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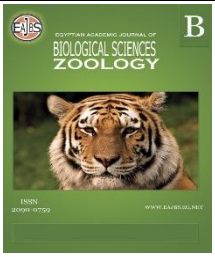

The Possible Antidiabetic Role of Dapagliflozin and /or Curcumin on Some Organs of Adult Male Albino Rats

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ABSTRACT

Background: diabetes is a prevalent endocrine metabolic disorder, particularly type 2 diabetes mellitus (T2DM), which is a serious worldwide health issue with serious complications, as diabetic nephropathy that necessitates ongoing treatment and supervision. A sodium-glucose cotransporter-2 (SGLT2) inhibitor called dapagliflozin (DAPA) is used to treat type 2 diabetes, but many diabetic drugs are costly and have adverse effects. Polyphenols like curcumin (CUR) are promising natural agents for reducing diabetic complications. **Aim of the work**: this study examined the potential therapeutic effects of DAPA and/or CUR in curing diabetic renal and pancreatic damage induced by a high-fat diet (HFD) combined with low-dose streptozotocin (STZ) in rats. **Materials and Methods**: Six groups of 36 male albino rats, each weighing between 190 and 200 g (6 rats/ group). Group I represented negative control, and group II received 80 mg/kg/day of curcumin orally. Groups III to VI underwent induction of T2DM by feeding rats with HFD for 3 weeks and injecting one dose of 40 mg/kg STZ, whereas group III was a diabetic group (positive control). However, group IV was treated with DAPA(1 mg/kg/day), group V was treated with curcumin (80 mg/kg/day), and group VI was treated with a combination of DAPA and curcumin. After 30 days, kidney functions, malondialdehyde (MDA), superoxide dismutase (SOD), glutathione (GSH), tumor necrosis factor-alpha (TNF-α), interleukin 1 beta (IL-1β), histopathological and immunohistochemical changes in renal and pancreatic tissues were evaluated. **Results:** the diabetic group showed elevated kidney parameters, oxidative stress, inflammation markers, and apoptosis, accompanied by a significant decrease in the antioxidant markers along with and severe renal and pancreatic tissue damage. Treatments with DAPA, CUR, or their combination significantly restored antioxidant levels (GSH, SOD), lowered MDA levels, decreased inflammatory markers (TNF-α, IL-1β) resulting in notable amelioration of renal and pancreatic tissues damage. Improved renal and pancreatic tissue structure and immunohistochemical analysis were confirmed by nearly standard structure of both organs and the reduction of caspase-3 expression, respectively. The combined DAPA/CUR treatment demonstrated superior protective effects compared to monotherapy. **Conclusion**: diabetes-induced complications are mitigated effectively by regulating oxidative stress, inflammation, and apoptosis, providing robust pancreatic-renal protection using combined DAPA/CUR treatment.

INTRODUCTION

Diabetes mellitus (DM) is a severe, long-term metabolic disease caused by a complicated interplay between environmental and genetic variables. At the same time, a number of potentially fatal diabetes complications can arise from uncontrolled and chronically elevated blood sugar (Alam *et al.,* 2021). The most widespread form of diabetes, type 2 diabetes mellitus (T2DM), is closely characterized by insulin resistance and pancreatic β-cell dysfunction (Skovsø, 2014). The primary symptom of DM is hyperglycemia, which is linked to significant changes in the metabolism of fat and glucose as well as elevated oxidative stress that is implicated in the development of diabetic complications (Xiao *et al*., 2021). The accumulation of oxidative stress markers is associated with elevated pro-inflammatory cytokine expression (Abdulmalek *et al*., 2021) and increases the organ dysfunction, especially diabetic nephropathy (El-Serag *et al.*, 2004).

The kidneys are essential for maintaining glucose homeostasis, since the glomerulus filters the majority of the glucose (Millar *et al.,* 2017). In the proximal tubule segments 1 and 2 (S1/2), sodium-glucose cotransporter-2 (SGLT2) reabsorbs over 90% of the filtered glucose load, while SGLT1 normally reabsorbs the remaining glucose in the proximal tubule segment 3 (Saisho, 2020). In the presence of hyperglycemia, SGLT2 induces the absorption of glucose by 30% (DeFronzo, 2017).

One medication used to treat type 2 diabetes is dapagliflozin (DAPA), which inhibits SGLT2 and causes glucose to be excreted into the urine. In a diabetic kidney, SGLT2 inhibition decreased oxygen consumption, tubular oxidative stress, and hyperfiltration (Panchapakesan *et al.,* 2013; Neill *et al.,* 2015; Chang *et al.,* 2016). DAPA is effective as both monotherapy and combination therapy, depending on the severity of the disease (Molugulu *et al.,* 2017; Kalra *et al.,* 2018; Maksud *et al.,* 2024). Since dapagliflozin especially acts on the kidneys and has no direct effect on ß-cell activity, Merovci *et al.* (2015) provided strong proof that dapagliflozin medication enhances ß-cell activity in type 2 diabetes by controlling hyperglycemia. Unfortunately, several oral antidiabetic medications that act via various modes of action have demonstrated adverse effects, such as SGLT2 inhibitors, which include dehydration, orthostatic hypotension, as well as genital infections and urinary tract infections caused by glycosuria (Karaca *et al*., 2022). It has been established that these infections can develop into greater complications such as acute kidney damage, pyelonephritis, urosepsis, vulvovaginitis, balanitis, and bladder cancer (Ayuob *et al*., 2015). Furthermore, diabetic ketoacidosis, metabolic bone disease, limb amputation, Fournier gangrene, and elevated hematopoiesis have all been linked to DAPA (McCullough *et al*., 2018). Therefore, medicinal plants have become the mainstay of many accessible therapies due to their low cost, accessibility, and few adverse effects (Abdulmalek *et al.*,2021). The curcumin (CUR) is a natural phenolic antioxidant that effectively scavenges free radicals due to its phenolic hydroxyl group (Wojcik *et al*., 2018; Rege *et al*., 2019). It has also been shown to reduce numerous other complications related to diabetes such as diabetic neuropathy, fatty liver, musculoskeletal diseases, vascular diseases, and islet viability (Kunwar and Priyadarsini, 2016; Gad El-Hak and Mobarak, 2020; Ermiş and Çiftci 2024). Notably, it can improve T2DM by lowering blood sugar, cholesterol, oxidative stress, and inflammation while enhancing insulin resistance, which is important for patients with hyperlipidemia (Quispe *et al*., 2022). The current investigation aimed to examine the potential therapeutic effects of DAPA and/or CUR in curing diabetic renal and pancreatic damage induced by a combination of low-dose STZ and HFD in rats.

MATERIALS AND METHODS

Experimental Animals:

Thirty-six male Wistar albino rats, all mature and healthy, weighing between 190 and

200 grams, were divided into six groups each. One week before that start of the experiment, the animals were acclimatized.

Induction of Type 2 Diabetes mellitus (T2DM):

The present protocol was used to introduce a proper animal model that mimics the type 2 diabetes features among humans by combining an HFD, which induces insulin resistance (IR), with a low dose of STZ injection, resulting in initial β-cell dysfunction (impairment in insulin production) (Furman, 2021). HFD was prepared according to Srinivasan *et al.* (2004**)** and calculated as a proportion of total caloric intake: 17% carbohydrate, 58% fat, and 25% protein. HFD and water were administered to the rats *Ad libitum.* After 3 weeks, one intraperitoneal (IP) injection of streptozotocin (STZ 40 mg/kg), freshly dissolved in citrate buffer (0.1 M), pH 4, at a dose of 1 ml/kg body weights (b. wt.), to fasted (6-8h) rats. To avoid fatal hypoglycemia, diabetic-induced rats were allowed to consume a 20% glucose solution overnight. Diabetes mellitus was determined by measuring fasting blood glucose levels from tail vein using a glucometer (ACCU-CHEK) **(**Gandhi *et al*., 2013). At the end of the fourth week, animals with consistent fasting hyperglycemia (FBS ≥ 250 mg/dl) were utilized (**Gad *et al*., 2010**). Until the completion of the experiment, the diabetic rats in the various diabetes groups were permitted to continue HFD feeding.

Materials:

1- **Streptozotocin (**STZ) and 0.1 M citrate buffer (pH 4-4.5) were purchased from Sigma–Aldrich Inc. (St. Louis, MO, USA) from the Egyptian branch (Sigma pharma chemicals company, Cairo, Egypt). STZ solution was freshly prepared by dissolving STZ (40 mg/kg) powder in cold 0.1M citrate buffer.

2- **Dapagliflozin:** 10 mg tablets (AstraZeneca Pharmaceuticals LP, Mount Vernon, Indiana, USA) were obtained from a local pharmacy. Aqueous solution of DAPA was prepared and administered orally by gastric tube at a dose of 1 mg/kg/day according to Jaikumkao *et al*. (2018).

3- **Curcumin:** was obtained as Theracurmin (60 Vegetarian capsules; the absorbed form of curcumin) extract from turmeric (*Curcuma longa* root) from Natural Factors Chemical Company in CANADA website: https://naturalfactors.com. Curcumin was dissolved in dimethyl sulfoxide (DMSO), then diluted to the appropriate volume with distilled water and orally administered through a gastric tube at a dosage of 80 mg/kg/day according to Zhang *et al.* (2013).

Experimental Design*:*

The animals were split into six groups, with 6 rats in each group as follows:

Group 1 normal (C): normal rats with fasting blood glucose less than 110 mg/dl that were intraperitoneally (IP) injected with one dose of 1.0 ml/kg of 0.1 M citrate buffer (pH 4). The animals were kept untreated and fed a regular diet.

Group 2: Curcumin group (CUR): rats received oral administration of CUR (80 mg/kg/day) for 4 weeks and were fed with a typical diet.

Group 3: Diabetic untreated group (D): this group served as the reference group for the corresponding diabetic-treated groups.

Group 4: Diabetic+ Dapagliflozin (D+DAPA): dapagliflozin was orally administered daily to diabetic-induced rats at a 1 mg/kg/day dose for 4 weeks.

Group 5: Diabetic + Curcumin (D+CUR): curcumin was orally administered daily to diabetic-induced rats at an 80 mg/kg/day dose for 4 weeks.

Group 6: Diabetic+ Dapagliflozin+ curcumin (D+DAPA+CUR): diabetic-induced rats were treated orally with dapagliflozin (1 mg/kg/day) followed by curcumin (80 mg/kg/day) for 4 weeks.

Collection of Samples*:*

Using a metabolic cage, a 24-hour urine sample was taken from the control and treated groups at the end of the experiment. To eliminate any elements, the samples of urine have been

centrifuged for 15 minutes at 3000 rpm. The supernatant was then kept at -20°C until it was needed for biochemical analysis. Following urine collection, the rats were weighed and given an intraperitoneal dose of 1 g/kg urethane (99%, Sigma-Aldrich, Dorset, UK) for anesthetizing. The blood samples from the retro-orbital venous plexus of rats were collected, coagulated at room temperature, and centrifuged for 15 minutes at 4000 rpm. The sera were stored at -20°C for biochemical analysis. Then, the rats were dissected; the kidneys and pancreas were quickly removed and divided into two parts. For biochemical analysis, the first part was homogenized (10%, w/v) in ice-cold PBS (5 mM, containing 0.15 M NaCl, pH 7.4). Meanwhile, the second part was used for histological and immunohistochemical studies.

Biochemical Studies:

A-Estimation of the Serum Parameters:

Serum creatinine and uric acid were determined according to Burtis and Ashwood (1999) and Tietz (1995), respectively**.** It was calculated by using the colorimetric assay kit (SPINREACT, S.A./S.A. U Ctra. Santa Coloma) according to the manufacturer's instructions.

B-Estimation of the Urine Parameters:

The urine glucose, albumin and creatinine, were determined using a colorimetric/ fluorometric assay Kit provided by Life Span Bio-Sciences, Inc. (Fourth Avenue, Seattle, WA.). The Albumin/Creatinine Ratio (ACR) were calculating by using a colorimetric/ fluorometric assay Kit provided by Life Span Bio-Sciences, Inc. (Fourth Avenue, Seattle, WA.) according to the formula:

$$\frac{\text{Albumin } (\frac{\text{mg}}{\text{dL}})}{\text{Creatinine } (\frac{\text{g}}{\text{dL}})} = \text{ACR } \frac{\text{mg Albumin}}{\text{g Creatinine}} \approx \frac{\text{Excreted Albumin (mg)}}{\text{24 hr}}$$

C-Estimation of the Tissue Homogenate Parameters:

Pancreas and kidney tissues homogenate levels of malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione (GSH) were determined by using a commercial Enzyme-linked immunosorbent assay (ELISA) Kit provided by My BioSource. Furthermore, tumor necrosis factor-alpha (TNF-α) and interleukin 1 beta (IL-1β) contents were determined using ELISA kit provided by CUSABIO in the pancreas and kidney tissue homogenate.

Histopathological And Immunohistochemical Studies:

Following 24-hour fixation in 10% neutral formalin, the second portion of the pancreatic and renal tissues was dried, cleaned in xylene, and embedded in paraffin wax. Hematoxylin and eosin (H&E stain) are used to stain tissues with a thickness of 5 μm in order to determine their general histological structure (Suvarna *et al.*, 2013). Eissa and Shoman (1998) stated that caspase 3 was used to identify apoptotic markers.

Morphometric Analysis*:*

Image Synthesis: to digitize the slides, an Olympus digital camera (Olympus LC20-Japan) placed atop an Olympus microscope (Olympus BX-50, Tokyo, Japan) with a 1/2X picture adapter and a 40X objective was employed to digitize the slides. On an Intel® Core I3® computer, the resulting images were examined using Video Test Morphology 5.2 software (Russia), which has a specialized stain quantification and immunohistostaining evaluation technique built in.

Quantitative Immunohistochemical Analysis:

The optical density of caspase-3 positive expression in the kidney and pancreas of the experimental groups was recorded using Image Pro Plus 4.5.1.22 analysis software.

Statistical Analysis:

The statistical package for social sciences (SPSS), version 16, was employed to statistically examine the results obtained. Each value is indicated as mean ± standard error. After comparing means using a one-way ANOVA, Tukey's post hoc analysis was applied. $P < 0.01$ was regarded as a significant value.

RESULTS

Effect of DAPA and/or Curcumin on The Serum Parameters:

The effect of oral dapagliflozin and curcumin on serum creatinine and uric acid as indicators of renal function in the current investigation was demonstrated by the data in Figure 1. In this study, the untreated rats revealed a significant increase in serum creatinine levels and uric acid compared to the normal rats. Despite their levels continuing to record a significant increase over the control group, the administration of DAPA or CUR to diabetic rats showed a significant reduction in these parameters when compared to the untreated group. Distinctively, treatment of diabetic rats with a combination of DAPA and CUR returned the creatinine levels to nearly the control group values. However, in the same group, uric acid decreased compared to that of the diabetic group but was still higher than that of the normal animals.

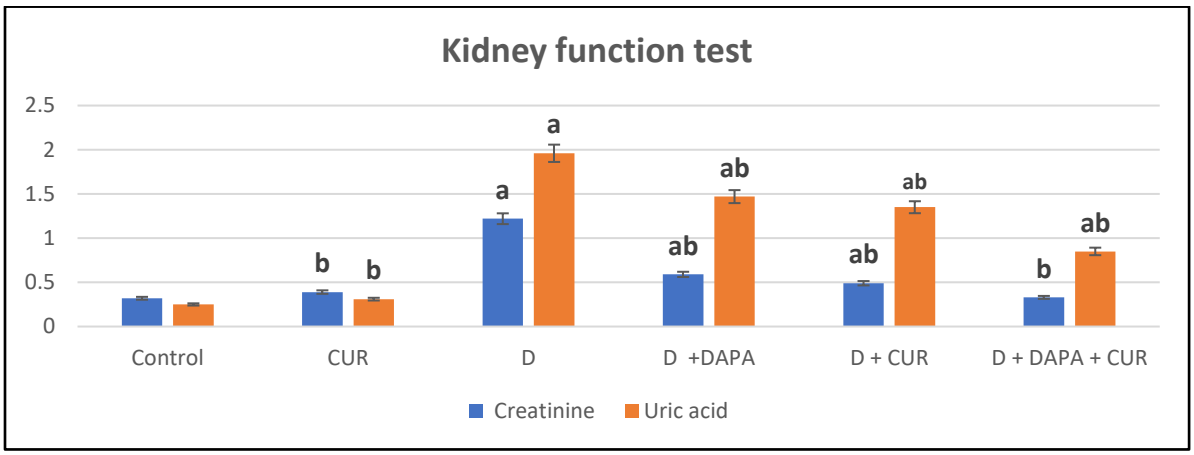


Fig.1: Effects of oral administration of dapagliflozin and/or curcumin on serum creatinine and uric acid (mg/dl) in the different experimental rats. Data represent means ± SE (n=6). ([a]) are statistically different as compared to the control, and ([b]) are statistically different as compared to the diabetic group at $p < 0.01$. D: diabetic, DAPA: dapagliflozin, CUR: curcumin.

Effect of DAPA and/or Curcumin on the Urine Parameters:

The data in Table (1), illustrate the effect of dapagliflozin and/or curcumin on urinary glucose (mg/24hr), albumin (g/24hr), creatinine (mg/24hr), as well as the albumin/ creatinine ratio (mg/mmol) in the experimental rats. Significant increases in urinary glucose and albumin levels in the diabetic untreated rats have been recorded compared to the normal animals. Meanwhile, the urinary creatinine level recorded a significant decrease in the same group compared to the control group. The curcumin administration to the diabetic animals significantly decreased the glucose and albumin levels in D+ CUR and D+ DAPA+CUR groups compared to the diabetic untreated group. Distinctively, the administration of DAPA in the D+DAPA group recorded a significant increase in the level of urinary glucose compared to its level in the untreated diabetic group. Meanwhile, the diabetic group treated with DAPA revealed a significant reduction in albumin levels compared to the diabetic untreated animals. On the contrary, D+DAPA, D+CUR, and D+DAPA+CUR recorded significantly increased urinary creatinine levels compared to the untreated group. The elevation of creatinine levels in the urine was demonstrated in D+DAPA+CUR, even more than the levels of the control. In the same context, these changes in the urinary albumin and creatinine levels are reflected in the urinary albumin /creatinine ratios in all diabetic groups. The DAPA and curcumin diabetic treated group demonstrated a significantly decreased ratio compared to the untreated rats and restored the ratio to the normal level.

Table 1: Effects of oral administration of dapagliflozin and/or curcumin on urinary glucose, urinary albumin, urinary creatinine, and albumin/ creatinine ratio in the different experimental rats.

Parameter / Groups	Urinary glucose (mg/24hr)	Urinary albumin (g/24hr)	Urinary creatinine (mg/24hr)	Urinary Alb/creatinine ratio
Control	104.18 ± 0.68	0.126 ± 0.035	10.19 ± 0.19	12.52± 3.49
CUR	104.32 ± 0.71[b]	0.163 ± 0.015 [b]	9.95 ± 0.25 [b]	16.43 ± 1.5 [b]
Diabetic (D)	708.66 ± 9.36 [a]	1.723± 0.05[a]	5.84 ± 0.58 [a]	288.48 ± 38.03[a]
D +DAPA	760.75 ± 13.97 [ab]	0.505 ± 0.03 [ab]	6.79 ± 0.55 [ab]	77.83 ± 9.82 [ab]
D + CUR	303.38 ± 68.28 [ab]	0.750 ± 0.06 [ab]	7.52 ± 0.27 [ab]	99.73 ± 7.46 [ab]
D + DAPA+ CUR	300.75 ± 17.29 [ab]	0.280 ± 0.02 [ab]	12.36± 0.61 [ab]	21.6 ± 1.19 [b]

Values represent means ± SE (n=6). Means with ([a]) superscript are statistically different as compared to control, ([b]) superscript are statistically different as compared to the diabetic group at $p < 0.01$. DAPA, dapagliflozin; CUR, curcumin; D, diabetic and SE, standard error.

Effect of DAPA and/or Curcumin on The Tissue Parameters:

1-The Oxidant and Antioxidant Parameters in the Pancreatic and Renal Tissues:

The levels of MDA, GSH contents and SOD activity as an indicator of oxidative stress in the pancreas tissues, are depicted in Table (2). No significant change in the MDA, SOD activity and GSH levels was recorded in the normal rats treated with curcumin without inducing diabetes. However, the group with diabetes demonstrated a significant increase in the MDA content that was accompanied by significant decreases in the SOD activities and GSH levels compared to the control levels. Meanwhile, the treated groups D+DAPA, D+ CUR, and D+DAPA+ CUR revealed a significant decrease in the MDA level and increases in both SOD activity and GSH levels compared to the diabetic group levels. Notably, D+DAPA+ CUR illustrated MDA content with no significant change compared to the normal levels.

Table 2: Effects of oral administration of DAPA and/or CUR on MAD, GSH and SOD in the pancreatic tissues of the different experimental animals.

Parameter / Groups	MDA (µmol/L)	GSH (ng/ml)	SOD activity (U/ml)
Control	0.49 ± 0.07	79.67 ± 0.66	42 ± 1.95
CUR	0.71 ± 0.05 [b]	83.7 ± 2.69 [b]	39.67 ± 1.25 [b]
Diabetic (D)	8.87 ± 0.74 [a]	17.95± 1.34 [a]	10.98 ± 0.42[a]
D +DAPA	4.06 ± 0.09 [a b]	52.63 ± 2.02[a b]	22.54 ± 0.7[a b]
D + CUR	4.66 ± 0.11 [a b]	57.54 ± 0.88 [a b]	22.46 ± 0.78 [a b]
D + DAPA + CUR	1.55 ± 0.162 [b]	59.59 ± 0.827 [a b]	29.195 ± 0.430 [ab]

Values represent means ± SE (n=6). Means with ([a]) superscript are statistically different as compared to control, ([b]) superscript are statistically different as compared to the diabetic group at $p < 0.01$. DAPA, dapagliflozin; CUR, curcumin; D, diabetic; MDA, malondialdehyde; SOD, superoxide dismutase; GSH, reduced glutathione content and SE, standard error.

On the same context, the data illustrated in Table (3), showed the effect of curcumin and /or dapagliflozin on MAD, GSH and SOD activity in the kidney tissues of the experimental rat**s.** The kidney tissues of the nondiabetic curcumin group illustrated no significant change in renal MDA levels that was accompanied by a significant increase in SOD and GSH compared to their levels in the control rats. The diabetic group showed a significant increase in the

content of MDA. It showed a significant decrease in SOD activity and GSH ($p< 0.01$) when compared to their levels in the normal rats. Meanwhile, the D+DAPA and D+CUR recorded a significant decrease in the MDA and significant increases in the SOD activity and GSH content when compared to that of the diabetic group. In addition, the D+DAPA+ CUR demonstrated a significant decrease in the MDA and significant increases in the SOD and GSH compared to that of the diabetic animals. This group demonstrated an impressive restoration to their normal levels for these parameters.

Table 3: Effects of oral administration of DAPA and/or CUR on MAD, SOD and GSH in the kidney tissues of the different experimental rats.

Parameter / Groups	MDA (µmol/L)	GSH (ng/ml)	SOD (U/ml)
Control	0.49 ± 0.031	202.8 ± 1.96	210.2 ± 5.692
CUR	0.695 ± 0.107 [b]	241.55 ± 10.781 [ab]	244.1 ± 1.819 [a b]
Diabetic(D)	11.68 ± 0.614[a]	36.92 ± 4.577[a]	43.64 ± 5.173 [a]
D +DAPA	2.82 ± 0.164 [a b]	152.03 ± 3.672 [a b]	168.45 ± 10.978 [a b]
D + CUR	3.68 ± 0.148 [a b]	162.50 ± 3.960 [a b]	162.41 ± 10.001 [a b]
D+ DAPA + CUR	0.94 ± 0.051[b]	192.47 ± 3.585 [b]	206.50 ± 15.389 [b]

Values represent means ± SE (n=6). Means with ([a]) superscript are statistically different as compared to control, ([b]) superscript are statistically different as compared to the diabetic group at $p < 0.01$. DAPA, dapagliflozin; CUR, curcumin; D, diabetic; MDA, malondialdehyde; SOD, superoxide dismutase; GSH, reduced glutathione content and SE, standard error.

2-The Inflammatory Markers in The Pancreatic and Renal Tissues:

The data in Table (4), showed the effect of dapagliflozin and/or curcumin on TNF-α and IL-1β in the pancreatic tissues of the normal and diabetic animals. The levels of TNF-α and IL-1β in the pancreatic tissues of the diabetes group were significantly higher than those of the control rats. Meanwhile, the D+DAPA, D+ CUR, and D+DAPA+ CUR showed significant decreases in both parameters ($p< 0.01$) compared to their levels in the diabetic groups. The combined treatment gives the best effect in downregulated TNF-α and IL-1β levels. Meanwhile, the curcumin non-diabetic group recorded no significant changes in the TNF-α and IL-1β compared to the normal group.

Table 4: Effects of oral administration of DAPA and/or CUR on TNF-α and IL-Iβ in the pancreatic tissues of the different experimental rats.

Parameter / Groups	TNF-α (pg/ml)	IL-Iβ (pg/ml)
Control	24.35 ± 1.507	32.68 ± 3.065
CUR	15.01 ± 1.132 [b]	23.9 ± 0.953 [b]
Diabetic (D)	161.75 ± 10.92 [a]	150.09 ± 11.51[a]
D +DAPA	77.43± 1.633 [ab]	71.43 ± 1.242 [ab]
D + CUR	85 ± 1.704 [ab]	74.65± 1.349 [ab]
D + DAPA + CUR	48.96 ± 1.309 [ab]	45.05 ± 4.249 [ab]

Values represent means ± SE (n=6). Means with ([a]) superscript are statistically different as compared to control, ([b]) superscript are statistically different as compared to the diabetic group at $p < 0.01$. DAPA, dapagliflozin; CUR, curcumin; D, diabetic; TNF-α, tumor necrosis factor-alpha; IL-Iβ, interleukin-1β and SE, standard error.

The data in Table (5), demonstrated the effect of curcumin and/or dapagliflozin on TNF-**α** and IL-1β in the kidney tissues of the experimental groups. Comparing the curcumin non-diabetic group to the normal group, no significant difference was found in the levels of TNF-α. Meanwhile, the IL-1β levels indicated a significant drop ($p< 0.01$) compared to the control group. For these parameters, the diabetic group showed a significant increase ($p< 0.01$)

compared to their levels in the control group. The D+DAPA, D+ CUR, and D+DAPA+ CUR showed significant decreases in the TNF-**α** and IL-1β at ($p< 0.01$) compared to the diabetic group. Nonetheless, there were still significant elevations in TNF-α and IL-1β levels when compared to the normal animals ($p< 0.01$).

Table 5: Effects of oral administration of DAPA and/or CUR on TNF-α and IL-1β in the kidney tissues of the different experimental rats.

Parameter / Groups	TNF-α (pg/ml)	IL-1β (pg/ml)
Control	14.20 ± 0.543	18.75 ± 0.442
CUR	18.41 ± 0.338 [b]	10.88 ± 0.089 [ab]
Diabetic (D)	140.97 ± 12.089 [a]	84.68 ± 0.744[a]
D +DAPA	80.45 ± 0.519 [a b]	75.86 ± 1.595 [a b]
D + CUR	73.66 ± 1.763 [a b]	61.27 ± 1.975[a b]
D + DAPA + CUR	38.06 ± 2.325 [ab]	36.73 ± 1.923 [ab]

Values represent means ± SE (n=6). Means with ([a]) superscript are statistically different as compared to control, ([b]) superscript are statistically different as compared to the diabetic group at $p < 0.01$. DAPA, dapagliflozin; CUR, curcumin; D, diabetic; TNF-α, tumor necrosis factor-alpha; IL-Iβ, interleukin-Iβ; and SE, standard error.

Effect of DAPA and/or Curcumin on Diabetes-Induced Renal and Pancreatic Cellular Injury:

Histopathological Analysis of The Kidney:

Figure 2 (A) showed the normal kidney cortex of the untreated control rats. Renal corpuscles appear as dense, rounded structures surrounded by renal tubules. Each glomerulus is surrounded by a narrow Bowman's space and Bowman's capsule. The cortical tubules consist mainly of the proximal and distal convoluted tubules, which terminate in the collecting ducts. The proximal tubules consist of simple cuboidal epithelium and narrow lumens with intensely stained cytoplasm. The distal convoluted tubules are differentiated from the proximal ones by the absence of brush borders and larger, defined lumens with less staining affinity**.** Examined sections from the kidney of curcumin treated rats showed that the proximal and distal convoluted tubules, Bowman's capsules, Bowman's space, and glomeruli all had histological appearances that were nearly normal (Fig. 2 B).

However, renal serial sections of diabetic rats revealed large and small hemorrhagic areas, moderate vascular dilation, perivascular edema and ill distinct inflammatory reaction. Additionally, there are variable degrees of degenerative changes including cloudy swelling, vacuolar and hydropic degeneration, beside moderate dilatation of some distal convoluted tubules with partial atrophy of their lining epithelium were recorded. Enlarged Bowman's space, tubular degeneration and partial shrinkage, and atrophy of some glomeruli and other lobulated or degenerated areas were also seen. Desquamated epithelial cells in tubule lumens. A few apoptotic cells were observed in the tubular epithelium. Pyknotic or karyolitic nuclei and mononuclear cell infiltration in the interstitial were also present (Figs. 3 A- D). Examination of kidney cortex tissue of diabetic rats treated with dapagliflozin showed somewhat normal appearance of glomerulus, Bowman's capsule, Bowman's space, and the proximal and distal convoluted tubules, as compared to the diabetic group. A few renal tubules appear mildly dilated (Figs. 4 A&B). Sections from the kidney of diabetic rats, followed by oral treatment with curcumin, revealed nearly normal histo-morphology of kidney tissue. A few sections revealed mild congestion of renal blood vessels, degenerative changes (cloudy swelling and hydropic degeneration), sporadic glomerular lobulation, besides dilatations in some distal convoluted tubules (Figs. 5A&B). Nearly normal

histological appearance of glomeruli, Bowman's capsules, Bowman's space, and the proximal and distal convoluted tubules of diabetic rats that received a combination of curcumin and dapagliflozin was observed. Still, renal tubules were mildly dilated (Figs. 6 A&B).

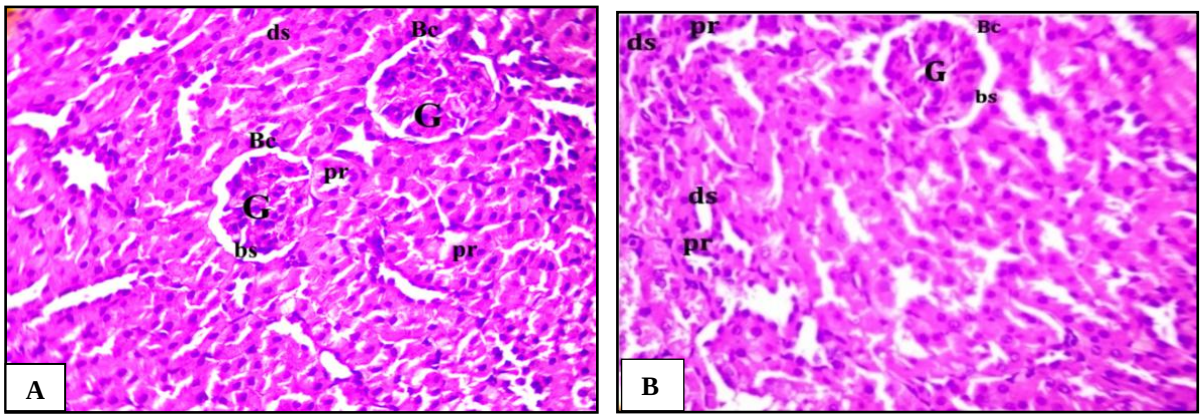


Fig. 2: Photomicrographs from sections of kidney cortex tissue of the control group (**A**) and from renal cortex tissue of rats treated with curcumin **(B**) showing: A&B- normal appearance of glomeruli **(G)**, Bowman's capsules **(Bc)**, Bowman's spaces (**bs),** the proximal **(pr)** and distal tubules **(ds)**. **A & B (H&E, X400).**

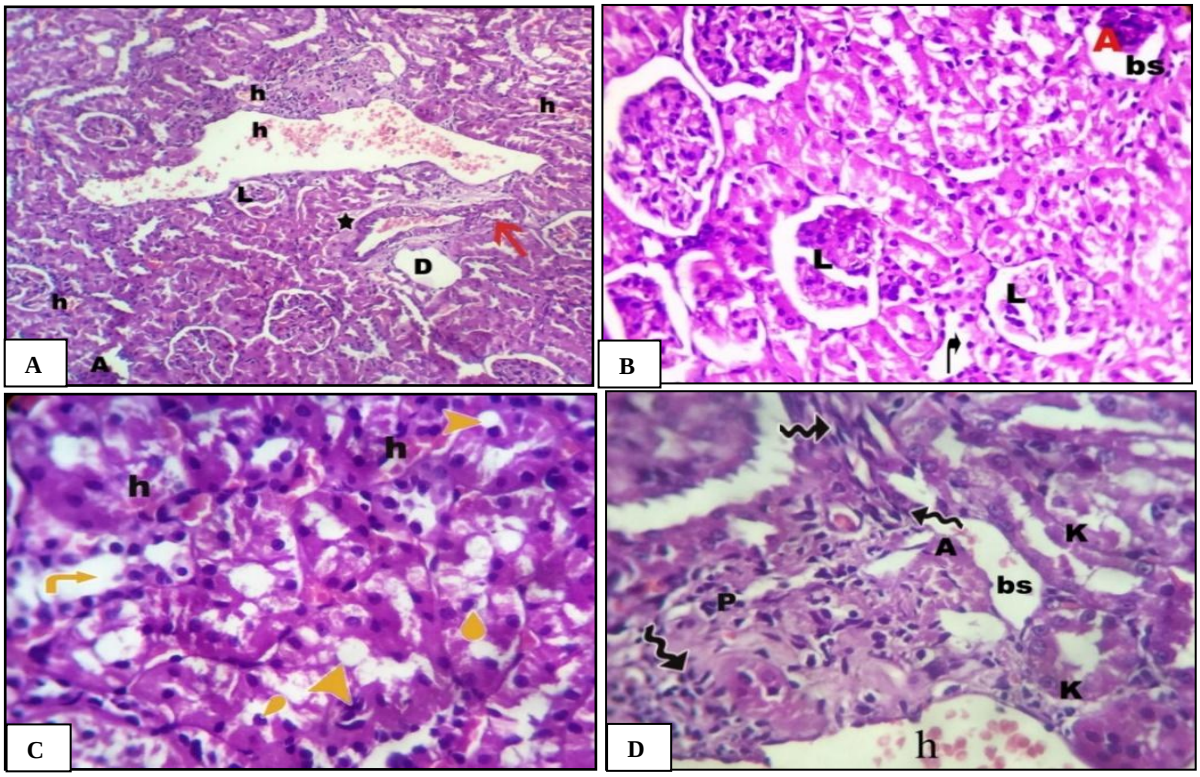


Fig. 3: Photomicrographs from sections of renal tissues of HFD/STZ-induced rats showing: **A-D:** large and small hemorrhagic areas **(h),** moderate vascular dilation (**red arrow**), perivascular edema (**star**), shrinkage and atrophy of some glomeruli **(A)** and the other lobulated **(L)** or totally degenerated (**D**). Enlarged Bowman's space **(bs),** additionally various degrees of degenerative alterations in renal tubules, such as cloudy swelling, vacuolar, and hydropic degeneration (**arrowhead**), desquamated epithelial cells in tubule lumens **(drop),** some distal convoluted tubules have dilated, and their lining epithelium has partially atrophy **(curved arrows).** Pyknotic **(P)** or karyolitic nuclei **(K)** and mononuclear cell infiltration in the interstitial are also present (**corrugated arrow**). **A (H&E X 200), B, C& D (H&E X 400)**.

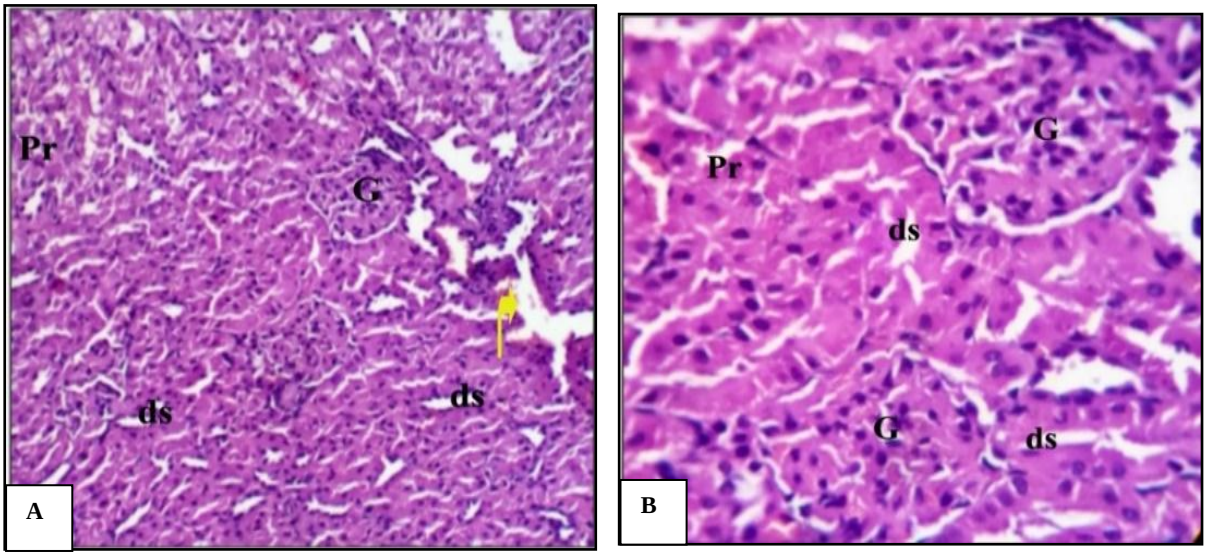


Fig. 4: Photomicrographs (A& B)from kidney cortex sections of diabetic rats treated with dapagliflozin showing: nearly normal histomorphology of the glomeruli (G), proximal (pr) and distal convoluted tubules (ds). A few renal tubules appear mildly dilated (**curved arrows). A-(H &E X 200) B -(H&E X 400**).

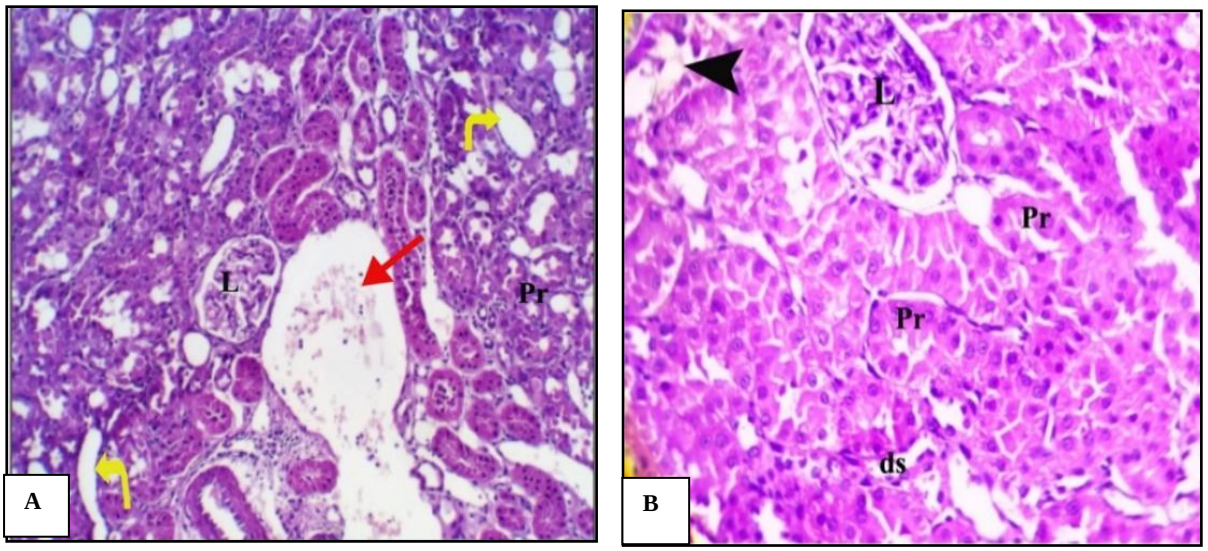


Fig. 5: Photomicrographs **(A &B)** from kidney cortex tissue of diabetic rats treated with curcumin showing somewhat normal histo-morphology of kidney tissue with a keeping normal feature of glomeruli **(G)** and renal tubules (proximal (**pr)** and distal convoluted tubules**(ds)).** Mild congestion of renal blood vessels (**red arrow**), degenerative changes (cloudy swelling and hydropic degeneration) (**arrow head)**, sporadic glomerular lobulation (**L**) beside dilatations in some distal convoluted tubules are also seen (**curved arrow). A-(H &E X 200), B-(H&E X 400**).

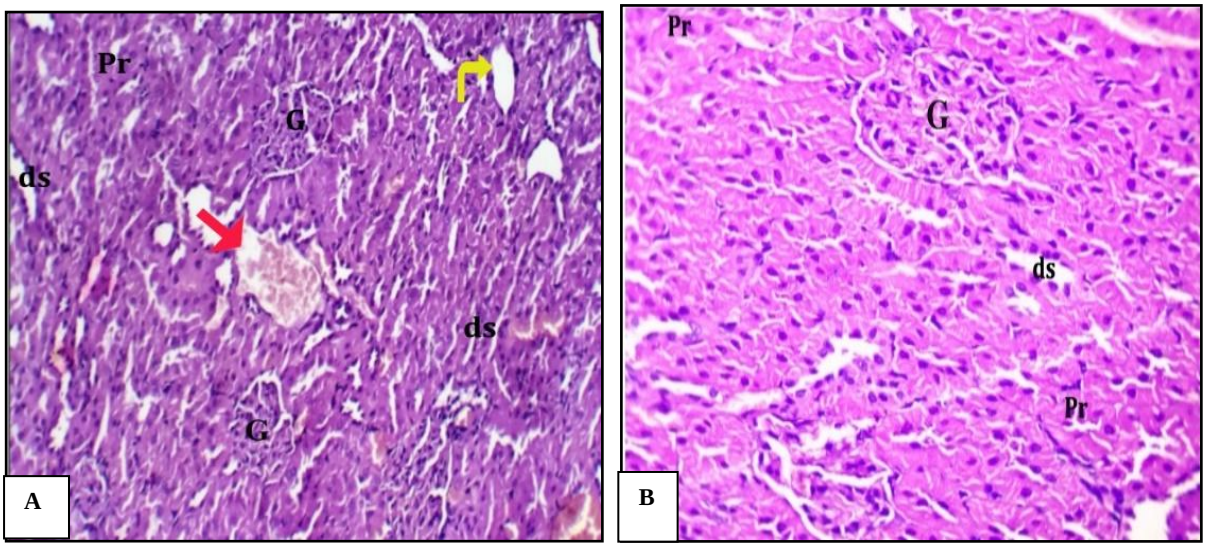
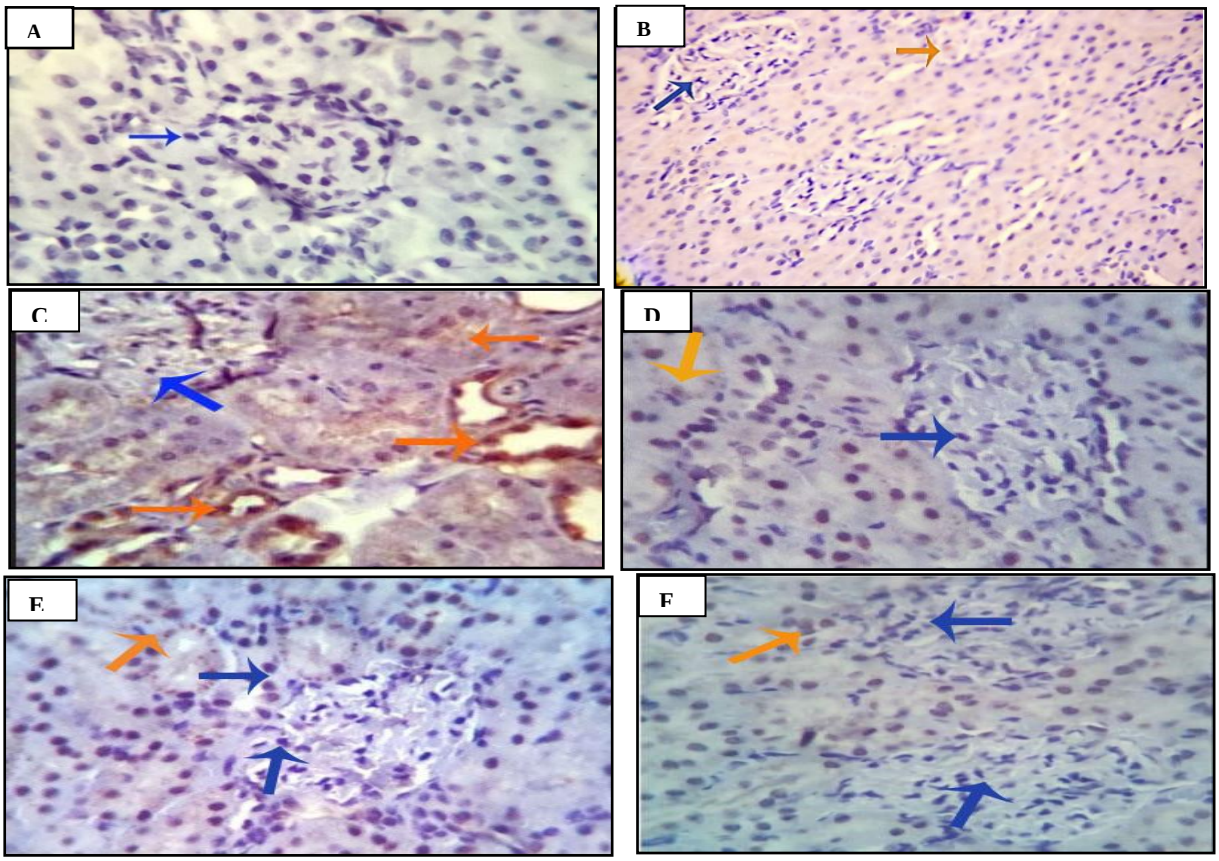


Fig. 6: Photomicrographs) A**& B(** from kidney cortex sections of diabetic rats treated with curcumin+ dapagliflozin showing somewhat normal appearance of the glomeruli **(G),** renal tubules (proximal (**pr)** and distal convoluted tubules**(ds))** and vascular structures (**red arrow**). A few renal tubules appear mildly dilated (**curved arrows)**. **A- (H &E X 200), B-(H &E X 400).**

The Immunohistochemical Studies:

Immunohistochemical stained renal tissue sections from the control group showed a negative cytoplasmic and/or nuclear reactivity to caspase 3 monoclonal antibodies (Fig. 7 A) . Meanwhile, the non-diabetic group CUR showed weak expression of caspase-3 (Fig. 7 B). Immunohistochemical examination of kidney sections from HFD-STZ rats revealed a significant increase in caspase-3 immunopositive region expression as compared to those without diabetes (Fig. 7 C). DAPA or CUR treatments promoted a significant decrease in caspase-3 expression within the renal tubular epithelium of HFD -STZ rats. However, the combination group showed mild expression of caspase-3 in the kidney sections of HFD - STZ animals (Figs. 7 D, E&F respectively).



Figs. (7 A-F): Photomicrographs from kidney cortex of different experimental groups immunohistochemically stained for caspas-3 showing brownish cytoplasmic expression of variable intensities. Positive cells are pointed by orange arrows and negative cells by blue arrows. **A**: control, **B**: CUR, **C**: Diabetic(D), **D**: D+ DAPA, **E**: D+ CUR, **F**: D+ DAPA+ CUR **(Caspase-3 antibody X400).**

Quantitative Immune-Histochemical Measurement:

The results illustrated in Figure (8), showed variations in the mean density of caspase-3 immunohistochemical expression in the kidney cortex of the different experimental rats. The current results demonstrated that the morphometric analysis of immunoreactive area for caspas-3 recorded a non-significant change in the non-diabetic rats treated with CUR when compared with the control group. However, the diabetic group recorded a significant elevation compared to the control group. This elevation was reversed in the D+DAPA, D+CUR and D+DAPA+CUR groups. These groups showed a significant attenuation of the caspase-3 immunoreactivity when compared with the control group.

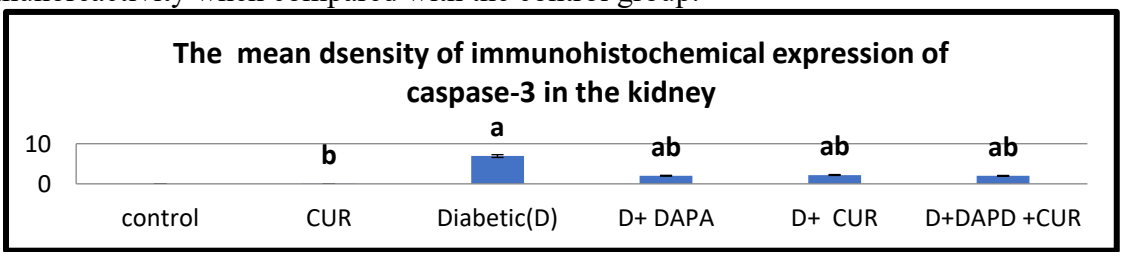


Fig. 8: Effects of oral administration of dapagliflozin and/or curcumin on the optical density of immunohistochemical expression of caspase-3 in the kidney cortex of the different experimental rats. Data represent means ± SE (n=6). (a) are statistically different as compared to the control, (b) are statistically different as compared to the diabetic group at $p < 0.01$. D: diabetic, DAPA: dapagliflozin, CUR: curcumin.

Histopathological Analysis of the Pancreas:

Figure (9 A&B) showed normal structure of the pancreas of the control group with normality in both exocrine and endocrine counterparts. Examined serial sections from the pancreas of curcumin treated rats revealed normal exocrine and endocrine structures, with a characteristic feature of the pancreatic acini with the active secretory profile. The endocrine islets assumed a proportional increase in the functional beta cells at the expense of alpha ones (Figs. 10 A&B). Contrary to the above-mentioned changes, serial slices of the diabetic group's pancreatic tissue showed distinctive alterations that were represented by highly atrophied islets of Langerhans with hypo-cellularity in their different cells. Abnormal septa (thick) and hemolyzed blood in highly dilated arteries were also seen. Oedematose area around the pancreatic acini with degenerative changes of some pancreatic acini were recorded (Figs. 11 A&B). Highly congested vein with ruptured wall, fibrosis, hydropic degenerations, and cellular infiltration of inflammatory cells, especially around the blood vessels, were also observed (Fig. 11 C). Pancreatic tissue of diabetic rats treated with dapagliflozin revealed a comparative increase in the sizes of the islets of Langerhans with a characteristic increase in the cellular population of both α and β-cells. The exocrine pancreas also showed a minor change in the form of cystically dilated interlobular pancreatic ducts (Figs. 12 A &B). Pancreatic sections of diabetic rats, followed by oral treatment with curcumin were mild and promising, where the islets of Langerhans were comparatively larger with activated β- cells and capillary network. A few β-cells suffered degenerative changes, mainly cloudy swelling and hydropic degeneration or apoptosis. Additionally, the exocrine pancreas was almost normal (Figs. 13 A &B). Pancreatic tissue of diabetic rats treated with a combination of curcumin and dapagliflozin revealed a comparative increase in size of the islets of Langerhans with a characteristic increase in the cellular population of both α and β-cells. The exocrine pancreas also showed nearly normal architecture (Figs. 14A & B).

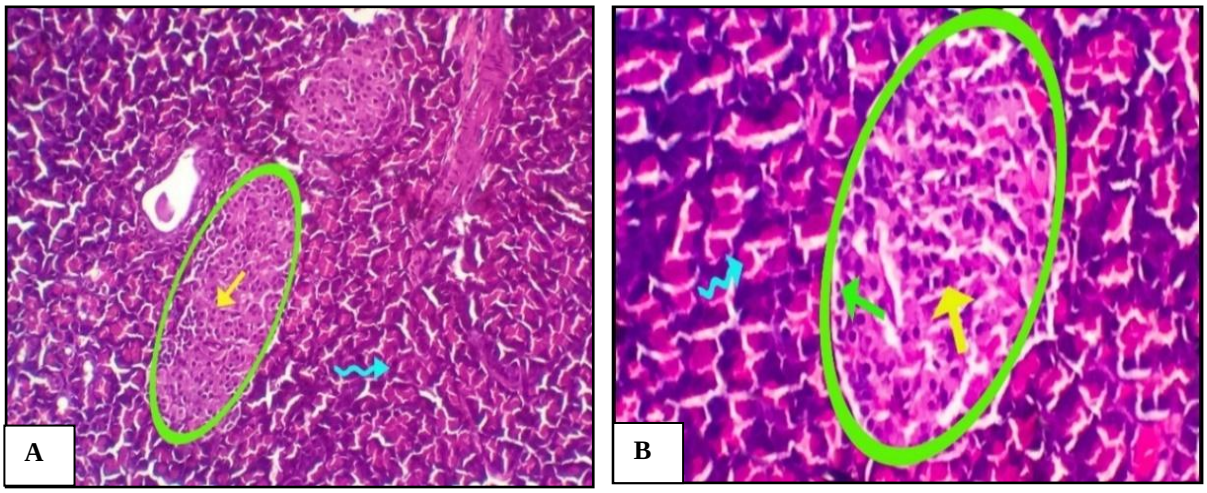


Fig. 9: Photomicrographs of the pancreatic tissue of the control group showing: **A&B:** normality in both exocrine and endocrine counterparts. Notice: the pancreatic acini (**light blue corrugated arrows**), pancreatic islets (**green circle),** and the beta cells (**yellow arrows)** beside alpha cells (**green arrows**). **(H&E, AX 200; BX 400).**

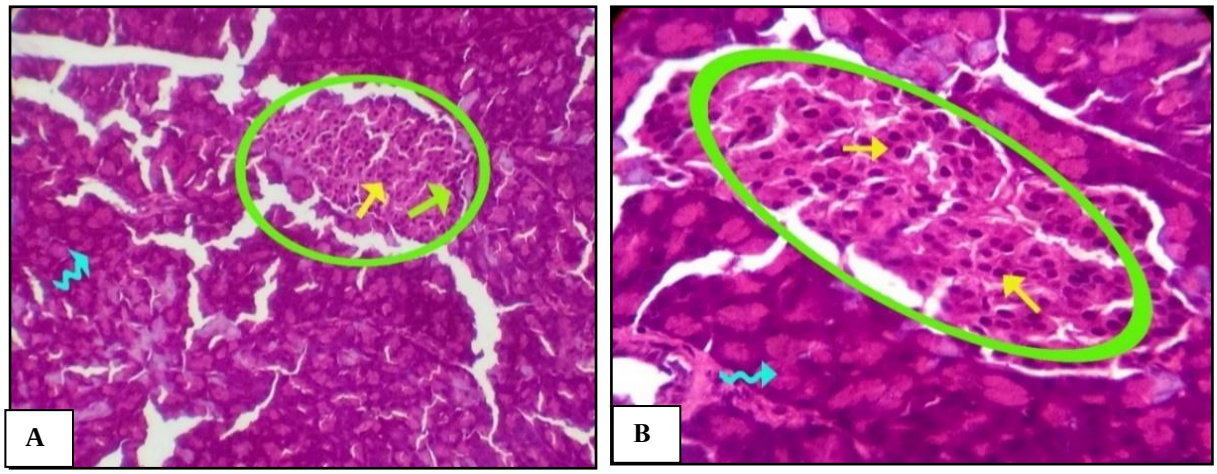


Fig.10: Photomicrographs from pancreatic tissue of rats treated with curcumin showing: **A& B-** normality in both exocrine and endocrine counterparts. Note: the pancreatic acini (**light blue corrugated arrows**), pancreatic islets **(green circle),** and the beta cells (**yellow arrows)** beside alpha cells **(green arrows) A&B-(H&E X 400**).

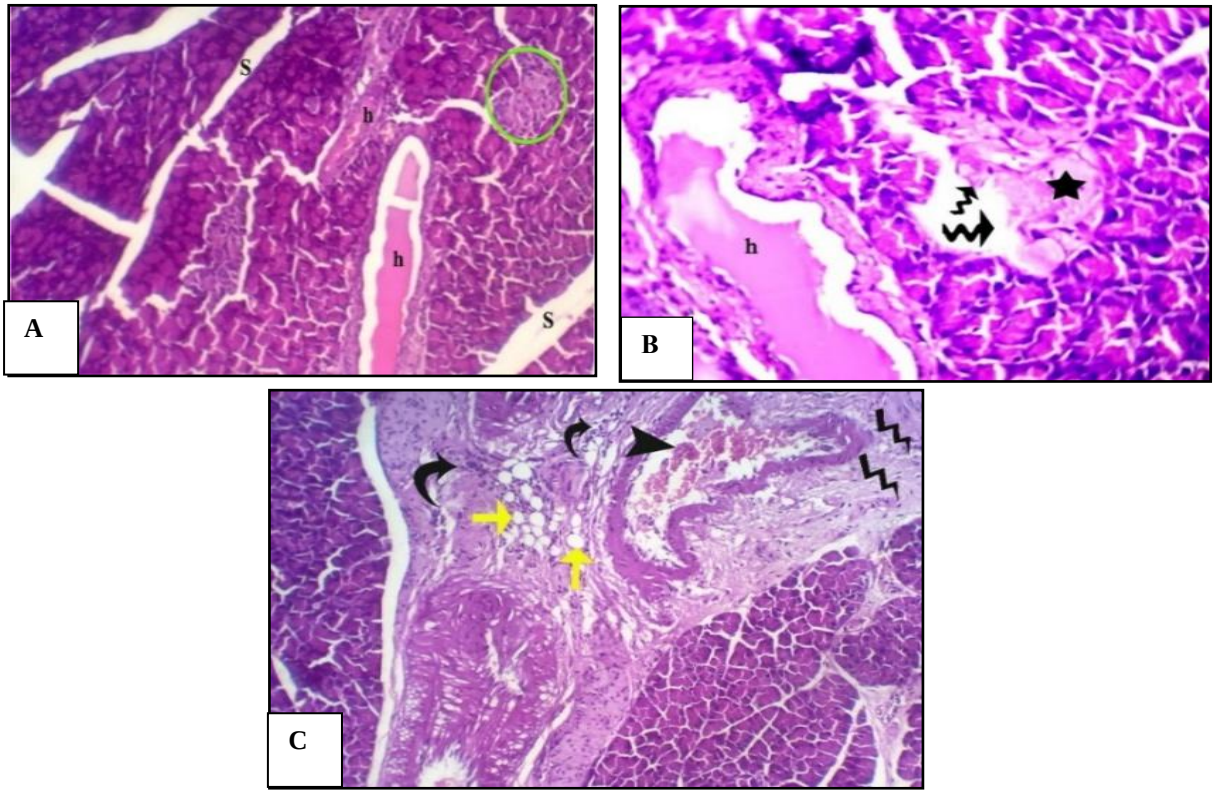


Fig. 11: Photomicrographs from pancreatic tissue of HFD/STZ-induced rats showing: **A&B** showing highly atrophied islets of Langerhans (**green circle)** with hypo-cellularity in their different cells. Abnormal septa (thick) **(S)** and hemolyzed blood(**h)** in highly dilated arteries. Oedematous area around the pancreatic acini **(star**) with degenerative changes of some pancreatic acini (**corrugated arrow). A-(H&E X 200)**, **B- (H&E X 400**), **C-** showing highly congested vein **(arrow head**) with the ruptured wall, fibrosis **(corrugated line)**, hydropic degenerations **(yellow arrows),** and cellular infiltration of inflammatory cells especially around the blood vessels **(curved arrow)**. **C-(H&E X 200).**

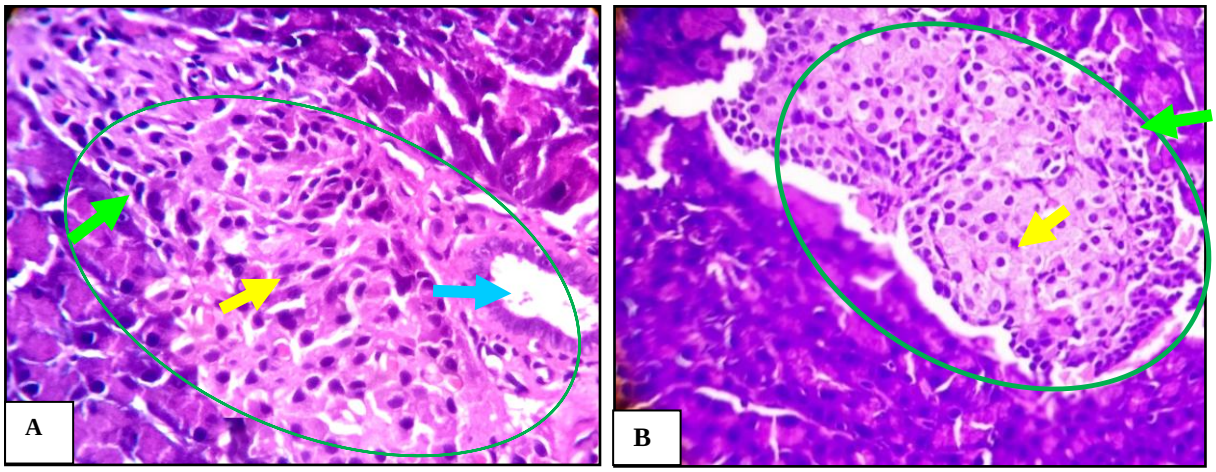


Fig. 12: Photomicrographs from diabetic rats treated with dapagliflozin showing: **A& B-** comparative increase in sizes of the islets of Langerhans with a characteristic increase in cellular population of both α **(green arrow)** and β-cells **(green circles, yellow arrow)**. The exocrine pancreas also showed a minor change in the form of cystically dilated interlobular pancreatic ducts **(light blue arrow)**. **A&B -(H&E X 400**).

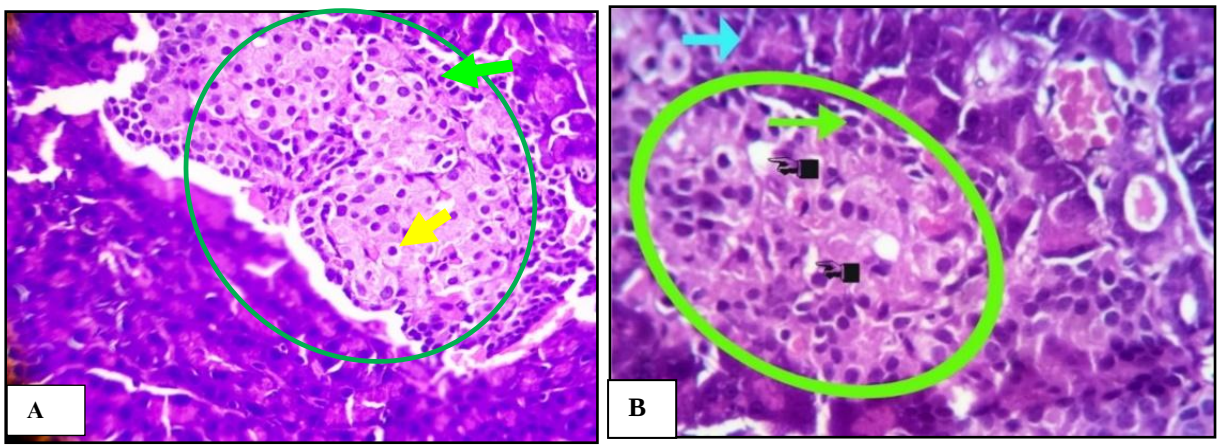


Fig. 13: Photomicrographs **from diabetic rats treated with curcumin showing: A-**islets of Langerhans, which are comparatively larger (**green circle)** with activated β- cells (**yellow arrow)**, **α**-cells are apparently normal (**green arrows**). **B-** A few β -cells suffer degenerative changes (**green circles, hand**), mainly cloudy swelling and hydropic degeneration. The exocrine pancreas is almost normal (**light blue arrow). A&B -(H&E X 400**).

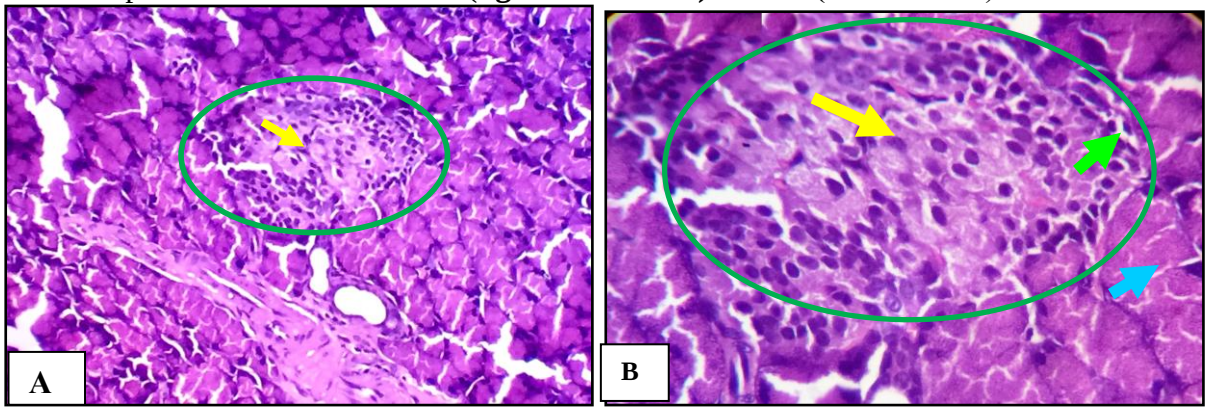


Fig. 14: Photomicrographs from diabetic rats treated with dapagliflozin and curcumin showing: **A&B-** improved architecture of islets of Langerhans (green circles) and the pancreatic acini as compared to the diabetic group, with a characteristic increase in the cellular population of both α and β- cells (**green and yellow arrows respectively**). The exocrine pancreas is also nearly normal (**light blue arrow**). **A-(H&E X 200)**, **B-(H&E X 400**).

Immunohistochemical Studies:

Immunohistochemically stained pancreatic tissue sections from control group pointed out weak caspase-3 immunoreactivity in the islet (β-cells) (Fig. 15A). Meanwhile, the other non-diabetic curcumin group showed weak expression of caspase-3 in the immuno-positive area (Figs. 15 B). Pancreatic tissue sections of diabetic rats demonstrated an apparent increase in the caspase-3 expression in beta and acinar cells in comparison to non-diabetic ones (Fig. 15 C). Diabetic curcumin treated group or diabetic treatment by curcumin and dapagliflozin promoted a patent decrease in caspase-3 expression within the pancreatic tissue of HFD-STZ rats (Figs. 15 E &F). However, the diabetic dapagliflozin treated group showed mild expression of caspase-3 in the pancreas sections of HFD-STZ rats (Figs. 15 D).

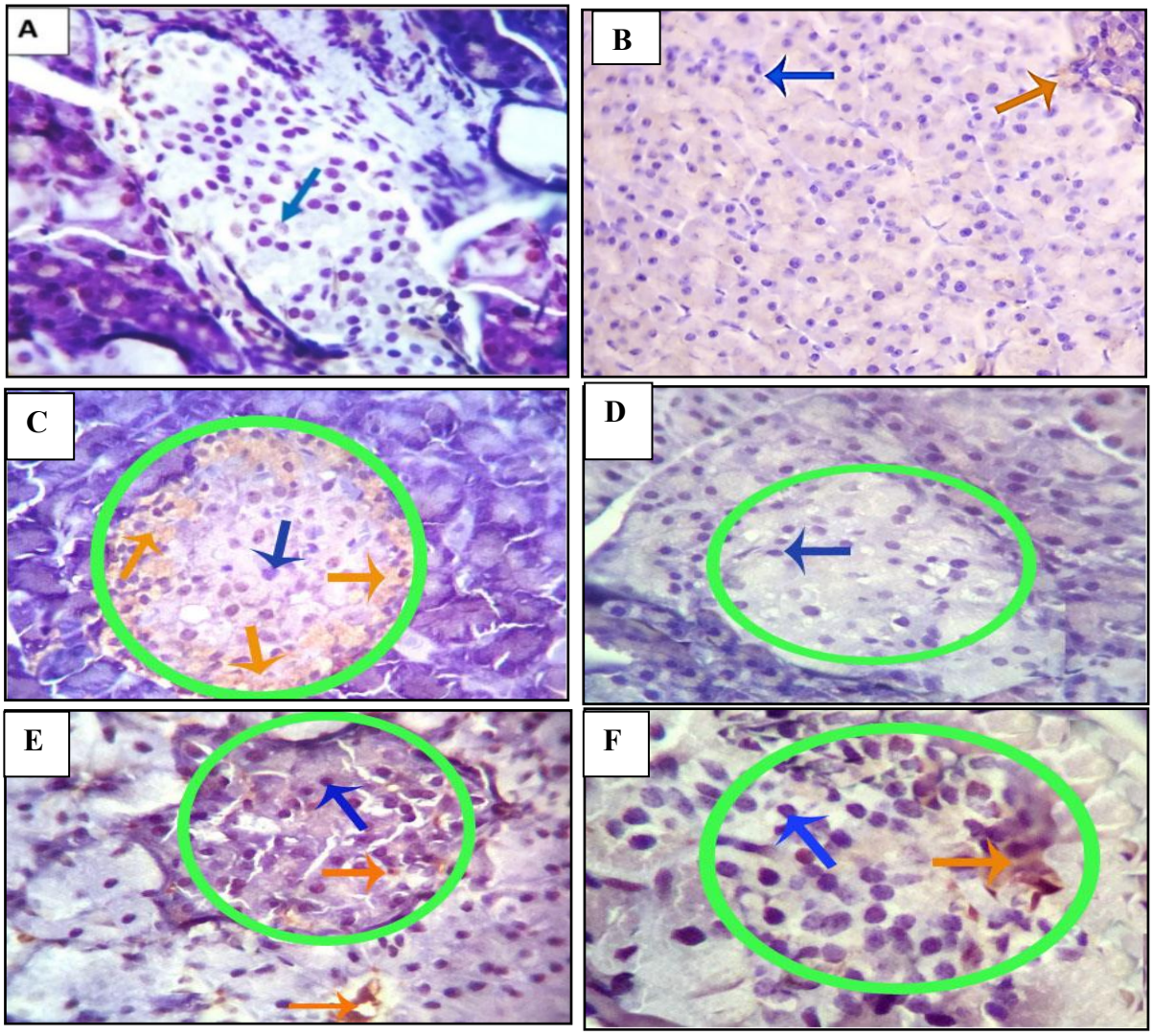


Fig. 15: Photomicrographs from the pancreas of different experimental groups immunohistochemically stainedby **caspase 3** antibody**,** showing brownish cytoplasmic expression of variable intensities. Positive cells are pointed by **orange arrows** and negative cells by **blue arrows**. **A**: control, **B**: CUR, **C**: Diabetic(D), **D**:D+ DAPA, **E**: D+ CUR, **F**: D+ DAPA+ CUR. **(Caspase-3 antibody X 400)**

Quantitative Immune-Histochemical Measurement:

The results illustrated in Figure (16), showed the changes in the optical density of immunohistochemical expression of caspase-3 in the pancreas after treatment of the experimental rats with DAPA and/or curcumin in comparison with the normal group. The non-

diabetic group which was treated with (CUR) recorded a non-significant change in the morphometric analysis of the immunoreactive area for caspase-3 when compared with the control group. However, the diabetic group recorded a significant increase when compared to the control group. In the D+DAPA, D+CUR and D+DAPA+CUR groups, this elevation was inverted. These groups showed significant decreases in the immunoreactive area for caspase-3 when compared with the control group.

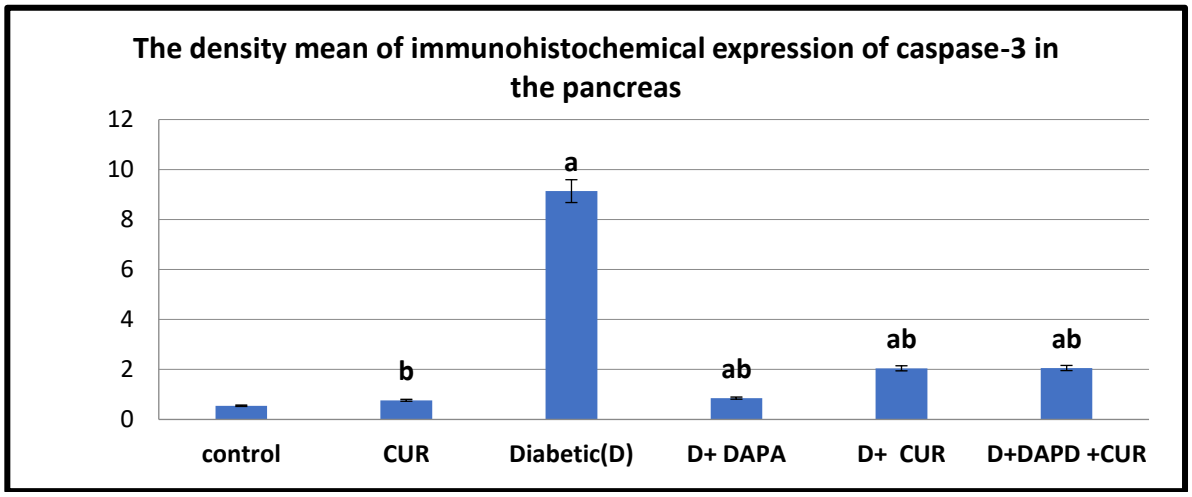


Fig. 16: Effects of oral administration of dapagliflozin and/or curcumin on the optical density of immunohistochemical expression of caspase-3 in the pancreas of the different experimental rats. Data represent means ± SE (n=6). (a) are statistically different as compared to the control, (b) are statistically different as compared to the diabetic group at $p < 0.01$. D: diabetic, DAPA: dapagliflozin, CUR: curcumin.

DISCUSSION

Diabetes is considered a chronic metabolic disorder marked by hyperglycemia, often due to insulin deficiency, leading to glycosuria (Rahman and Islam, 2024). One of the most common and polygenic diseases is type 2 diabetes (Pearson, 2019). It is characterized by pancreatic β-cell dysfunction, or the inability of β-cells to release enough insulin, and an inhibition in insulin action, which is also referred to as insulin resistance (Srinivasan *et al.*, 2005). In the previous research published from this study, it was proved that our rats suffered from T2DM (El-Deeb *et al.*, 2025). However, there are several new treatments for type 2 diabetes. SGLT2 inhibitors, a unique family of antidiabetic drugs that prevent the kidneys from reabsorbing glucose, are emerging as a promising therapeutic option for treating diabetes (Chao and Henry, 2010; Jung *et al.*, 2014). Dapagliflozin (DAPA) became the first SGLT2 inhibitor approved for treating T2DM in 2014 (Boran *et al.*, 2023). It is prescribed both alone as a once-daily oral monotherapy (for those intolerants to metformin) (Tsushima *et al.*, 2021) or in combination with other blood sugar-lowering medications like insulin, sulfonylureas and metformin (Nicholson *et al.*, 2021). In addition to its glucose-lowering effects, DAPA has demonstrated cardiovascular and renal benefits as it slows the progression of chronic kidney disease (CKD) and reduces the risk of renal outcomes, including end-stage kidney disease, in patients with and without diabetes (Heerspink *et al.*, 2020). Nevertheless, the SGLT2 has positive effects, adverse effects such as increased urination, dehydration, and the potential for euglycemic diabetic ketoacidosis. Therefore, their clinical use necessitates carefully weighing the treatment's benefits and risks (Lupsa and Inzucchi, 2018; Zheng and Sun, 2025). Therefore, it is suggested that natural substances that can tackle these adverse effects, such as medicinal plants, which have become the most crucial part of all accessible

treatments due to their affordability and accessibility (Mofokeng *et al.*, 2022). The rhizomes of *Curcuma longa*, or turmeric, are the source of curcumin, a naturally occurring polyphenolic chemical. Its many pharmacological qualities, including anti-inflammatory, antioxidant, anticancer, antibacterial, and antidiabetic actions, have been well investigated (Aggarwal *et al.*, 2007, and Prasad & Aggarwal, 2011). Curcumin's structure has several chemically active keto/enol groups that give the molecule antioxidant properties (Asadi *et al.*, 2019).

The current study created the T2DM model in rats by using a high-fat diet (HFD) to induce insulin resistance and a low dose of streptozotocin (STZ) to induce moderate β-cell dysfunction (Furman, 2021) that reflects metabolic characteristics and natural progression of type 2 diabetes as in humans (Watts *et al.*, 2005; Shatwan *et al.*, 2013). This study aimed to evaluate the therapeutic potential of DAPA and/or CUR on the kidney and pancreas diabetic complications.

Effect of DAPA and/or Curcumin on the Serum Parameters:

Kidneys are essential for maintaining the body's homeostasis by regulating the chemical balance of bodily fluids through processes like urine acidification, which helps control blood pH, and by managing serum osmolality and electrolyte levels to ensure proper fluid and electrolyte balance (Guyton and Hall, 2020). The excretion of waste materials and toxic substances, including ions, urea, creatinine, and uric acid (UA), is facilitated by the kidneys (Ezekiel *et al*., 2019). Creatinine is the most widely used renal dysfunction indicator as highlighted by Mehrdad *et al.* (2011) that evaluates glomerular function (Loeb, 1991, and Ani *et al*., 2020). Meanwhile, the final metabolic byproduct of purine molecules is UA, which has been highlighted for developing of various metabolic disorders, including T2DM (Yang *et al.*, 2012). Serum creatinine and UA levels were significantly higher in the HFD/STZ-induced diabetic rats in the current investigation than in the control group. This aligns with Stanfield's (2011) research, which linked elevated serum creatinine in type-2 diabetes to diabetic nephropathy. Additionally, Jaramillo-Juarez *et al.* (2008), supported that hyperglycemia leads to renal dysfunction, including conditions like glomerulonephritis and tubular necrosis, which impairs urea and creatinine excretion, raising serum creatinine levels.

In the present study, DAPA supplementation in animals significantly reduced serum creatinine and UA levels compared to the diabetic rats, which aligns with the findings of Yang *et al*. (2022). The DAPA protective effect on creatinine is attributed to DAPA's action as an SGLT2 inhibitor, which lowers intraglomerular pressure by reducing sodium reabsorption in the proximal tubule, improving renal hemodynamics, and preserving glomerular filtration rate (GFR) (Cherney *et al.*, 2014). Additionally, DAPA lowers UA levels by increasing its urinary excretion, facilitated by its osmotic diuretic effect, which reduces UA reabsorption in the proximal tubule (Chino *et al.*, 2014; Iwata *et al.*, 2023; Patel and Strong, 2019). In the current study, curcumin demonstrates significant potential in protecting kidney function and mitigating diabetes-related complications as it significantly reduced serum creatinine and UA levels in the D+ CUR group compared to the diabetic group. This agreement with Ghasemi *et al.* (2019) findings, who noted that diabetes leads to elevated UA and creatinine levels due to impaired carbohydrate metabolism and increased protein breakdown. Diabetic nephropathy further exacerbates this by reducing kidney excretion of these substances. Curcumin alleviated diabetes and diabetic nephropathy symptoms, increasing urinary creatinine and decreasing serum levels. Curcumin derivatives are suggested to protect kidney function in diabetic rats by improving renal function markers like creatinine and UA (Wu *et al.*, 2014; El-Hadary and Sitohy, 2021). Curcumin's strong antioxidant activity reduces oxidative stress, a key factor in diabetes progression and complications. By scavenging free radicals and boosting endogenous antioxidant enzymes, curcumin protects renal tissues (Mahesh *et al.*, 2004; Trujillo *et al.*, 2013). It also directly protects renal tissues by modulating apoptosis and fibrosis pathways, inhibiting transforming growth factor-beta (TGF-β) and other fibrotic pathways that cause structural kidney damage in diabetes (Soetikno *et al.*, 2013). Additionally, curcumin inhibits

xanthine oxidase, an enzyme involved in UA production, thereby lowering UA levels, which is beneficial in diabetic hyperuricemia (Paultre *et al.*, 2021). Notably, diabetic rats treated with both DAPA and CUR showed normalized creatinine levels compared to the control group. However, UA levels in this group decreased relative to the diabetic group, they remained higher than those in the control group.

Effect of DAPA and/or Curcumin on the Urine Parameters:

This study observed significant hyper hyperglycosuria, albuminuria and the urinary albumin/creatinine ratio (UACR), alongside a significant decrease in urinary creatinine compared to the control rats. These results align with Mogensen (1984), who noted that diabetic nephropathy impaired the (GFR), affecting creatinine excretion. Over time, reduced kidney function in T2DM patients may lead to decreased urinary creatinine levels. Additionally, diabetes is strongly linked to increased urinary albumin excretion, known as microalbuminuria or macroalbuminuria, depending on severity. This results from damage to the glomerular filtration barrier, causing albumin to leak into the urine, with microalbuminuria serving as an early marker of diabetic nephropathy (Stehouwer and Smulders, 2006). DeFronzo *et al.* (2015) explained that hyperglycemia often exceeds the renal threshold for glucose reabsorption, leading to glucosuria (glucose in the urine) as the kidneys cannot reabsorb all the filtered glucose due to high blood glucose levels.

In the present study, compared to the diabetic rats, the diabetic group treated with DAPA showed an important reduction in urine albumin and urinary UACR levels and a significant increase in urinary creatinine and glucose levels. These results are consistent with those of Tang *et al.* (2017), who confirmed that the administration of DAPA enhanced glucosuria and lowered blood glucose by blocking SGLT2. Meanwhile, Vallon *et al.* (2011) reported the DAPA role in enhancing renal function in diabetic rats by lowering serum creatinine levels and improving estimated glomerular filtration rate, that linked to its ability to reduce intraglomerular pressure and hyperfiltration. Furthermore, Cherney *et al.* (2014) confirmed the role of DAPA in decreasing kidney workload, leading to better renal hemodynamics and reduced creatinine levels by promoting sodium excretion (natriuresis) and osmotic diuresis. In the same context, DAPA reduces urinary albumin excretion by improving glomerular hyperfiltration and reducing renal oxidative stress and inflammation, that mediated by DAPA's ability to lower blood pressure and blood glucose, as well as its direct renal protective effects by restoring the integrity of the glomerular filtration barrier and reducing podocyte injury (Kojima *et al.,* 2013; Gembardt *et al.,* 2014; and Gallo *et al.,* 2015).

In the current study, curcumin treatment in diabetic rats significantly reduced glucosuria and albuminuria levels while increasing urinary creatinine levels compared to untreated diabetic rats. These findings agreement with Ghasemi *et al*. (2019), who observed that curcumin therapy increased creatinine excretion in diabetic rats. Curcumin alleviated diabetes and diabetic nephropathy symptoms, improving kidney function and raising urine creatinine levels. Additionally, CUR reduced urinary glucose levels by enhancing insulin sensitivity and glucose uptake in peripheral tissues. It also inhibited hyperglycemia by regulating key glucose metabolism enzymes (e.g., hexokinase, glucose-6-phosphatase) and promoting the expression of glucose transporters like GLUT4 (El-Moselhy *et al.,* 2011; Zhang *et al.,* 2013). However, curcumin reduced albuminuria by activating transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2) signaling to alleviate pathophysiologic alterations and oxidative stress on the glomerulus. As the Nrf2 can play an important role in inhibiting oxidative stress and lipid accumulation in T2DM and HFD (Tanaka *et al.,* 2008; Nakai *et al.,* 2014).

DAPA and CUR diabetic-treated groups revealed a significant renoprotective impact, and the combined treated group showed a greater response. DAPA reduces blood glucose levels by promoting urinary glucose excretion. This mechanism also alleviates glomerular hyperfiltration, a key contributor to diabetic nephropathy. By lowering intraglomerular

pressure, dapagliflozin reduces renal stress and protects kidney tissue (Zinman *et al.,* 2015). CUR has been found to improve renal function markers such as serum creatinine and albuminuria in diabetic rats. A study by Ghosh *et al.* (2014) demonstrated that curcumin treatment significantly lowered these markers, indicating improved kidney function (Sharma *et al.,* 2025).

Effect of DAPA and/or Curcumin on the Tissue Parameters:

1-The Oxidant and Antioxidant Parameters in The Pancreatic and Renal Tissues:

Oxidative stress plays a vital role in the pathophysiology of DM and its associated complications. Disruption of the normal equilibrium of free radicals has been linked to the impairment of pancreatic β-cell function (Francescato *et al.,* 2014). Moreover, free radical production is brought on by the oxidation of glucose and the non-enzymatic glycation of proteins, which damages macromolecules, cellular components, and antioxidant enzymes (Asmat *et al.,* 2016). Numerous research investigations have demonstrated that elevated blood sugar levels result in increased development of reactive oxygen species (ROS), which have a role in the development of various diabetic complications, such as diabetic nephropathy (King and Loeken 2004; Cheng *et al.,* 2013). GSH is essential for maintaining the antioxidant status of plasma and for scavenging free radicals. Superoxide is changed by superoxide dismutase into hydrogen peroxide, a less reactive ROS, which catalase then further reduces to water. Therefore, catalase aids SOD in totally neutralizing ROS (Mestry *et al,* 2017). MDA is a byproduct of late-stage lipid oxidation and a crucial marker of lipid peroxidation caused by free radicals (Cheng *et al.,* 2013).

In the present study, there are harmful changes in the antioxidant status of the untreated diabetic group in renal and pancreas tissues that have been established by increasing lipid peroxidation end product like MDA and reduction of SOD activity and GSH content compared to the tissues of the control group. These results are in agreement with Mestry *et al.* (2017) that reported significant increase of MDA levels in proximal tubule cells, mesangial cells, renal cortex, and plasma, meanwhile, the levels of GSH content and SOD activity were reduced in the diabetic-bearing animals. However, Abuja and Albertini (2001) attributed the increase in MDA contents in diabetic animals, to streptozotocin-promoted pancreatic lipid peroxidation. On the parallel side, the reduction of SOD activity and GSH concentration due to the production of oxygen free radicals is compelling evidence of the oxidative stress carried on by diabetes, according to Cheng *et al.* (2013). Meanwhile, Zhang *et al. (*2021) attributed the increased ROS production and decreased antioxidant GSH and SOD levels to morphological defects and loss of mitochondrial activity due to hyperglycemia. This imbalance between oxidative products and antioxidants leads to the development of oxidative stress and the advancement of renal fibrosis (Braga *et al.,* 2022). According to the study results of diabetic rats, the diabetes treatment options, namely 1mg/kg DAPA, successfully restored antioxidant enzyme activities in the kidney and pancreas and decreased the oxidative stress marker (MDA) in both organs. In the present study, administration of DAPA improved the antioxidant status and reduced the elevation of lipid peroxidation as compared to the diabetic group. In accordance with Zeng *et al.* (2023), who showed that DAPA reduced the amount of MDA, enhanced SOD activity, and increased the content of GSH in diabetic mice. Dapagliflozin's ability to improve glycemic control and reduce hyperglycemia-induced oxidative stress is linked to its SGLT2 inhibition, which promotes urinary glucose excretion and reduces glucose toxicity in tissues. This mechanism indirectly supports the restoration of antioxidant enzyme activities (Zinman *et al.,* 2015)

The present study showed that administration of curcumin improved the antioxidant system and reduced the elevation of lipid peroxidation as compared with the diabetic group. SOD activity and GSH content were raised in diabetic animals after curcumin administration. On the parallel side, the level of MDA in the D + CUR group decreased as compared to the diabetic group. These findings were in line with those of Sharma *et al.* (2006), who

demonstrated that curcumin (15 and 30 mg/kg per day) significantly reduced the enhanced lipid peroxidation and raised GSH in renal tissue in diabetic rats. Importantly, curcumin can increase overall antioxidant activity and regenerate pancreatic islets by improving islet viability and preventing the generation of ROS (Meghana *et al.,* 2007; Potphode *et al.,* 2018). Also, curcumin can increase SOD activity and GSH level as compared to the diabetic group. This is because curcumin has an antioxidant and free radical scavenger ability that could be attributed to either the methylene group or the phenolic hydroxyl group of the β-diketone (heptadiene-dione) moiety (Gupta *et al.,* 2012; Al-Saud, 2020). However, the curcumin's potential to significantly reduce MDA may be attributed to the decreased hydrogen peroxide (H_2O_2) production, which causes lipid peroxidation (Borra *et al.,* 2014; Mehta *et al.,* 2018).

The combination of both treatments in group D+ DAPA+ CUR revealed a greater efficacy than DAPA or CUR single treatment alone as it significantly restored the SOD activity, GSH and MDA contents in the renal tissues compared with the normal group. However, in the pancreatic tissues no significant change in MDA level and significant decrease in the SOD and GSH levels have reported compared to the normal animals. This effect for the combined treatment may be attributed to the mechanism of action for each treatment. DAPA has been demonstrated to reduce oxidative stress by inhibiting the production of ROS. This is achieved through its ability to improve mitochondrial function and reduce hyperglycemia-induced oxidative damage (Ding *et al.,* 2025). Consistent with these results, elevated urinary creatinine levels in the diabetic rats could be associated with renal dysfunction due to hyperglycemia-induced oxidative stress and inflammation. CUR exerts a nephroprotective effect by reducing oxidative stress through the upregulation of antioxidant enzymes such as SOD and glutathione peroxidase. It also inhibits the formation of advanced glycation end products and suppresses inflammatory pathways, such as nuclear factor-kappa B (NF-κB) and Tumor necrosis factor-α (TNF-α), thereby preserving renal function and normalizing creatinine levels (Tapia *et al*., 2014.

2-The Inflammatory Markers in The Pancreatic and Renal Tissues:

An important component of renal failure was oxidative stress and inflammation (Meng *et al.,* 2014; Rayego- Mateos and Valdivielso, 2020). Macrophages and T lymphocytes release TNF-α, a potent inflammatory cytokine that is essential to diabetes mellitus because it promotes the growth of insulin resistance and microvascular issues (Dokumacioglu *et al.,* 2018). The development of diabetic blood vessel disease and other cardiovascular problems of diabetes mellitus is believed to be mostly dependent on interleukin (IL-1β), whose release from fatty acids might impact distant organs such as the heart or vessels due to increased vascular and systemic inflammation (Peiró *et al.,* 2017). DM is thought to be a low-grade chronic inflammatory disease marked by excessive pro-inflammatory cytokine release (Peiró *et al.,* 2017). One of the main characteristics of type 2 diabetes is insulin resistance, which is strongly linked to elevated TNF-α and IL-1β levels. It is well established that TNF-α, in particular, disrupts insulin signaling pathways by encouraging serine phosphorylation of insulin receptor substrate-1 (IRS-1), which reduces the effectiveness of insulin (Chen *et al.,* 2015).

Results in this study have demonstrated significant increases in the level of TNF-α and IL-1β in the diabetic group compared with the control group. In renal fibrosis, mitochondrial failure may trigger inflammation, leading to increased concentration of pro-inflammatory cytokines such as TNF-α and IL-1β (Chung *et al.,* 2019). However, Boran *et al.* (2023) reported that inflammation is one of the potential processes that lead to kidney damage, and TNF-α is thought to be a significant inflammatory mediator in the onset and course of diabetic nephropathy and kidney damage (Chow *et al.,* 2006; Akcay *et al.,* 2009). In both renal and pancreatic tissues, the treatment of diabetic animals with dapagliflozin showed a significant improvement in the level of TNF-α and IL-1β in comparison with the untreated group. This is consistent with Kıngır *et al.* (2019), who revealed a statistically significant increase in TNF-α and IL-1β levels in the diabetic animals as compared to the normal group. The elevated levels

of TNF-α and IL-1β cytokines in the diabetic animals were suppressed by DAPA treatment due to its ability to reduce inflammatory responses through blocking NF-κB activation, a critical route in the control of inflammation-related gene transcription (Yang *et al.,* 2012 and Coelho *et al.*, 2021)**.**

The present study results showed that curcumin administration improved inflammatory markers compared to the diabetic rats. These findings are in agreement with Boarescu *et al.* (2019), where curcumin inhibited the elevation of TNF-α and IL-1β cytokines because it can lower inflammatory responses by interfering with NF-κB activation, a crucial pathway in the regulation of transcription of genes related to inflammation. CUR modulates various signalling pathways involved in inflammation, such as the mitogen-activated protein kinase (MAPK) pathway, which reduces the synthesis and release of TNF-α and IL-1β in diabetic animals (Shamsnia *et al.*, 2023). In addition, the combination D+ DAPA+ CUR group recorded a significant decrease in the level of TNF-α and IL-1β in the renal and pancreatic tissues compared to the untreated group. Meanwhile, in renal tissue in the same group, there was no significant change in the level of IL-1β when compared with that of the normal group. However, this group showed a greater efficacy than dapagliflozin or curcumin treatment alone for attenuating inflammatory markers that decrease the side effects of diabetes mellitus. It has been demonstrated that SGLT2 inhibitors have anti-inflammatory effects in numerous experimental illness types (Scisciola *et al.,* 2022).

The Histological and Immunohistochemical Studies in the Renal and Pancreatic:

1-The Renal Tissues:

In the current study, the kidney cortex of diabetic rats showed marked degenerative changes. These changes included: vascular dilation, perivascular edema, ill-defined inflammatory reaction, cloudy swelling, vacuolar, and hydropic degeneration, in addition to some distal convoluted tubules' moderate dilatation and partial atrophy of their lining epithelium. Shrinkage and atrophy of some glomeruli were seen. A few apoptotic cells were observed in the tubular epithelium. Habib (2013) demonstrated that elevated glucose was a major contributor to diabetic nephropathy, which was typified by early hypertrophy, a progressive loss of renal mass, sclerosis and fibrosis, and ROS-induced cell death. Apoptosis plays a role in the latter process in both humans and animals.

The present findings are corroborated by El-Nabawia *et al.* (2017), who showed that Bowman's space was either widened or destroyed in the diabetic animals. This indicates a sequential progression of the disease from an early to a late stage, with the glomerular capillary tuft diminishing, potentially contributing to the widening of the capsular space. They also mentioned that necrosis and apoptosis, two types of cell death, were seen in the group generated by chronic renal failure. The increased ROS generation leads to oxidative stress, triggering various cellular alterations. Saleh *et al.* (2020) reported that the reduction in renal function was linked to changes in the renal histological structure in the diabetic group, including glomerulosclerosis, hyalinosis, and interstitial fibrosis. In the kidneys of diabetic rats, Jain and Saha (2017) noticed thickening of the capillary basement membrane, which they attributed to elevated oxidative stress, activation of the renin-angiotensin system, and production of growth factors and inflammatory cytokines. By creating mechanical stress, glomerular hyperfiltration results in the supply and reabsorption of small and large molecular weight solutes more often, which causes hypertrophy, tubulointerstitial inflammation, and fibrosis (Chagnac *et al.,* 2019). According to Nassar *et al.* (2019), the experimental animals that received an intraperitoneal single dose of STZ (60 mg/kg body weight) developed many lesions, including necrotic proximal convoluted tubules, severely damaged distal convoluted tubules in the macula dens, damaged, and sclerotic. In addition to there were lobulated glomeruli with narrowing of the urinary space, and multiple necrotic foci in the renal tissue that could be linked to the oxidative stress caused by hyperglycemia.

In the current investigation, the proximal and distal convoluted tubules of the

curcumin group, as well as glomeruli, Bowman's capsules, and Bowman's space, all showed normal histological appearance. This finding agrees with those of El-Mahalaway (2015), who demonstrated that no histological alterations were found in the curcumin group when compared to the control group. As an active ingredient in turmeric, curcumin effectively reduces the toxicity experienced by mice's kidneys by scavenging free radicals and preventing their production, protecting cells from oxidative stress, and increasing renal blood flow. Additionally, curcumin increases the activity of detoxifying enzymes such glutathione peroxidase (GSH-Px), reduced GSH, catalase and superoxide dismutase (SOD) (Abd El-Rahman and Al-Jameel, 2014).

In the present study D+DAPA group, dapagliflozin markedly corrected and nearly normalized the renal histological structure. The current results go in parallel with the results of Tuttle (2017), who showed that dapagliflozin has glycemic control, antioxidant, anti-inflammatory, and reno-protective properties in addition to possible direct benefits through regulation of glomerular hemodynamics. The histological findings also reported that DAPA improved diabetes-induced morphological damage (Boran *et al.,* 2023). In the renal structure of the CKD group, H&E staining demonstrated glomerular hypertrophy, enlargement of the mesangial region, thickening of the glomerular basement membrane, and infiltration of inflammatory cells in the interstitium. The previously mentioned lesions were considerably lessened following dapagliflozin treatment (Yang *et al.,* 2022). In addition to helping to update T2DM management guidelines, the numerous clinical trials utilizing SGLT2 inhibitors (iSGLT2) medications have provided significant information that suggests they may be able to provide nephroprotection (Oliveira, 2020). According to Xue *et al.* (2023), STZ can cause collagen deposition in the renal interstitium, thickening of the tubular basement membrane, and a notable thickening of the glomerular basement membrane in the renal tissue of T2DM rats. Thus, STZ has the ability to cause renal fibrosis in rats. The pathological alterations were lessened with DAPA medication; taken as a whole, dapagliflozin can successfully reduce renal tissue fibrosis in T2DM rats. Additionally, the molecular mechanism by which DAPA ameliorated renal fibrosis in rats with type 2 diabetes was investigated.

Curcumin improved kidney histological alterations in the D+ CUR group in this investigation. In addition to dilatations in certain distal convoluted tubules, a few sections showed sporadic glomerular lobulation, minor renal blood vessel congestion, and degenerative alterations (cloudy swelling and hydropic degeneration). These findings agreed with Asadi *et al.* (2019), who observed that curcumin reduced the morphological changes linked with diabetes in rats. The beneficial anti-diabetic activity of curcumin is probably due to its strong capacity to suppress oxidative stress (Fazel-Nabavi *et al.,* 2015). The kidney tissues of STZ-induced diabetic rats showed several abnormalities upon histological examination, including fibrosis, congestion, and the infiltration of inflammatory cells. Curcumin therapy has a preventive effect against kidney injury since it dramatically decreases these tissue alterations. According to earlier research, natural goods' bioactive ingredients preserve the structure of kidney tissue (Alsulaim *et al.,* 2023). In the current study, examination of the kidney cortex of diabetic rats treated with dapagliflozin+ Curcumin showed a lowering incidence of renal pathological changes induced by HFD/STZ, a remarkable restoration of normal cell structure, the cells restored their regularity, sizes, and normal homogenous cytoplasm with rounded nuclei. Ameliorated levels of creatinine, uric acid, urinary albumin, urinary creatinine, SOD activity, GSH, MDA, TNF-α and IL-1β in the kidney of rats of group supplemented with dapagliflozin+ Curcumin indicated the protective effect of DAPA+ CUR and its ability to scavenge free radicals caused by hyperglycemia.

Furthermore, the immunohistochemical analysis of the kidney tissue revealed that mean density of caspase-3 positivity in the diabetic group was significantly higher than in the control group. Apoptosis is an important mechanism that inhibits prolonged inflammation (Lawrence, 2009). It is recognized to be connected to renal failure that results in the loss of

renal cells (Servais *et al.,* 2008). There was a significant increase in the genetic and protein expression of caspase-3 in the kidneys, which increased in the establishment of apoptosis. This was linked to an increased oxidative status associated with diabetes mellitus and an increased production of TNF in the liver and kidney tissues in the diabetic group (El-Sherbiny *et al.,* 2022). The cysteine-aspartyl-specific proteases known as caspases are essential for apoptosis (Pandurangan and Esa 2014). Mitogen-activated protein kinase activation in the apoptotic pathway triggers the inflammatory response, which leads to nephrotoxicity with cell infiltration and fibroproliferative alterations (Francescato *et al.,* 2007). Li *et al. (*2021) showed that the results indicated that caspase-3 was activated in diabetic nephropathy (DN) mice.

In the present study**,** the immunohistochemical observations of kidney tissue, the mean density of caspase-3 immunoreactivity has no significant change in healthy rats treated with CUR when compared to the control group. According to Aggarwal *et al.* (2024), curcumin is a powerful phytochemical that has anti-aging, anti-inflammatory, anti-cancer, and antioxidant properties. It is believed that curcumin's antioxidant and anti-inflammatory qualities outweigh its other biological effects. Because of its anti-inflammatory qualities, curcumin may help reduce symptoms and be a good option for treating and preventing pro-inflammatory diseases. However, the mean density of caspase-3 of the kidney tissue in the diabetic rats treated with DAPA showed a significant decrease when compared to the diabetic group. In contrast, a significant increase was observed when compared to the control group. This is in agreement with Oliveira *et al.* (2020), who observed that in the diabetic models of nephropathy, various other proteins were successfully downregulated by iSGLT2, diverse members of the caspase family, namely Caspase12, Cleaved caspase-3, and Caspase-7. Lastly, poly-ADP-ribose polymerase (PARP) was also reduced by iSGLT2 in CKD model and an *in vitro* model insulted by hypoxia. The previous evidence suggested that iSGLT2-mediated apoptosis inhibition is achieved by reducing activation of apoptosis pathways, independent of underlying disease. The previously discussed reduction in inflammation and oxidative stress is likely to cause this reduction.

In the current study, the mean density of caspase-3 of the kidney tissue in the diabetic rats treated with CUR (D+ CUR) showed a significant decrease when compared to the diabetic group. This is agreement with Abd El-Rahman and Al-Jameel (2014) who noted that curcumin had a strong antiapoptotic effect because it reduced the expression of pro-inflammatory genes like COX2 and caspase-3 as well as the pro-apoptotic gene. In contrast, it increased the expression of the anti-apoptotic gene Bcl-2 in various organs, including the kidney, testis, and lung. According to Awad and El-Sharif (2011), they demonstrated that curcumin treatment inhibits the apoptotic pathway via significant inhibition of caspase-3 in kidney tissue. Meanwhile, the combined treatment with DAPA and curcumin demonstrated a significantly decreased level of the mean density of caspase-3 positivity as compared to with the diabetic group. These results combined to the ameliorated levels of TNF- and IL-1β in the kidney of rats of dapagliflozin+ curcumin supplemented group indicated the protective effect of DAPA+CUR and its ability to reduce apoptosis caused by hyperglycemia.

2-The Pancreatic Tissues:

In this study, examination of the pancreatic tissue of diabetic rats revealed characteristic changes represented by a decrease in densities of the islet cells, degenerative changes in the β-cells of the islets, mainly cloudy swelling and hydropic degenerations, besides necrotic and apoptotic changes in a moderate number of β-cells. The exocrine pancreas showed minor changes, mainly cystic dilatation, highly atrophied islets of Langerhans with hypo-cellularity in their different cells. Abnormal septa (thick) and hemolyzed blood in a highly dilated artery were also seen. Odematose area around the pancreatic acini with degenerative changes of some pancreatic acini was also recorded. Highly congested veins with ruptured walls, fibrosis, hydropic degenerations, and cellular infiltration of inflammatory cells, especially around the blood vessels, were also recorded. These findings were in accordance

with other research by Zhou *et al*. (2013) and Hussien *et al.* (2017) which found that HFD combined with a low dose of STZ injection resulted in significant depletion of the number and size of islets as well as the number of cells per islet, apoptotic changes, and marked distortion of the islet histology. Matveyenko and Butler (2008) revealed that the diabetic untreated rats disrupted in the general shape of their pancreatic islets, which resulted in a decrease in the number of pancreatic islets of Langerhans and insulin-secreting pancreatic β cells. Soliman *et al.* (2024) reported that the pancreatic sections of the diabetic group showed marked decrease in number and atrophy of islets, congested blood vessels, interstitial hemorrhage, and perivascular inflammatory cellular infiltrate. Additionally, because β-cells express fewer antioxidants such as glutathione peroxidase and catalase, they are thought to be especially susceptible to oxidative stress (Lenzen, 2017).

In the present study, the pancreatic tissue of curcumin-treated rats revealed normal exocrine and endocrine structures, with a characteristic feature of the pancreatic acini with an active secretory profile. The endocrine islets assumed a proportional increase in the functional beta cells at the expense of alpha ones. Medicinal herbs are a great alternative to conventional medications because they have some effectiveness without the adverse side effects. Due to its potent antioxidant properties, curcumin can protect pancreatic islet cells by preventing β-cell apoptosis (Al-ali *et al.,* 2016). Meanwhile, in this study, the diabetic rats treated with dapagliflozin revealed a comparative increase in the sizes of the islets of Langerhans with a characteristic increase in cellular population of both α and β-cells. This is in line with the findings of Macdonald *et al.* (2010), who showed that improvement in islet morphology was observed in the group treated with dapagliflozin compared to diabetic rats. Karlsson *et al.* (2022) have demonstrated that after using SGLT2 inhibitors, clinical research in individuals with type 2 diabetes showed both enhanced insulin sensitivity and protective effects on beta cell function (Merovci *et al.,* 2015; Takahara *et al.,* 2015). Although many rodent studies have shown that pharmacological and SGLT2 inhibition maintain beta cell function (Macdonald *et al.,* 2010; Kimura *et al.,* 2018). Wei *et al.* (2020) demonstrated that one of the key pathophysiology features of diabetes is the malfunctioning of pancreatic beta cells, which results in insufficient insulin secretion. Research on animals has shown that SGLT2 inhibition enhances beta cell function in the short term and may sustain islet morphology and beta cell mass over time (Jurczak *et al.,* 2011; Guo *et al.,* 2020). Patients with type 2 diabetes who receive SGLT2 inhibitors as monotherapy or in addition to other treatments have demonstrated considerable improvement in beta cell activity after treatment, according to an increasing number of clinical investigations (Ferrannini *et al.,* 2014; Merovci *et al.,* 2015).

In the current study, the histological changes of pancreatic tissue in the diabetic rats treated with curcumin revealed nearly normality in both exocrine and endocrine counterparts with a healthy acinar epithelium and its secretory granules. A few β-cells suffered degenerative alterations, primarily hydropic degeneration and cloudy swelling. The exocrine pancreas was also nearly normal. This is in line with the findings of Badr *et al.* (2020), who showed that the administration of curcumin improved the pancreatic islets. Furthermore, there was a noticeable and significant rise in the number of β cells after curcumin. Curcumin's capacity to restore β cell function and stimulate the growth of new cells is similar to prior research that demonstrated islet neogenesis in diabetic mice after 12-week curcumin treatment (Chanpoo *et al.,* 2010) and an increase in the number of β cells (Walvekar *et al.,* 2016). Curcumin's stimulatory effects on pancreatic β cells may all be involved in diabetes hypoglycemia (Kharroubi and Darwish, 2015). Curcumin can lower blood sugar levels by reducing the liver's glucose production, reducing the inflammatory state brought on by hyperglycemia, boosting cellular absorption of glucose, and activating several enzymes and proteins that regulate insulin secretion and sensitivity. Curcumin can also lower insulin resistance and improve pancreatic cell function (Ghorbani *et al.,* 2014).

The current study found that the combination group of diabetic rats treated with

DAPA and CUR had a comparatively larger islet of Langerhans, accompanied by a characteristic increase in cellular population of both α and β-cells. The architecture of the exocrine pancreas was likewise almost normal. The pancreas of rats in groups treated with DAPA + CUR showed improved levels of SOD activity, GSH, MDA, TNF- α and IL-I β. This suggested that the combination of DAPA + CUR was protective and could scavenge free radicals brought on by hyperglycemia.

In reference to the immunohistochemical analysis of pancreatic tissue, the mean density of caspase-3 positive staining in diabetic group was significantly higher than that of the control group. This agreed with Shawky *et al.* (2019), who demonstrated that inducible nitric oxide (iNOS) and caspase-3 immunohistochemistry, both inflammatory and apoptotic mechanisms were involved in the beta-cell destruction in the animal pancreatic tissue model of type 2 diabetes (rat model of HFD/STZ). El-Tablawy *et al.* (2015) observed that the immunohistological examination of pancreatic tissue in STZ-treated rats showed a significant elevation of caspase-3 expression. The elevated expression of caspase-3 indicated that apoptosis is a major factor in the death of pancreatic β-cells. In agreement with the obtained results, the findings of Maedler *et al.* (2001) and Haligur *et al.* (2012) reported that caspase-3-dependent apoptotic pathways are essential for pancreatic β-cells apoptosis. Cell death is the last stage of cellular damage, and it can occur by apoptosis (Slauson and Cooper, 2002). Sun *et al.* (2021) demonstrated that patients with type 2 diabetes had a higher prevalence of apoptotic beta cells, according to research on human pancreatic tissue and that caspase-3 activation might be induced by metabolic stress, which could be an important pathophysiological mechanism in T2DM (Rhodes, 2005).

In the current study, the immunohistochemical observations of the pancreatic tissue showed that the mean density of caspase-3 immunoreactivity showed non-significant change in the rats treated with CUR when compared to the control group. Turmeric contains a naturally occurring substance called curcumin. Its various biological properties could help with diabetes treatment. Since inflammation seriously impairs the structural integrity of β-cells, curcumin's antidiabetic benefits are mainly due to its anti-inflammatory and antioxidant qualities (Bozkurt *et al.*, 2022). In the present study, the immunohistochemical observations of the pancreatic tissue showed that the mean density of caspase-3 immunoreactivity showed a significant decrease in the diabetic rats treated with DAPA when compared to the diabetic group. This is in agreement with the results of Hussein *et al.* (2020), who reported that dapagliflozin significantly attenuated caspase 3 expression and decreased apoptosis in the same model of diabetic cardiomyopathy (DCM). According to Faridvand *et al.* (2022), several experimental studies have demonstrated the anti-apoptotic, anti-inflammatory, and antioxidant properties of DAPA, a novel hypoglycemic medication. The outcomes demonstrated that pretreatment with DAPA enhanced cell viability. Furthermore, DAPA pretreatment reduced the levels of ROS, IL-6, and TNF-α. Furthermore, DAPA pretreatment markedly inhibited caspase-3 activity induced apoptosis in human umbilical vein endothelial cells (HUVEC).

According to the immunohistochemistry observations of the pancreatic tissue in the current investigation, the diabetic animals treated with CUR (D+ CUR) exhibited a significant decrease of caspase-3 positivity compared to the diabetic group. This is in agreement with the findings of Metawea *et al.* (2023), who noted that curcumin significantly reduced the immunoreactive beta cells and the caspase-3 production. Kamel *et al.* (2014) reported that the pancreas of diabetic rats had a markedly raised Caspase-3 level, but that the pancreatic Caspase-3 content was decreased without a dose-dependent effect when diabetic rats were treated with 50 or 300 mg/kg of curcumin. Curcumin therapy could lower apoptotic cell death by controlling the activation of Bcl-2 family proteins (Manna *et al.*, 2010). Fan *et al*. (2014) illustrated that curcumin reduced high glucose-induced apoptosis in cardiomyocytes, thereby preventing the progression of diabetic cardiomyopathy DCM progress. According to Wang *et al*. (2014), diabetic mice showed improved breakdown of pro-apoptotic protein (Bax) and

caspase-3, as well as a notable increase in anti-apoptotic protein (Bcl-2). Compared to the diabetic group, the mean density of caspase-3 immunoreactivity in the pancreatic tissue of the diabetic rats treated with DAPA and curcumin significantly decreased, according to the immunohistochemistry observations of the kidney tissue in the current investigation. Ameliorated levels of TNF- and IL- Iβ in the pancreas of groups supplemented with DAPA +CUR indicated the protective effect of DAPA+CUR and its ability to reduce apoptosis caused by hyperglycemia.

CONCLUSION

Overall, the current investigation discovered that DAPA, CUR, or both ameliorated physiological and histopathological alterations, improved antioxidant markers and kidney functions, and decreased inflammatory markers (TNF-α and IL-Iβ) and MDA to counteract the renal and pancreatic impairment brought on by HFD and STZ (diabetic effects). Furthermore, the combination of DAPA and CUR showed a synergistic effect that leading to greater improvement in most of the evaluated parameters.

Declarations:

Ethical Approval: The Institutional Animal Care and Use Committee (ZU-IACUC) of Zagazig University examined and approved this experimental protocol; its approval number is ZU-IACUC/1/F/22/2024.

Competing interests: The authors declare that there is no conflict of interest.

Author's Contributions: Fatma M. El-Deeb, carried out field execution to all experiment stages, collect blood samples and field data and contributed in wrote this article. Ahkam M. El Gendy wrote this article, helped in biochemical analysis, contributed in drafting the manuscript and revision. Rasha A. wrote this article and performed the statistical analysis of the results, contributed in drafting the manuscript and revision. Hemmat M. Abdelhafez wrote this article and contributed in drafting the manuscript and revision and performed the histo-morphological and immunohistochemical parameters. Responsible for paper idea; Ahkam M. El Gendy, Rasha A. and Fatma M. El-Deeb. All authors approved the final manuscript.

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