats receiving CFA (250 mg/kg), and diabetic Wistar rats receiving CFA (500 mg/kg).

A single serving of glibenclamide and CFA extracts were orally administered every day for 21 days. On the day of drug administration, the 4th, 7th, 14th, and 21st days in each animal that had fasted for 12 hours, the amount of glucose in their blood was measured with a glucometer (ACCU-CHEK Active, India). The animals were sacrificed in light-etheric anesthesia after 21 days. The blood sample was taken from the retro-orbital puncture, preserved in-plane tubes at 4° C until use. The liver, kidneys, and pancreas were all retrieved and cleansed in a saline solution that was ice cold. A segment of these organs was histologically prepared and kept in 10% formalin, while the liver was preserved in liquid nitrogen for enzymatic and non-enzymatic antioxidant assays.

2.4. Biochemical analysis of serum

Blood serum [10] was obtained by centrifuging blood samples at 3500 X g for 15 minutes and obtaining the supernatant for the measurement of Lipid profiles (Total Cholesterol (TC) [11], Triglycerides (TG) [12], High-Density Lipoprotein-Cholesterol (HDL-C) [13], Low-Density Lipoprotein-Cholesterol (LDL-C) and Very-Low-Density Lipoprotein-Cholesterol (VLDL-C) [14]); Kidney function test (Blood Urea Nitrogen (BUN) [15] and Creatinine [16]); Liver function test (Malondialdehyde (MDA) [17], Lipid Hydroperoxides (LH) [18]) and Serum Insulin [19].

2.5. Liver antioxidant studies

The liver was promptly removed after sacrifice, washed in saline, homogenized in 0.1M phosphate buffer (pH 7.4), and centrifuged undercooling for 15 minutes at
8500 g. The cell free extract was collected and used to estimate cellular oxidative markers [20] such as Superoxide Dismutase (SOD) [21], Catalase (CAT) [22], Peroxides (Px) [23], Glutathione Peroxidase (GPx) [24], Glutathione Reductase (Grd) [25] and the levels of non-enzymatic antioxidants such as Reduced Glutathione [26], Vitamin E [27], and Vitamin C [28].

2.6. Histopathological examination

The approach described by Drury and Wallington [29] was used to conduct the histopathological examination. Microtome (Almicro, India) was used to make a 5 mm average cuts in the organs. The Haematoxylin-Eosin (H and E) procedure was used to stain the sections. After that, they were observed and photographed using a light microscope (Leica, DM1000, Germany).

2.7. Statistical analysis

The mean and standard deviation (SEM) were used to define the results. Dunnett’s test was used to determine the disparity among each peer group, and One-Way ANOVA (GraphPad Prism, version 5) was used to examine the differences across groups. The values of probability less than 0.05 (P < 0.05) are considered significant, whereas less than 0.001 (P < 0.001) are considered highly significant.

3. Results

3.1. Acute toxicity studies

The experiment was done on Swiss albino mice according to the OECD-423 guidelines (Organization for Development in Economics and Cooperation). In this analysis, male Swiss albino mice were employed and chosen using a random sampling technique. The animals had fasted on free access to water for four hours. Animals reported no mortality at a dose of 2000 mg/kg after single CFA administration. CFA at 2000 mg/kg has shown a mild analgesic, CNS stimulating effect after 1 hour of drug administration, increased motor activity, and lacrimation. No major change was observed with the extract in overall behaviour, even after 24 and 72 hours at 2000 mg/kg. There were no deaths or toxic reactions identified during and after CFA administration.

3.2. Glucose levels

Hypoglycemic activity of CFA was investigated in Wistar rats of both sexes that had been given streptozotocin-nicotinamide (Table 1). Increased BGL after streptozotocin administration confirmed the development of diabetes in Wistar rats, and in this study, diabetes was described as blood sugar concentration greater than 200 mg/dl.

Glibenclamide, the reference control, significantly decreased BGL in group 3 starting on the 4th day, with BGL reaching 97.67 ± 2.59 mg/dl on the 21st day, marginally lower than group 1 (normal control). Group 4 (250 mg/kg CFA) had a modest (P < 0.01) decrease in BGL (105.67 ± 4.98) from the 4th to the 21st day, but this was substantially higher than group 5 (500 mg/kg CFA), which had a significant reduction (P < 0.001) in BGL (98.66 ± 4.27) relative to group 1 (NC). This indicates that when Wistar rats were given streptozotocin to induce diabetes, CFA has a strong anti-diabetic effect. From the post-7th day of administration through the end of the trial, CFA treated groups should have had lower increased BGL at all dose levels tested. BGL was reduced significantly (P < 0.001) by the 250 and 500 mg/kg dosages of CFA, to 105.67 ± 4.98 and 98.66 ± 4.27 mg/dl, respectively.

The effect of the CFA on serum insulin concentration in diabetic Wistar rats were measured at the finish of the trial. (Table 2). The control group displayed elevated serum insulin concentrations, while the diabetic control group had substantially lowered serum insulin concentrations. Insulin concentrations of reference control and treatment groups were raised compared to those recorded in the diabetic control, with close significance in reference control and Wistar rats receiving 500 mg/kg CFA.

| Table 2. Serum insulin level in diabetic wistar rats receiving acetone extracts of Capsicum frutescens. |

| Treatment       | Insulin (µU/ml) |
|-----------------|-----------------|
| NC              | 25.66 ± 1.37    |
| DC              | 5.95 ± 0.19     |
| RC              | 16.99 ± 0.88*** |
| CFA (250 mg/kg) | 11.24 ± 0.82*** |
| CFA (500 mg/kg) | 16.70 ± 0.96*** |
| NC – Normal Control; DC – Diabetic Control; RC – Reference Control; CFA – Capsicum frutescens Acetone Extract. |
| Values are expressed as the mean ± SEM (n = 5). |

| Table 1. Glucose concentration in diabetic wistar rats receiving acetone extracts of Capsicum frutescens. |

| Treatment       | Before STZ | Day Zero | Day 4   | Day 7   | Day 14  | Day 21  |
|-----------------|------------|----------|---------|---------|---------|---------|
| NC              | 104.67 ± 4.48 | 99.50 ± 4.81*** | 99.67 ± 4.66*** | 100.83 ± 4.33*** | 97.17 ± 3.03*** | 102.00 ± 5.39*** |
| DC              | 95.17 ± 4.62 | 219.33 ± 5.39 | 216.33 ± 5.82 | 232.17 ± 3.43*** | 226.50 ± 2.57*** | 222.17 ± 5.67*** |
| RC              | 105.00 ± 5.49 | 217.33 ± 5.38 | 143.17 ± 2.73*** | 117.00 ± 4.37*** | 112.67 ± 5.57*** | 97.67 ± 2.59*** |
| CFA (250 mg/kg) | 98.33 ± 5.35 | 214.17 ± 4.45 | 175.33 ± 5.59 | 161.67 ± 2.98*** | 123.17 ± 2.55*** | 105.67 ± 4.98*** |
| CFA (500 mg/kg) | 99.17 ± 3.47 | 219.33 ± 3.23 | 160.17 ± 4.70** | 131.33 ± 2.87*** | 117.83 ± 4.10*** | 98.66 ± 4.27*** |
| STZ – Streptozotocin; NC – Normal Control; DC – Diabetic Control; RC – Reference Control; CFA – Capsicum frutescens Acetone Extract. |
| Values are expressed as the mean ± SEM (n = 5); STZ – Streptozotocin. |
3.3. Biochemical analysis of serum
3.3.1. Lipid profiling
A notable gain in TC, TG, LDL-C, and VLDL-C was observed in the diabetic control group, as well as a parallel reduction in HDL-C, which is characteristic of diabetic circumstances; this revealed that streptozotocin treatment-induced dyslipidemia within the current investigation. Nevertheless, the reduction in TC, TG, LDL-C, and VLDL-C, as well as possibly a rise in HDL-C, subsequently administration with CFA, suggests that extracts improved the lipid disturbances in diabetic animals caused by streptozotocin. The Wistar rats were administered with streptozotocin to increase TC capacity were compared to normal control rats. Glibenclamide reduced streptozotocin-enhanced TC significantly. Both CFA doses exhibited a noteworthy decrease in cholesterol, compared to the diabetic control. The 500 mg/kg of CFA showed a substantial decrease (P < 0.01) in TC (122.50 ± 2.41) when compared to diabetic control (145.33 ± 5.14). The low dose (250 mg/kg) resulted in significant (P < 0.05) cholesterol reductions (127.33 ± 3.14) (Table 3).

Streptozotocin-induced diabetic control rats had significantly greater TG levels than normal rats. Glibenclamide substantially (P < 0.001) decreased the elevated TG measure (81.50 ± 2.41). Treatment of diabetic animals with 500 mg/kg CFA caused a substantial decrease in TG (88.50 ± 5.05), which paled in comparison to 250 mg/kg CFA, which resulted in TG levels of 98.17 ± 2.67.

The HDL-C of streptozotocin-treated rats in diabetic control was significantly reduced. Streptozotocin (250 mg/kg) 127.33 ± 2.41. CFA considerably (P < 0.001) lowered LDL-C (28.33 ± 0.72) than the glycemic group. In comparison to the glycemic group (19.67 ± 1.23), the animals fed with 500 mg/kg of CFA displayed a greater rise (P < 0.001) in HDL–C (35.00 ± 2.09). CFA considerably (P < 0.001) lowered LDL–C (69.80 ± 3.22) in animals treated with a maximum concentration of 500 mg/kg of CFA. Streptozotocin increased the LDL–C (65.03 ± 2.97) while Glibenclamide decreased it significantly (P < 0.001). When compared to diabetic monitoring, CFA’s low dose (250 mg/kg) impelled a less substantial (P < 0.01) decrease of LDL–C (79.37 ± 3.10).

The CFA had the same effect on LDL–C as the Glibenclamide reference control. Glibenclamide (P < 0.01) decreased VLDL–C significantly (16.30 ± 0.96) improved with streptozotocin in animals administered 500 mg/kg of CFA compared to diabetic control (24.53 ± 1.22) and to the level as they didn’t differ considerably from those given Glibenclamide in reference controls. In comparison to diabetic control, the 250 mg/kg CFA showed a less significant (P < 0.05) decrease in VLDL–C.

3.3.2. Kidney and liver function analysis
As seen in Table 4, experimental diabetes resulted in significant BUN increases as compared to controls. BUN levels in diabetic rats (group 2) were significantly higher (52.59 ± 3.97) than in normal control rats (22.65 ± 3.17). In diabetic rats, however, CFA was responsible for a considerable (P < 0.01) restoration of BUN and creatinine levels (Table 4). BUN and Creatinine levels were greater in diabetic rats than in control animals. Both renal markers in diabetic rats were substantially restored (P < 0.01) by both CFA doses in comparison (Table 4). The streptozotocin-induced increases in BUN (27.40 ± 2.3) and Creatinine (0.53 ± 0.05) were substantially reduced (P < 0.001) by glibenclamide. CFA lowered BUN by 35.99 ± 3.43 and 27.55 ± 2.53 mg/kg, respectively, at 250 and 500 mg/kg dosages. The 250 mg/kg of CFA resulted in a substantial (P < 0.01) reduction in creatinine (0.84 ± 0.07) when compared to diabetic control. When compared to diabetic control, the 500 mg/kg CFA resulted in a significantly lower (P < 0.001) creatinine (0.63 ± 0.02). The effect of CFA at 500 mg/kg was quite close to that of Glibenclamide.

To console our findings, we performed a renal histopathological examination on all the sample groups. In our investigation, CFA was proved to be efficient in repairing the renal dysfunction parameters to

| Table 3. Serum lipid profile in diabetic wistar rats receiving acetone extracts of Capsicum frutescens. |
|---------------------------------------------------------------|
| **Treatment** | **TC** | **TG** | **HDL–C** | **LDL–C** | **VLDL–C** |
| NC | 112.83 ± 3.66*** | 71.00 ± 1.69*** | 45.67 ± 3.23*** | 52.96 ± 2.64*** | 14.20 ± 1.04*** |
| DC | 145.33 ± 5.14 | 122.67 ± 1.47 | 19.67 ± 1.23 | 101.13 ± 5.33 | 24.53 ± 1.22 |
| RC | 118.00 ± 2.62** | 81.50 ± 2.41*** | 36.67 ± 4.86*** | 65.03 ± 2.97*** | 16.30 ± 0.96*** |
| CFA (250 mg/kg) | 127.33 ± 3.14* | 98.17 ± 2.67*** | 28.33 ± 0.72** | 79.37 ± 3.10** | 19.63 ± 1.50* |
| CFA (500 mg/kg) | 122.50 ± 2.41** | 88.50 ± 5.05*** | 35.00 ± 2.09** | 69.80 ± 3.22*** | 17.70 ± 0.98** |

| Table 4. Kidney function analysis in diabetic wistar rats receiving acetone extracts of Capsicum frutescens. |
|---------------------------------------------------------------|
| **Treatment** | **Blood Urea Nitrogen (mg/dl)** | **Creatinine (mg/dl)** |
| NC | 22.65 ± 3.17 | 0.51 ± 0.04 |
| DC | 52.59 ± 3.97 | 2.04 ± 0.18 |
| RC | 27.40 ± 2.3 | 0.53 ± 0.05*** |
| CFA (250 mg/kg) | 35.99 ± 3.43*** | 0.84 ± 0.07*** |
| CFA (500 mg/kg) | 27.55 ± 2.53** | 0.63 ± 0.02*** |
| NC – Normal Control; DC – Diabetic Control; RC – Reference Control; CFA – Capsicum frutescens Acetone Extract. Values are expressed as the mean ± SEM (n = 5). |
close proximity levels, implying that it has beneficial effects in diabetes (Table 4).

In diabetic control, MDA efficiency was high ($P < 0.001$) as compared to normal control (Table 5). CFA treatment significantly reversed the effect, having an average potency of 500 mg/kg indicating 0.98 ± 0.08 MDA compared to the reference control in group 3, which exhibited a substantial ($P < 0.001$) decrease in MDA development related to the normal control. The results of measuring lipid hydroperoxides are provided in Table 5 as nmoles of LH / min/mg protein. LH activity was shown to be greater in diabetic rats as compared to normal control rats. CFA treatment lowered LH levels with an increase in concentration. When compared to the reference control group ($P < 0.001$), the 500 mg/kg CFA caused a significant reduction ($P < 0.01$) in LH activity (0.88 ± 0.06). When diabetic animals were given 250 mg/kg acetone extracts, there remained a marginally lesser reduction ($P < 0.05$) in LH (0.99 ± 0.07) when compared to diabetic controls (1.29 ± 0.11). The observed rise in MDA and LH in rats fed CFA was normalized in this study. The documented results in these groups might have been attributed to the reduced cellular damage caused by hyperglycemia.

### 3.4. Enzymatic antioxidant analysis

Diabetes is linked to an increase in tissue oxidative stress, which may manifest as changes in the tissue antioxidant defense system. CAT, SOD, GRd, Px, and GPx activity in the control and treatment groups are revealed in Table 6. The activity of these enzymes drastically diminished in diabetic rats. CFA treatment raised the activities of enzymatic antioxidants; nevertheless, the effect was significantly positive ($P < 0.001$) in the animals that received a higher dose (500 mg/kg CFA). Our findings indicated that CFA improved antioxidant capacity and protected diabetic rats from secondary complications caused by oxidative stress.

### 3.5. Non-enzymatic antioxidant analysis

Table 7 identifies the extent of the non-enzymatic antioxidant in experimental animals. Compared to normal control, GSH values in diabetic control exhibited a substantial statistical differences, with a substantial decline ($P < 0.001$) in GSH contents. GSH levels in rats treated with 500 mg/kg were considerably ($P < 0.001$) greater than in diabetic control animals, and values were very near to those in rats treated with Glibenclamide. In diabetic rats induced by streptozotocin, vitamin C and vitamin E were significantly ($P < 0.001$) lowered in contrast to normal control animals. The oral dose of CFA (500 mg/kg) resulted in a substantial rise ($P < 0.01$) in the concentration of both vitamin C and E.

### 3.6. Histopathological studies

In our study, pancreatic β-cells of diabetic rats were significantly damaged. After CFA treatment, the native architecture of pancreatic β-cells was largely restored and maintained. Diabetic rats administered with glibenclamide retained or returned the original histoarchitecture of β-cells. Histoarchitectural investigation of the pancreas of diabetic control animals revealed a substantial decrease in islet volume, weakened β-cell populations, extensive necrotic changes, and passive

| Treatment | MDA | LH |
|-----------|-----|----|
| NC        | 0.69 ± 0.01*** | 0.71 ± 0.02*** |
| DC        | 1.66 ± 0.10    | 1.29 ± 0.11    |
| RC        | 0.78 ± 0.08*** | 0.75 ± 0.06*** |
| CFA (250 mg/kg) | 1.26 ± 0.17 | 0.99 ± 0.07    |
| CFA (500 mg/kg) | 0.98 ± 0.08** | 0.88 ± 0.06** |

NC – Normal Control; DC – Diabetic Control; RC – Reference Control; CFA – Capsicum frutescens Acetone Extract; MDA – Malondialdehyde; LH – Lipid Hydroperoxides.

Values are expressed as the mean ± SEM ($n = 5$).

| Treatment | Reduced Glutathione (nmoles/min/mg protein) | Vitamin C (µg/mg protein) | Vitamin E (µg/mg protein) |
|-----------|---------------------------------------------|----------------------------|---------------------------|
| NC        | Normal Control: 14.11 ± 1.16*** 5.48 ± 0.33*** 8.52 ± 0.23*** |
| DC        | 6.33 ± 0.56 2.50 ± 0.42 5.07 ± 0.33 |
| RC        | 12.40 ± 0.91*** 4.35 ± 0.39*** 7.11 ± 1.00*** |
| CFA (250 mg/kg) | 9.94 ± 0.65** 3.28 ± 0.36* 6.13 ± 0.26* |
| CFA (500 mg/kg) | 11.79 ± 0.88*** 3.74 ± 0.28* 6.84 ± 0.25** |

NC – Normal Control; DC – Diabetic Control; RC – Reference Control; CFA – Capsicum frutescens Acetone Extract.

Values are expressed as the mean ± SEM ($n = 5$).

| Treatment | CAT (µmol/min/mg protein) | SOD (nmoles/min/mg protein) | GRd (nmoles/min/mg protein) | Px (nmoles/mg protein) | GPx (nmoles/mg protein) |
|-----------|---------------------------|-----------------------------|-----------------------------|------------------------|------------------------|
| NC        | 40.59 ± 1.38*** | 6.01 ± 0.18*** | 38.36 ± 1.16*** | 8.12 ± 0.32*** | 12.56 ± 0.55*** |
| DC        | 28.02 ± 1.22    | 1.64 ± 0.60    | 18.15 ± 0.96    | 4.61 ± 0.17    | 7.30 ± 0.27    |
| RC        | 38.46 ± 1.19*** | 5.25 ± 0.14*** | 34.44 ± 1.09*** | 7.68 ± 0.44*** | 11.19 ± 0.76*** |
| CFA (250 mg/kg) | 34.46 ± 1.44** | 3.99 ± 0.19   | 25.05 ± 0.73*** | 6.32 ± 0.44**  | 9.57 ± 0.37*** |
| CFA (500 mg/kg) | 36.54 ± 1.29*** | 4.71 ± 0.17*** | 30.52 ± 1.13*** | 7.14 ± 0.27*** | 10.49 ± 0.36*** |

NC – Normal Control; DC – Diabetic Control; RC – Reference Control; CFA – Capsicum frutescens Acetone Extract; CAT – Catalase; SOD – Superoxide Dismutase; GRd – Glutathione Reductase; Px – Peroxides; GPx – Glutathione Peroxidase.

Values are expressed as the mean ± SEM ($n = 5$).
hyperemia (Figure 1B). CFA (500 mg/kg) was given to rats, which reversed necrotic alterations and enhanced the size and number of islets (Figure 1E). The islet cells in the pancreas of the control group had normal cellular architecture (Figure 1A). The Glibenclamide-treated group (Figure 1C) had similar changes in pancreatic architecture to the CFA-treated group. The simultaneous administration of CFA and glibenclamide to diabetic animals for three weeks significantly reduced BGL, which was most likely due to enhanced pancreatic insulin secretion from Langerhans islet-cells. CFA prevents the glycation cycle in diabetic animals by acting as an anti-diabetic, protecting the pancreatic β-cells from hyperglycemia-induced injuries.

The liver in the current study has well-preserved architecture in the normal control group (Figure 2A). A minor alteration of the liver architecture, periportal inflammation, widening of sinusoids, and normal activity of the kupffer cells were observed in diabetic rats (Figure 2B). The animals treated with CFA (500 mg/kg) had hepatocyte cells in their natural state and central veins. Even a mild inflammation was seen in the liver architecture of the treatment group (Figure 2E). The usual lobular structure in hepatocytes of Glibenclamide-treated rats were preserved, along with a regular central vein and sinusoids (Figure 2C).

In our study, no irregular morphological variations in rat kidney tissues, such as the size of the glomerulus and the thickness of the membrane were characterized (Figure 3A). Diabetic control animals were detected with mild enlargement of normal proximal and distal convoluted tubules with normal vascularity (Figure 3B). At 500 mg/kg, in the interstitium, CFA revealed hypercellular glomeruli, a thinning cortex, and blocked blood arteries, as well as inflammatory cells composed of lymphoplasmacytes (Figure 3E). Treatment with glibenclamide results in normal glomeruli, increased vascularity, and hydropic degeneration tubules (Figure 3C).

**Figure 1.** Histology of pancreas in diabetic rats receiving acetone extracts of *Capsicum frutescens*.

**Figure 1.** Continued.

**Figure 4.** Histology of liver in diabetic rats receiving acetone extracts of *Capsicum frutescens*.

**Figure 5.** Histology of kidney in diabetic rats receiving acetone extracts of *Capsicum frutescens*.

**4. Discussion**

Toxicological analyses are crucial to define the safety of medicinal plants’ continued use in developing
countries, particularly in the Asia-Pacific region, as they occupy a very significant part in illness prevention and treatment. However, clinical investigations that provide the scientific evidence in the clinical effectiveness of medicinal plants are important. Regardless of the fact that several populations in southern India use fruits of C. frutescens for therapeutic purposes, we are unaware of any investigation in the research that has looked into its in vivo toxicity and hypoglycemic potential. To provide a biological backing for its safety in humans, we examined acute oral toxicity in Swiss albino mice, and perhaps even the anti-hyperglycemic activity of its acetone extortion in diabetes-induced Wistar rats using streptozotocin to substantiate the anti-diabetic therapeutic effects.

In this investigation, Swiss albino mice were utilized to investigate acute toxicity. In the single dosage acute toxicity investigation, the OECD criteria for assessing substances (OECD 423 acute oral toxicity–Acute toxic class technique) were followed [30]. The rats were given 2 g/kg b.w. of CFA appeared to be in good health, with no signs of death or behavioural abnormalities. There were no substantial variations in animals at the end of the 14-day study among control and CFA-treated rats, indicating that CFA is non-toxic. The LD_{50} value for CFA is larger than 2000mg/kg b.w., as shown by the data. As a result, the CFA is classed as hazardous chemical compounds in Globally Harmonized System (GHS) Category 5 that is specified as 2000mg/kg < LD_{50} < 5000 mg/kg [31]. The present acute toxicity findings support the scientific consensus of Deivasigamani et al. [32] and Kiptisia et al. [33].

Streptozotocin at doses greater than 40 mg/kg in rats can impair pancreatic β-cells that lead to the development of chronic hyperglycemia, which is identical to diabetes in humans [34]. The current study found that the same dosage (45 mg/kg) of streptozotocin administered to rats increased BGL on the fourth day of the experiment, which could be attributed to the loss of islets in the pancreas and the death of β-cells [34]. As a result, glycemic profiles of diabetic animals are likely to be aberrant. The BGL was performed on day 21 of treatment to test the impact of the CFA on diabetic rats.
Table 1 shows the BGL data for control and diabetic-treated groups. CFA use, according to the current study, may help to lower diabetes. Recent studies [3] suggest the use of herbal medicines as a therapy for illnesses connected to effects of oxidative stress, such as hyperglycemia, heart disease, tumour, and other disorders. Numerous indigenous herbal plants have reported a strong hypoglycemic effect, which is consistent with our findings [35–38].

CFA therapy showed a negative influence on insulin release and glucose concentration in the serum of diabetic rats in the current study. Furthermore, in the current investigation, the insulin concentration of these CFA-administered rats was marginally lower ($P < 0.01$) than normal and reference controls, but higher than diabetes control. CFA treatment enhances insulin production in diabetic rats, based on the results of our investigation. Although the exact mechanism of CFA action is uncertain, a variety of different phytoconstituents have indeed remained documented to have antihyperglycemic effect by triggering insulin secretion actions [39–41]. Insulin deficiency further causes high free mobilization of fatty acids, resulting in increased LDL synthesis, and dyslipidemia in diabetic animals may be linked to impaired insulin, leading to increased protein catabolism and lowered protein synthesis [42–44].

Dyslipidemia is a prevalent complication of diabetes, with high TG, cholesterol levels (LDL-C and VLDL-C), and low HDL-C, all of which are substantial heart disease risk factors [45]. CFA has the ability to reverse and/or increase the consequences of diabetes, such as dyslipidemia, according to current experimental findings. A major shift of TC, TG, HDL-C, LDL-C, and VLDL-C levels in CFA administration (500 mg/kg) related to normal control in the current investigation indicates that CFA has a robust hypolipidemic effect in streptozotocin-induced diabetic rats. However, it is worth noting that the CFA-induced elevation in HDL-C will be therapeutically useful for the rats treated as higher HDL-C levels are related to a lesser menace of heart disease and improved atheroprotection. In terms of lipid profile, the current findings are comparable to those of Effiong and Essien [46], who studied the effects of...
of leaf fractions from Nauclea latifolia on diabetic rat parameters.

Renal impairment is caused by hyperglycemia, as seen by increased BUN and serum creatinine. Biomarkers of kidney impairment such as BUN and creatinine were found notably higher in diabetic control in comparison to normal control. Our outcomes are reliable to those of Ashraf et al. [47] and de Castro et al. [48], who observed that similar markers were widely expressed in diabetic rats induced by streptozotocin. Extreme protein breakdown could explain the substantial increase in specific indices of renal impairment in the group of animals induced with diabetes. Elevated creatinine and urea contents in diabetic rats, which corresponded to the histological evaluation of kidney cells done during this study, are potential markers for diabetic nephropathy and confirm renal failure in diabetic animals. Remarkably, CFA treatment established a comparable restoration of renal impairment in a similar way to glibenclamide, with reversed serum creatinine and urea levels. Restoration of the architecture of kidneys in diabetic rats treated with CFA, as seen in histology, further confirmed the preventive role over diabetes. Other phytoconstituents produced positive results [49–51]. Gupta et al. [52] revealed that unrefined phytoconstituents improve kidney balance and albuminuria, reducing diabetes-mediated kidney damage and death of cells in diabetic rats. According to the current study, CFA is successful in reestablishing these indices of kidney function to close proximity values, suggesting its therapeutic promise in diabetes.

A healthy balancing between reactive oxygen species generation and antioxidant defense mechanisms reduce toxicity caused by free radicals. While this balancing is broken, oxidative stress is produced. By increasing ROS generation, hyperglycemia enhances oxidative stress [53]. As a result of lipid peroxidation, TBARS and MDA are produced which were dramatically elevated in diabetic rats [54]. In Type II diabetic erythrocytes, MDA concentration will be significantly greater than in the control group [Banerjee et al., 2020]. MDA and LH levels in serum samples were measured as part of a liver function analysis to assess oxidative stress in this investigation. Both are higher in diabetic controls (group 2), demonstrating oxidative tissue damage; however, CFA treatment provided dose-dependent tissue protection against oxidative damage. The results of our research revealed that streptozotocin-induced impact has a significant oxidative effect. Other research [55, 56] has found similar variances in parameters measured.

The findings of the LH showed that CFA may reduce oxidative stress in diabetic animals by increasing activities of antioxidant enzymes efficiently. Hyperglycemia induces the formation of free radicals, and it affects the cellular functions [57]. Endogenous enzymes, lipid-soluble and water-soluble antioxidant compounds, and phytonutrients are all used by life forms to combat oxidative stress [58]. Enzymes involved in antioxidant defense include SOD, CAT, GPx, and GRd. Antioxidant enzymes preserve cells from oxidative tissue damage. Antioxidants, both enzyme-based and non-enzymatic, convert free radicals produced by hyperglycemia into more stable molecules. Glucose undergoes autooxidation in hyperglycemia, resulting in superoxide free radicals. The superoxide anion is converted to H$_2$O$_2$ by an antioxidant enzyme called SOD, which is then degraded into oxygen and water by CAT enzyme [59]. Reduced glutathione is a non-enzymatic antioxidant and a co-substrate for GPx. It is thought to be a key regulator of intrinsic redox status since it directly scavenges lipid peroxidation [60, 61].

In streptozotocin-induced diabetic rats, we studied the effect of CFA as well as the impact of oxidative stress on enzymatic and non-enzymatic antioxidants. The amounts of SOD, CAT, GPx, Px, and GRd were considerably lower in streptozotocin-induced diabetic rats compared to the normal control. Rats treated with CFA (500 mg/kg) significantly (P < 0.001) reduced lipid oxidation by boosting the activities of enzymatic antioxidants. CFA treatment boosted the activity of enzymes in a dose-dependent way in diabetic rats. The antioxidant activity of streptozotocin-induced rats decreased but were quickly restored after CFA administration, indicating the high antioxidative potential of the extract. Ahmed et al. [62], Jia et al. [63], and Amaral et al. [64] all corroborate with the findings of this investigation.

Apart from enzymatic antioxidants, non-enzymatic antioxidants, such as vitamins C and E as well as GSH, are excellent for protecting cells from oxidative threats [65]. This study also assessed the efficacy of non-enzymatic antioxidants in the livers of diabetes-induced and treatment groups. All non-enzymatic antioxidants investigated in this study were observed to be decreased in diabetic control, with a substantial (P < 0.001) rise upon the administration of CFA (500 mg/kg) and glibenclamide enabling cytoplasmic membrane preservation from oxidative damage. The natural non-enzymatic antioxidant system relies heavily on glutathione. The enzyme glutathione peroxidase primarily functions as a reducing agent and helps remove hydrogen peroxide when it is present. Vitamin C, a potent non-enzymatic antioxidant that is water-soluble, quickly intercepts oxidizing agents in the aqueous phase before they target and cause oxidative damage. Vitamin E is the most powerful natural antioxidant, combined with oxygen radicals to protect membranes [66]. The decrease in vitamin C concentrations in diabetes individuals are consistent with prior research [67]. Our data indicate that CFA improved antioxidant capacity and shielded diabetic
rats against subsequent problems caused by oxidative stress.

This histopathologic study depicts the pathologic status of pancreatic β-cells in streptozotocin-induced diabetic circumstances, as well as the assessment of CFA in restorative and protective effects. In this study, the pancreas of diabetic rats underwent histological investigation, which revealed the loss of islets cells, a reduction in pancreatic β-cell populations, and a significant necrotic difference. CFA action on diabetic rats resulted in improved regeneration of islets cells and also enhanced insulin secretion by preventing oxidative stress in pancreatic β-cells via antioxidant enzymes. This has resulted in CFA having a regulatory mechanism and also carrying out pancreatic β-cell regeneration by alleviating oxidative stress [68]. In contrast to a prior study of phytoconstituents on healing and decrease of pancreatic β-cell destruction [69], the present investigation yielded better findings.

Numerous cell types, including parenchymal liver cells, are responsible for keeping blood glucose levels within a reasonable range. They perform an important role both as a carbohydrate reservoir and a producer amid hormonal conditions [70]. In the present study, histopathological modifications in the liver of diabetic control rats revealed periportal inflammation and enlargement of sinusoidal areas. CFA-treated diabetic rats, on the other hand, have seen a significant improvement in hepatocyte degeneration to close proximity levels. Compared to diabetic rats treated with glibenclamide, CFA preserved hepatocytes higher. Glycosylation of proteins causes anomalies in hepatic histoarchitecture, which leads to pathophysiological alterations in the diabetic liver [71, 72].

In addition, streptozotocin-induced hyperglycemia in rats was connected with particular kidney changes such as enlargement of normal proximal and distal tubules, according to this study. Our findings corroborated those of Fagbohun et al. [73], Maezawa et al. [74], and Pourghasem et al. [75], who claimed that any injury or malfunction impacting one type of cell has an impact across all renal cell types and impairs the functional status of the kidney. Histological investigation of diabetic rats treated with CFA revealed a significant recovery in tubular and glomerular damage to a close proximity physiological state. The antioxidant capabilities of CFA may be responsible for this modification of prior changes. As mentioned in that other antioxidant section, CFA improved antioxidant enzyme activity and free radical scavenging, reversing prior changes and clearly attesting to a protective mechanism in renal injury in diabetes mellitus. The preliminary results indicate that CFA suppressed the development of reactive oxygen species caused by streptozotocin, boosted antioxidant defense, and diminished kidney oxidative stress sensitivity, all of which support the core concept of this investigation. The preventive advantages of CFA against renal damage in diabetic rats are well demonstrated in this study.

5. Conclusion

The study discovered that CFA had significant antihyperglycaemic, antihyperlipidemic, and defensive actions in diabetic rats by lowering blood glucose levels, improving lipid profiles, and increasing antioxidant status. Notably, the higher dose (500 mg/kg) had a greater effect. Additionally, the data indicated that CFA treatment reduced pancreas, liver, and kidney damage. The current investigation shed more light on numerous of the beneficial characteristics of *Capsicum frutescens* fruit administration, assisting in its validation. While there is no evidence that *Capsicum frutescens* has a favourable effect on the treatment of diabetes, this research will establish the hypoglycemic effect of fruit, to the knowledge of authors for the first time. Additional robust gene expression research will expand indigenous knowledge across a broad spectrum, making diabetes care more approachable.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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