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# Effects of Multi-extracts of Mori Folium and of Exercise on Serum Lipid Profiles and Tissue Differentiation in Streptozotocin-induced Diabetic Rats

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**This research was performed to investigate the effects of the supplementation of multi-extracts of *mori folium (MF)* and of exercise on blood lipid profiles and tissue differentiation in streptozotocin (STZ)-induced diabetic rats. The animal groups consisted of a normal-control group, a STZ-control group, three STZ-induced diabetic groups supplemented ad libitum with various amounts of MF extracts (MF-720, MF-360, and MF-180 groups), and a STZ-induced diabetic group supplemented with MF-360 combined with exercise; eight male Sprague-Dawley rats, 4 weeks old, were assigned to each experimental group and were raised in the laboratory for a 10 week experimental period. The MF supplementation group showed a significant reduction in levels of serum total cholesterol and triglyceride compared to the STZ-control group. HDL-cholesterol levels were significantly increased in the MF supplementation group compared to STZ-control group. The ratio of HDL-cholesterol to total cholesterol was significantly higher in MF supplementation group compared to the STZ-control group. The Atherogenic Index (AI) values in the MF supplementation groups were found to be significantly lower than in the STZ-control group. Serum AST and ALT levels were significantly reduced in the MF-supplementation groups compared to the STZ-control group. Total cholesterol level in the liver tissue was significantly decreased in the MF-360 group and in the MF-360 + exercise group compared to the STZ-control group. In immunohistochemical staining of the pancreatic islets of the MF-supplemented groups, a significantly higher number of insulin-immunoreactive cells were observed compared to the STZ-control group. In the MF supplementation groups, Bowman's capsules were clearly observed as hypertrophy of the glomeruli was not obvious. In the MF supplementation groups, a relative reduction in the hypertrophy of the basement membrane of the glomeruli and a significant reduction in the mesangium were observed compared to the STZ-control group. The results of this study suggest that supplementation of MF has beneficial effect in improving plasma lipid and tissue metabolism in streptozotocin-induced rats.**

**Key words :** Mori Folium, streptozotocin, serum lipids, immunohistochemical staining, diabetes, rat

## INTRODUCTION

The increase in the incidence of diabetes mellitus in Korea as well as elsewhere in the world is stimulating researchers' interest in finding better ways of preventing and treating this disease and its complications. Diabetes is a disease affected by genetic factors as well as by environmental factors such as obesity, diet, lack of exercise and stress.[1),2)] Modern medicine has not been successful in developing fundamental cures. The best treatment option at present is to stabilize blood glucose levels, and the major treatment methods for diabetes include drugs, exercise and diet therapies.[3),4)]

Long-term diabetes disturbs glucose metabolism; lipids and proteins become major suppliers of energy to tissues. Due to the increased lipid metabolism, β-oxidation in lipid tissue is stimulated, and the increased concentrations of fatty acids in the blood increase ketogenesis in the liver.[5)] The increased lipid peroxide concentration is known to accelerate aging and chronic degenerative diseases, and the risk of complications common in diabetes. Mori folium consists of the leaves of common mulberry trees or other trees of the Genus *Morus;* research into Mori Folium's physiological effects has confirmed that it lowers blood triglyceride and cholesterol levels, and reduces atherosclerosis and hyperlipidemia.[6)] Presently, research on the physiological effects of Mori Folium and its chemical components is being actively pursued, and Mori Folium is now being used in functional foods.[7)]

This study was undertaken to determine the effects of the supplementation of mulberry leaf extracts (Mori Folium) and of exercise on serum and liver lipid meta-

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bolism in STZ-induced diabetic rats.

## MATERIALS AND METHODS

### 1. Multiple extraction of Mori Folium

Dry Mori Folium (70%), Portulacea Herba (5%), Corni Fructus (5%), Euronymus alata Siebold (5%), Maydis Stigmata (5%), Dioscoreae Rhizoma (5%) and Anemarrhenae Rhizoma (5%) was purchased in the Kyung-dong market and pulverized. The resulting powder was added to distilled water and was then placed in a water bath which was attached to a device for circulating cold air. The extract was filtered in warm temperature conditions. This process was repeated three times for three hours. 3% Mori Folium and Multiple extracts was added to distilled water. Rats were given free access distilled water and experimental diets.

### 2. Experimental animal and diets

Forty-eight male Sprague-Dawley rats, approximately four-weeks old, were kept on a pellet diet for 7 days in the laboratory. After this one week of adjustment, animals weighing 120 to 140g were assigned to 6 groups by a randomized complete block design. There were 8 rats in each of the six groups - 1 normal control group and 5 treatment groups. The non-diabetic (normal) control group and the STZ-induced diabetic control group were each given distilled water ad libitum. The other four STZ-induced diabetic groups were given the following treatments; three of the groups were given 720mg, 360mg, and 180mg MF extracts dissolved in distilled water ad libitum, respectively, while the fourth group was given 360mg MF extracts dissolved in distilled water at the same time as being subjected to an endurance exercise regime. Experimental animals were housed individually in stainless wire cages.

### 3. Inducement of diabetes

Rats were fasted for 16 hours before the inducement of diabetes; streptozotocin (STZ, Sigma Chemical Co.)[8,9] dissolved in 0.01M citrate buffer (pH 4.5) was injected through the tail vein at a concentration of 45mg/kg body weight. The normal-control group was injected with the same amount of 0.01M citrate buffer solution.

### 4. Collection of samples for analysis

After the 10 week experimental period, the rats were fasted for 12 hours. They were then anesthetized, and blood was collected from the abdominal artery. Blood was kept at 4℃ for 30 minutes, and was then centrifuged at 3,000rpm for 20 minutes to obtain serum. The resulting serum was frozen until further analysis. After blood collection, the liver, lungs, kidneys, spleen and pancreas were excised, and were washed with physiological saline. A piece of liver was taken away for lipid determination and was frozen at -70℃. The rest of the liver, the kidneys and pancreas, were fixed in 10% neutral formalin, and were stained by H&E, periodic acid-Schiff (PAS), and an immunohistochemical staining method.

### 5. Determination of hematocrit, serum AST, ALT, and total protein (TP)

Hematocrit values were determined by the microhematocrit method,[10] using a microcapillary centrifuge at a high speed and a microcapillary reader. Serum transaminases such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT), total protein (TP), and glycated hemoglobin, were measured by using an automatic biochemical analyzer (EKTA Chem; DT60II, DTSC II module, DTEII module, Johnson Ortho-clinical diagnostics).

### 6. Serum MDA determination

Serum lipid peroxide levels were determined by using the Ohakawa et al method[11] which determines malondialdehyde using thiobarbituric acid (TBA); the values of each of the experimental groups were expressed as a percentage of the values obtained from the normal-control group.

### 7. Serum and liver lipid determination

Serum total cholesterol (TC), HDL cholesterol and triglyceride (TG) were measured using Asan kits from Allain at al.'s method.[12]

0.5g of liver tissue was cut into small slices, a 5ml chloroform : methanol (2 : 1) combination was added to the sample, and these were then homogenized. The homogenate was filtered through Whatmann No. 1 filter paper, and the same process was repeated 3 times. The extracts were dried under nitrogen gas at 60℃; 1ml chloroform : methanol (2 : 1) was added, and the extracts were again dried under nitrogen gas. To provide samples for liver lipid determination, 1 ml ethanol was added to the extracts; then, a 200 μl sample of the mixture was taken and was dissolved in 500 μl distilled water. Liver lipid levels of the prepared samples were detemined using the same method used for serum lipid determination.[13]

### 8. Immunocytological staining of the pancreas

Immunocytochemical staining was conducted by using the peroxidase anti-peroxidase (PAP)[14] method. After paraffin was removed from the sliced pancreatic tissue, the slices were immersed in 100% methanol for 30 minutes, followed by hydrogen peroxide for 30 minutes in order to suppress the internal tissue peroxidase. The

tissue was washed three times in phosphate buffered saline (PBS : 0.01M, pH 7.4) for 30 minutes each time. In order to prevent a non-specific combination with immunoglobulin, the tissue was kept in normal goat serum at room temperature for an hour. Subsequently, the tissue was added to guinea pig insulin polyclonal antibody (GioGenex, USA) and kept at less than 4℃ for 24 hours; the mixture was then washed three times in PBS for 30 minutes each time. The tissue was then added to secondary anti-rabbit IgG goat serum at room temperature for an hour, and subsequently washed three times in PBS. The tissue was added to peroxidase anti-peroxidase complex (Sigma, USA) at room temperature for an hour, and was subsequently washed three times in PBS. The color was developed in DAB solution (3,3'-diaminobenzidine tetrahydrochloride) containing 0.01% hydrogen peroxide in Tris-HCl buffer (0.05M, pH7.6), and contrast staining was achieved using Mayer's hematoxylin. An optical microscope was used for observation.

### 9. Statistical analysis

All experimental results are expressed as mean ± S.D., and tests of significance between groups were performed by using one way analysis of variance (ANOVA). The significance of differences among the groups was tested by using Duncan's new multiple test ($p < 0.05$).[15]

## RESULTS AND DISCUSSION

### 1. Serum MDA (malondialdehyde)

Serum lipid peroxide levels are shown in Fig 1.; all STZ-induced diabetic groups had significantly higher levels compared to the normal-control group. The STZ-control group had a 69% higher lipid peroxide level compared to the normal -control group; the reductions in the MF-720, MF-360, MF-360+exercise, MF-180 groups were 9.5%, 20.1%, 21.5%, and 17.2%, respectively, and all were significantly lower, compared with the STZ-control group.

Serum lipid peroxide, which is an index of peroxidation damage in the body, was shown to be high in STZ-induced diabetic rats; these results support the theory that increased lipid peroxide and free radicals are important factors inducing the complications of diabetes.[16),17] The significant reduction seen in the MF groups suggests that kaemferol and naringenin derivatives in MF work as antioxidants.[18]

### 2. Blood lipid metabolism

Serum total cholesterol was increased by 38.9% in the STZ-control group compared to the normal control group. Compared to the STZ-control group, the MF-720, MF-360, MF-360+exercise and MF-180 groups showed 6%, 18.3%, 21.2%, and 13.4% reductions of blood cholesterol, respectively; the greatest reduction was observed in the MF-360 + exercise group.

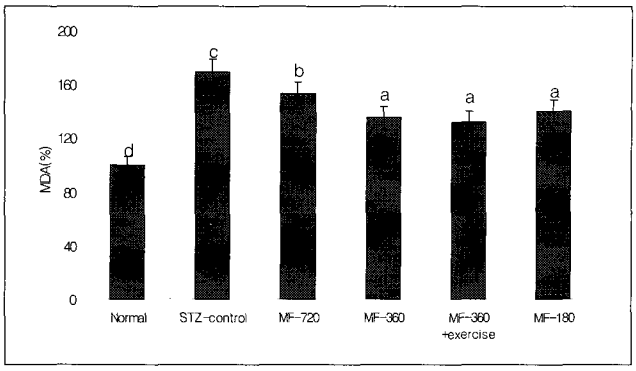



**Fig 1.** Serum MDA concentration in rats fed the experimental diets for 10 weeks[1),2)]

1) Values are mean ± S.D., N=8.
2) Values with different superscript within the row are significantly different at 5% level.
MDA concentration(%) are compared with normal group mean in serum(normal group mean=100%)
3) Normal : basal diets.
STZ-control : basal diets + STZ(45mg/kg · B.W.).
MF-720 : basal diets + STZ(45mg/kg · B.W.) + MF 720 mg/kg/day.
MF-360 : basal diets + STZ(45mg/kg · B.W.) + MF 360 mg/kg/day.
MF-360+exercise : basal diets + STZ(45mg/kg · B.W.) + MF 360 mg/kg/day + exercise.
MF-180 : basal diets + STZ(45mg/kg · B.W.) + MF 180 mg/kg/day.

Serum triglyceride levels were significantly higher in the STZ-induced diabetic groups compared to the normal-control group; all MF groups, especially the MF-360 + exercise group, showed significant decreases compared to the STZ-control group.

HDL cholesterol was decreased by 12.8% in the STZ-control group; in the MF-720, MF-360, MF-360+ exercise and MF-180 groups, HDL-cholesterol was increased by 3.9%, 11.7%, 8.2%, and 5.4%, respectively, compared to the STZ-control group. The ratio of total cholesterol to HDL cholesterol was 37.2% higher in the STZ-control group compared to the normal-control group and the difference was significant; in the MF-720, MF-360, MF-360+exercise and MF-180 groups, the ratios were 10.6%, 36.7%, 38.9%, and 21.7% higher, respectively, than the STZ-control group.

The Atherogenic Index (AI) in the STZ-control group was double the value obtained in the normal-control group; AI was reduced in the MF groups compared to the STZ-control group (Table 1). The present study demonstrated that blood lipid metabolism improved with MF supplementation; this agrees with the study by Kim et al[19] who reported that there was a reduction of blood total cholesterol and triglyceride in experimental hyperlipidemic rats who were given MF extracts. The reduction may be due to fiber in MF extracts, which increases the excretion of toxic material and facilitates transit through

the intestines, and to oleic acid, linoleic acid and small amounts of plant sterol such as β-sitosterol which facilitate the excretion of cholesterol, thereby decreasing blood cholesterol.[20]

**Table 1.** Serum lipid profiles of diabetic rats fed on experimental diets for 10 weeks[1,2]

| Items | Groups[3] | | | | | |
|---|---|---|---|---|---|---|
| | Normal | STZ-control | MF-720 | MF-360 | MF-360+exercise | MF-180 |
| Total-cholesterol (mg/dl) | 93.60 ±6.87$^{d}$ | 130.02 ±18.78$^{c}$ | 122.17 ±23.86$^{bc}$ | 106.20 ±18.94$^{ab}$ | 102.43 ±17.92$^{a}$ | 112.63 ±19.94$^{ab}$ |
| HDL-cholesterol (mg/dl) | 39.89 ±3.17$^{d}$ | 34.80 ±6.37$^{c}$ | 36.17 ±5.93$^{c}$ | 38.86 ±6.82$^{cd}$ | 37.66 ±8.04$^{cd}$ | 36.70 ±5.24$^{c}$ |
| HDL-cholesterol / Total-cholesterol | 42.61 ±3.06$^{d}$ | 26.77 ±6.92$^{c}$ | 29.61 ±4.60$^{bc}$ | 36.59 ±7.06$^{a}$ | 37.20 ±18.94$^{a}$ | 32.58 ±5.14$^{ab}$ |
| Triglyceride (mg/dl) | 122.21 ±6.66$^{d}$ | 192.57 ±31.33$^{c}$ | 185.39 ±21.25$^{c}$ | 169.70 ±24.38$^{b}$ | 166.70 ±28.94$^{b}$ | 178.83 ±29.84$^{bc}$ |
| AI(atherosclero-ticindex)[4] | 1.34 ±0.31$^{d}$ | 2.74 ±0.79$^{c}$ | 2.38 ±0.85$^{bc}$ | 1.73 ±0.83$^{a}$ | 1.66 ±0.91$^{a}$ | 2.07 ±0.54$^{a}$ |

1) Values are mean ± S.D., N=8.
2) Values with different superscript within the row are significantly different at 5% level.
3) Normal : basal diets.
STZ-control : basal diets + STZ(45mg/kg · B.W.).
MF-720 : basal diets + STZ(45mg/kg · B.W.) + MF 720 mg/kg/day.
MF-360 : basal diets + STZ(45mg/kg · B.W.) + MF 360 mg/kg/day.
MF-360+exercise : basal diets + STZ(45mg/kg · B.W.) + MF 360 mg/kg/day + exercise.
MF-180 : basal diets + STZ(45mg/kg · B.W.) + MF 180 mg/kg/day.
4) Atherogenic index : ([T-C]-[HDL-C])/[HDL-C]

## 3. AST, ALT, HbA1, and Total Protein

Serum protein levels decreased in all STZ-induced diabetic rats compared to the normal-control group; the MF supplemented groups showed a slightly higher serum total protein level than the STZ-control group, although these differences were not significant.

Serum AST activities were significantly increased (by 77.1%) in the STZ-control group compared to the normal-control group; in the MF-720, MF-360, MF-360+exercise and MF-180 groups, the reductions in serum AST activity compared to the STZ-control group were 3.7%, 12.4%, 17.7%, and 7.1%, respectively.

Serum ALT activities showed a similar trend to serum AST activities. ALT was significantly increased in STZ-induced diabetic groups; in the MF-720, MF-360, MF-360+exercise and MF-180 groups, the reductions in serum ALT activity compared to the STZ-control group were 5.2%, 18.6%, 24.1%, and 12.8%, respectively. The supplementation of multi-extracts of *mori folium (MF)* in the MF groups resulted in reduced levels of AST and ALT activities, which may be due to a reduction of gluconeogenesis and protection of -SH radicals, leading to the eventual improvement of liver functions. (Table 2)[21]

**Teble 2.** Serum AST, ALT, HbA1, TP activities and Hematocrit levels of diabetic rats fed on experimental diets for 10 weeks[1),2)]

| Items | Groups[3] | | | | | |
|---|---|---|---|---|---|---|
| | Normal | STZ-control | MF-720 | MF-360 | MF-360+exercise | MF-180 |
| AST(u/ℓ) | 83.38 ±8.47$^{d}$ | 147.63 ±11.36$^{c}$ | 142.13 ±13.56$^{c}$ | 129.38 ±17.83$^{b}$ | 121.55 ±19.13$^{b}$ | 137.16 ±12.83$^{b}$ |
| ALT(u/ℓ) | 25.88 ±6.74$^{d}$ | 91.38 ±8.37$^{c}$ | 86.63 ±6.08$^{bc}$ | 74.38 ±5.45$^{a}$ | 69.34 ±6.95$^{a}$ | 79.67 ±5.93$^{ab}$ |
| HbA1(%) | 7.67 ±1.89$^{d}$ | 10.95 ±1.78$^{c}$ | 9.44 ±1.14$^{b}$ | 8.58 ±1.54$^{b}$ | 8.51 ±1.34$^{b}$ | 8.92 ±1.27$^{b}$ |
| T-Protein (g/dl) | 11.23 ±0.98$^{d}$ | 5.46 ±2.04$^{c}$ | 5.53 ±2.19$^{c}$ | 6.74 ±1.87$^{c}$ | 6.86 ±1.46$^{c}$ | 6.02 ±1.38$^{c}$ |
| Hematocrit (%) | 44.3 ±3.7$^{NS4)}$ | 45.7 ±5.4 | 44.1 ±3.4 | 43.7 ±2.8 | 44.9 ±3.8 | 45.2 ±3.1 |

1) Values are mean ± S.D., N=8
2) Values with different alphabet within the same column are significantly different at p<0.05 by Duncan's multiple range test.
3) Normal : basal diets.
STZ-control : basal diets + STZ(45mg/kg · B.W.).
MF-720 : basal diets + STZ(45mg/kg · B.W.) + MF 720 mg/kg/day.
MF-360 : basal diets + STZ(45mg/kg · B.W.) + MF 360 mg/kg/day.
MF-360+exercise : basal diets + STZ(45mg/kg · B.W.) + MF 360 mg/kg/day + exercise.
MF-180 : basal diets + STZ(45mg/kg · B.W.) + MF 180 mg/kg/day.
4) NS : not significant at p<0.05 by Duncan's multiple range test.

## 4. Liver lipid metabolism

Table 3 shows the effects of MF supplementation on liver lipid levels. Total liver cholesterol was significantly higher (by 28.1%) in the STZ-control group compared to the normal-control group; a reduction in total liver cholesterol was observed in the MF groups compared to the STZ-control group, by 11.2% and 12.96% in the MF-360 group and MF-360 + exercise group, respectively. Triglyceride levels were found to be significantly lower in the STZ-induced diabetic groups; MF supplementation increased triglyceride level relative to the STZ-control group, but the difference was not significant.

**Teble 3.** Hepatic lipid profiles in diabetic rats fed on experimental diets for 10 weeks[1),2)]

| Items | Groups[3] | | | | | |
|---|---|---|---|---|---|---|
| | Normal | STZ-control | MF-720 | MF-360 | MF-360+exercise | MF-180 |
| Total-cholesterol (mg/dl) | 6.21 ±0.76$^{c}$ | 8.64 ±1.37$^{b}$ | 8.25 ±1.35$^{ab}$ | 7.67 ±1.46$^{a}$ | 7.52 ±1.46$^{a}$ | 7.95 ±1.06$^{ab}$ |
| Triglyceride (mg/dl) | 28.64 ±2.85$^{c}$ | 23.08 ±3.87$^{b}$ | 24.52 ±4.38$^{b}$ | 25.61 ±3.81$^{b}$ | 24.11 ±4.86$^{b}$ | 23.96 ±4.90$^{b}$ |

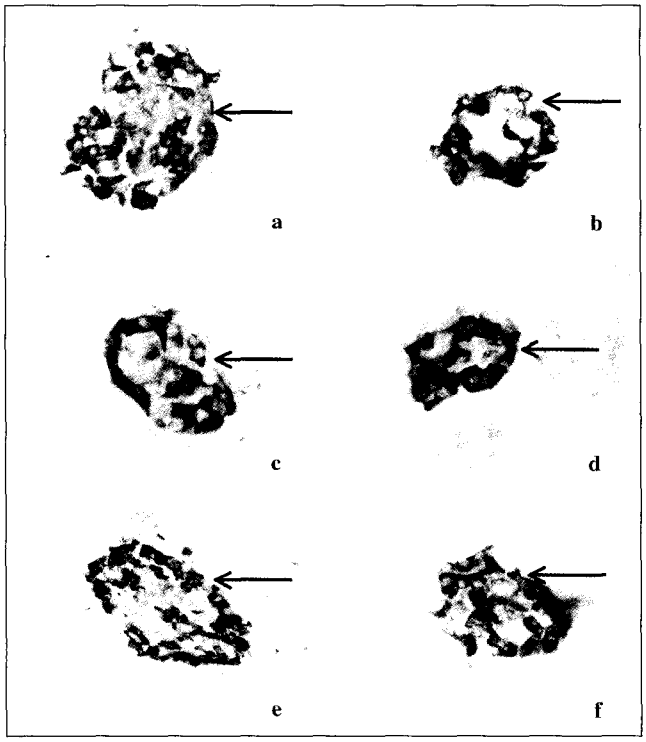
1) Values are mean ± S.D., N=8.
2) Values with different alphabet within the same column are significantly different at p<0.05 by Duncan's multiple range test.
3) Normal : basal diets.
STZ-control : basal diets + STZ(45mg/kg · B.W.).
MF-720 : basal diets + STZ(45mg/kg · B.W.) + MF 720 mg/kg/day.
MF-360 : basal diets + STZ(45mg/kg · B.W.) + MF 360 mg/kg/day.
MF-360+exercise : basal diets + STZ(45mg/kg · B.W.) + MF 360 mg/kg/day + exercise.

It is reported[22] that accumulation of cholesterol in the liver after STZ injection is due to lowered insulin levels; the resulting inadequate glucose metabolism increases acetyl-CoA accumulation which facilitates lipid accumulation in the liver giving the fatty liver condition. Our study showed that MF supplementation reduced the incidence of fatty liver, despite the high blood triglyceride levels.

## 5. Immunocytological staining of pancreatic tissue

Glucagon immuno-reactive cells were stained using an immunocytological method. In the normal-control group, glucagon-immunoreactive cells were widely distributed in the pancreatic islets, with increased concentrations being found on the outer boundaries (Fig 2-a). In the STZ-control group, glucagon-immunoreactive cells were almost entirely concentrated in the outer boundaries of the islets (Fig 2-b). In the MF-supplemented groups, there were higher numbers of glucagon-immunoreactive cells, and a higher proportion of these cells was found in central locations in the islets, compared to the STZ-control group; however, these differences were not significant, possibly because STZ specifically acts only on beta-cells and there was no great effect seen on alpha cells (Fig 2-c, d, e, f).[23]

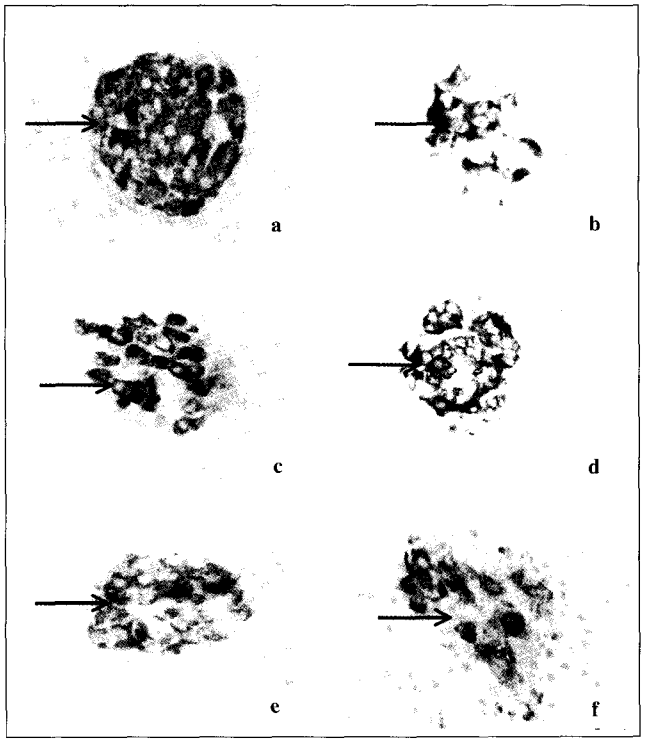
**Fig 2.** The alpha cells of the pancreatic islets




Immunohistochemistry for glucagon, PAP stain. ×400
a : Normal group, The alpha cells are found at peripheral zone in the islet.
b : STZ-control group, Deeply stained alpha cells are no longer restricted to the periphery of the atrophic islet.
c : MF-720 group,
d : MF-360 group
e : MF-360 + exercise group
f : MF-180 group
The alpha cells are relatively increased in number and distributed throughout the atrophic islet.(c-f)

Insulin-immunoreactive cells were evenly distributed in the normal-control group (Fig 3-a), while a significant decrease in insulin-immunoreactive cells was seen in the STZ-control group due to destruction of beta cells (Fig 3-b). MF supplemented groups showed a significant increase in insulin-immunoreactive cells (Fig 3-c, d, e, f) compared to the STZ-control group, which suggests that MF extracts provide some protection to pancreatic beta-cells.

**Fig 3.** The beta cells of the pancreatic islets

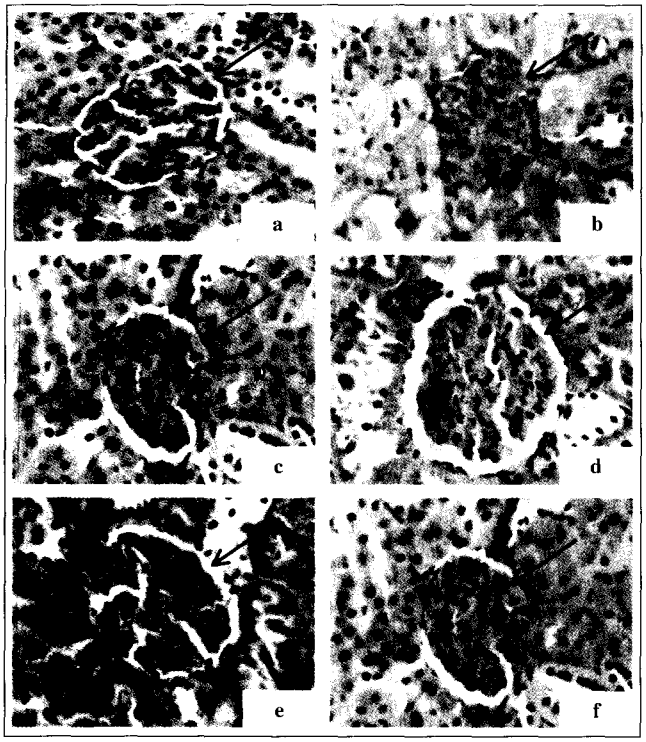



Immunohistochemistry for insulin, PAP stain. ×400
a : Normal group, The well granulated beta cells are numerous and tend to be concentrated in the center of the islet.
b : STZ-control group, Number of the beta cells are decreased, and residual beta cells degranulated.
c : MF-720 group
d : MF-360 group
e : MF-360 + exercise group
f : MF-180 group
Note that a number of the beta cell for insulin are destructed.

## 6. Optical microscopy of renal tissue

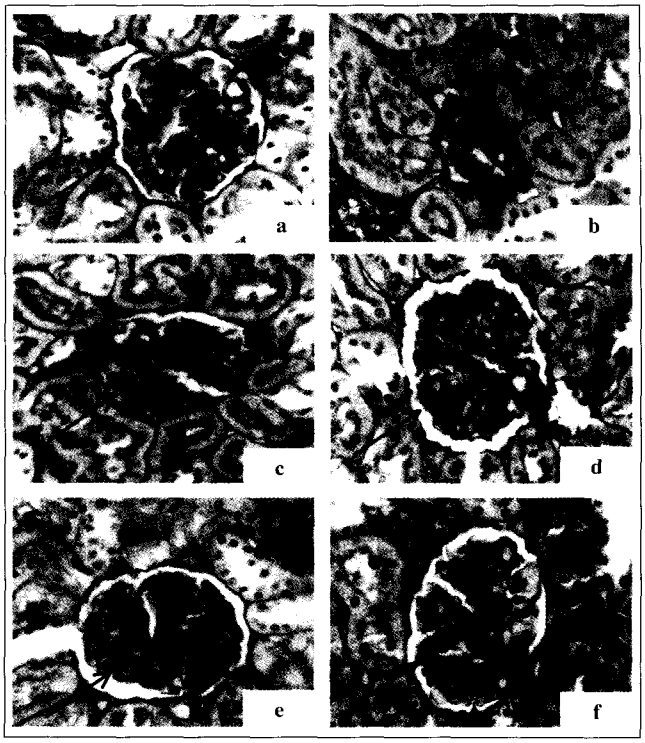
In the normal-control group, Bowman's capsules were observed in glomerular cells of the kidney tissue (Fig 4-a), while, in the STZ-control group, the hypertrophy of the glomeruli resulted in a reduction of Bowman's capsules (Fig 4-b). In the MF-supplementation groups, hypertrophy of the glomeruli was not obvious and

**Fig 4.** The glomerulus of the kidney




a : Normal group, Normal glomerulus, proximal segment, and distal segment are observed.
b : STZ-control group, Degeneration of tubular epithelium and severe necrosed Bowman's capsule and glomerulohypertrophy in kidney.
c : MF-720 group,
d : MF-360 group
e : MF-360 + exercise group
f : MF-180 group
Mild glomerulohypertrophy and decreased Bowman's space compared to that of STZ-control group.(c-f)

**Fig 5.** The mesangium of the kidney




PAP stain. ×400.
a : Normal group, The mesangium is normal in appearance. Illustrating normal structure of glomerular and tubular cells.
b : STZ-control group, Amount of the PAS-positive mesangium is increased, glomerular alteration was also observed.
c : MF-720 group,
d : MF-360 group
e : MF-360 + exercise group
f : MF-180 group
Amount of the mesangium is decreased.

Bowman's capsules were consistently observed (Fig 4-c, d, e, f).

PAS staining resulted in a clear image of the renal glomeruli, showing an equal thickness of the basement membranes in the normal-control group (Fig 5-a). In the STZ-control group, there was an increase in tunica vasculosa cell in the glomeruli, accompanied by an increase in the size of the mesangium and a hypertrophy of the basement membrane, which resulted in the contraction of renal capillaries and fibrosis that resembles diabetic renopathy (Fig 5-b). In this study, MF supplementation reduced the relative weight of the kidneys, reduced the enlargement of the basement membranes, and increased the mesangium (Fig. 5-c, d, e, f). Flavonoids such as rutin and quercetin control capillary transmission and lipid metabolism, resulting in lower blood glucose thereby improving renal lipid metabolism and reducing the level of pathological changes in the mesangium.[24]

## CONCLUSION

The effects of supplementation of MF extracts and exercise on serum lipid profiles and immunohistochemical observation of organs in STZ-induced diabetic rats can be summarized as follows;

Blood lipid peroxide level was significantly increased in all STZ-induced diabetic rats, but the MF groups showed a significant decrease in serum MDA level compared to the STZ-control group.

The MF-supplemented groups tended to have lower serum total cholesterol compared to the STZ-control group. The MF treated groups showed a significant reduction compared to the STZ-control group. The ratio of total cholesterol to HDL-cholesterol was significantly lower in the MF-supplemented groups compared to the STZ-control group. The atherogenic index(AI) of MF supplementation groups were significantly lower than in the STZ-control group.

MF supplementation reduced serum AST activities compared to the STZ-control group. Serum ALT showed

similar results to serum AST levels.

Total cholesterol level in the liver tissue was significantly decreased in the MF-360 and MF-360 + exercise groups compared to the STZ-control group.

MF supplementation resulted in a significant increase in numbers of immunoreactive cells compared to the STZ-control group.

MF supplementation groups showed an insignificant hypertrophy of the glomeruli and the Bowmans's capsules were clearly observed. MF supplementation resulted in less hypertrophy of the basement membrane of the glomeruli and a smaller increase in the mesangium, compared to the STZ-control group.

In conclusion, the results of this study suggest that the supplementation of multi-extracts of Mori Folium has beneficial effects in improving serum lipid and tissue metabolism of STZ induced rats by decreasing serum triglyceride, total cholesterol and by increasing serum HDL-cholesterol. The results have shown that the multi-extracts of Mori Folium could improve plasma lipid and tissue metabolism.

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