RESULTS

I. In vivo experiments:

1. The effects of telmisartan administration in a dose of (5 mg/kg/day) for two weeks on arterial blood pressure, fasting plasma insulin level, fasting blood glucose, HOMA-IR, triglyceride level in fructose-induced metabolic syndrome group:

It should be mentioned that there was no significant difference between the vehicle group (group II) which received 0.5% carboxy-methyl cellulose and the control group (group I) so all statistical analysis was done in comparison to the control group (group I).

1.1-The effect on arterial blood pressure

A- Systolic blood pressure :

Administration of 10% fructose solution in the drinking water for 5 weeks resulted in significant ($P < 0.001$) rise of systolic blood pressure (SBP) from 110 ± 1.89 mmHg in control group (group I) to 160 ±1.27 mm Hg in metabolic syndrome induced group (group III).Treatment of metabolic syndrome induced group with telmisartan in a dose of (5 mg/kg/day) for 2 weeks ((group IV) resulted in a significant ($P < 0.001$) decrease in SBP to 86.75±1.05 mmHg compared to 160 ±1.27 mm Hg in metabolic syndrome induced group (group III). Comparing the result of telmisartan –treated group (group IV) to that of control group (group I)there was significant ($P < 0.001$) difference between the 2 groups. (Table 5, Fig.13,20,21,22,23).

***B- Diastolic blood pressure*:**

In the control group (group I) the diastolic blood pressure (DBP) was 89.38±1.47 mmHg and it increased significantly ($P < 0.001$) to 108.75± 1.26 mmHg in metabolic syndrome induced group (group III)

if compared with the control group. Treatment of metabolic syndrome induced group with telmisartan in a dose of (5 mg/kg/day) for 2 weeks (group IV) resulted in a significant ($P < 0.001$) decreased in DBP to 61±1.50 mmHg compared to group III. The result of the telmisartan treated group (group IV) 61±2.50 mmHg showed significant ($P < 0.001$) decrease in DBP compared to the result 89.38±1.47 mm Hg in control group (group I) (Table 5, Fig.14,20,21,22,23).

c- Mean arterial blood pressure:

By calculating the mean arterial blood pressure (MBP), it was of 96.25±1.32 mm Hg in control group(group I) and it increased significantly ($P< 0.001$) to a mean of 125.83±1.86 mm in metabolic syndrome induced group (group II) . Treatment of metabolic syndrome induced group with telmisartan in a dose of (5 mg/kg/day) for 2 weeks (group IV) resulted in a significant ($P < 0.001$) decreased in the MBP to a mean of 67.92±2.28 compared to non treated group (group III) . Comparing the result of telmisartan –treated group (group IV) to that of control group (group I)there was significant ($P < 0.001$) difference in between. (Table 5, Fig.15,20,21,22,23).

Table (5): Effect of telmisartan treatment (5 mg/kg/day) for 2 weeks on arterial blood pressure in metabolic syndrome -induced group in rats by administration of (10%L-fructose solution in drinking water for 5 weeks):

Parameter / Groups	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Mean arterial blood pressure (mmHg)
Control group	110 ± 1.89	89.38 ± 1.47	96.25 ± 1.32
Vehicle group	112.12± 0.23	89.90± 1.40	97.03 ± 1.12
Metabolic syndrome induced group	160 ± 1.27*****	108.75 ± 1.26*****	125.83 ±1.86*****
Percent change (%)	↑ 45.5%	↑ 21.7%	↑ 30.6%
Telmisartan-treated group.	86.75 ± 1.05***** #	61 ± 1.50***** #	67.92 ± 2.28***** #
Percent change (%)	↓ 47.9%	↓ 44.9%	↓ 46.02%

Data represented as Mean ± SEM (n = 8)

***** significant ($p < 0.05$) compared to control group

significant ($p < 0.05$) compared to metabolic syndrome –induced group.

1.2- The effect on plasma insulin level (PIL) :

Administration of 10% L-fructose solution in the drinking water for 5 weeks resulted in significant ($P < 0.001$) rise of (PIL) from 29.12±1.59µIU/mL in control group(group I) to 52.38±2.24 µIU/mL in metabolic syndrome –induced group (group III). Treatment metabolic syndrome –induced group with telmisartan (5mg/kg /day) for 2weeks (group IV) resulted in significant ($P < 0.001$) decrease in the insulin level to 37.88±1.76 µIU/mL compared to metabolic syndrome –induced group (group III). Comparing the result of the treated group (group IV) to that of control group(group I) there was significant ($P < 0.05$) differences between the two groups (Table 6, Fig.16).

1.3- The effect on fasting blood glucose level (FBG):

Metabolic syndrome –induced group (group III)showed significant ($P < 0.001$) rise of (FBG) level from 80.25 ±1.06mg/dl in control group (group I) to 149.38±2.49mg/dl . Treatment of metabolic syndrome –induced group (group IV) with telmisartan (5mg/kg /day) for 2weeks resulted in significant ($P<0.001$) decrease of (FBG) to132.50±1.79 mg/dl if compared with non treated group (group III). Comparing the result of telmisartan treated group (group IV) to that of control group (group I) there was significant differences ($P < 0.05$) between the two groups (Table 6, Fig.17).

1.4-The effect on HOMA-IR index:

By calculating the homeostasis model assessment (HOMA-IR) index it was 5.75±0.30 in control group (group I). In metabolic syndrome –induced group (group III) there was significant ($P < 0.001$) rise to 19.23±0.62 compared to control group (group I). Treatment of metabolic syndrome –induced group (group IV) with telmisartan (5mg/kg /day) for

2weeks resulted in significant (P < 0.001) decrease of (HOMA-IR) to 12.33±0.44compared to non treated group (group III) .In comparison there was significant (P < 0.001) difference between telmisartan –treated group (group IV) and control group (group I) (Table 6, Fig.18).

Table (6): Effect of telmisartan treatment (5 mg/kg/day) for 2 weeks on hyperinsulinemia parameters in metabolic syndrome induced group in rats by administration of (10%L-fructose solution in drinking water for 5 weeks):

Parameter / Group	Plasma Insulin level (µIU/ml)	Fasting blood glucose (mg/dl)	HOMA-IR Index
Control group	29.12 ± 1.59	80.25 ± 1.06	5.75 ± 0.30
Vehicle group	29.87 ± 1.11	81.85 ± 1.31	5.98 ± 1.04
Metabolic syndrome-induced group	52.38 ± 2.24*	149.38 ± 2.49*	19.23 ± 0.62*
Percent change %	↑ 79.8%	↑86.1%	↑ >100%
Telmisartan-treated group	37.88±1.76* #	132.50 ± 1.79* #	12.33 ± 0.44* #
Percent change %	↓ 27.7%	↓ 11.3%	↓ 35.9%

Data represented as Mean ± SEM (n = 8)

* significant (p < 0. 05) compared to control group

significant (p < 0. 05) compared to metabolic syndrome –induced group.

1.5- The effect on triglyceride level:

Regarding triglyceride level it was 116.19±2.04 mg/dl in control group (group I) , by adding 10 % fructose solution in the drinking water for 5 weeks to (group III) there was significant (P < 0.001) rise to 264.03±1.05mg/dl compared to control group . Treatment of metabolic syndrome –induced group (group IV) with telmisartan (5mg/kg /day)for 2weeks resulted in significant (P < 0.001) decrease to177.23±1.57 mg/dl compared to non treated group (group III). Comparing the result of telmisartan treated group (group IV) to that of control group (group I) there was significant (P < 0.001) difference in between. (Table 7,Fig.19)

Table (7): Effect of telmisartan treatment (5 mg/kg/day) for 2 weeks on triglyceride in metabolic syndrome- induced group in rats by administration of (10%L-fructose solution in drinking water for 5 weeks):

Parameter / Group	Triglyceride mg/dl
Control group	116.19 ± 2.04
Vehicle group	118.80± 1.57
Metabolic syndrome -induced group	264.03 ± 1.05*
Percent change	↑ > 100%
Telmisartan-treated group	177.23 ± 1.57* #
Percent change	↓ 44.9%

Data represented as Mean ± SEM (n = 8)

* significant (p < 0. 05) compared to control group

significant (p < 0. 05) compared to metabolic syndrome –induced group.

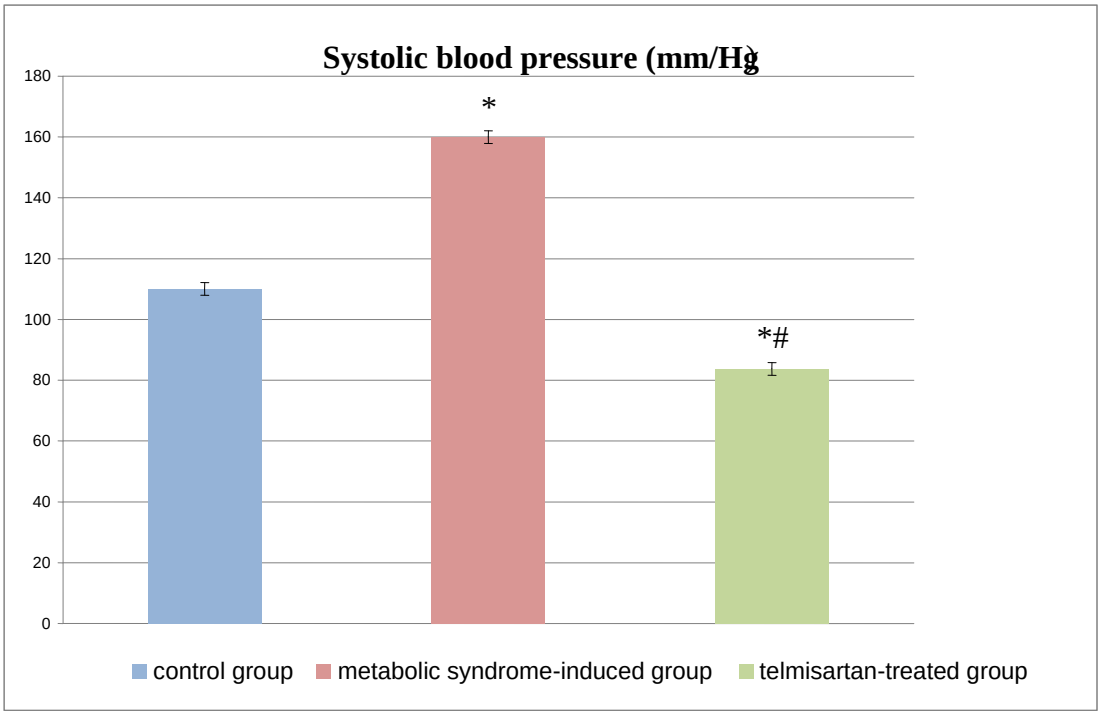


Figure (13): Histogram showing effect of telmisartan (5mg/kg/day) for 2 weeks on systolic blood pressure in experimentally induced metabolic syndrome (by administration of 10%L-fructose solution in drinking water for 5 weeks).

Data are presented as mean ± SEM

***** significant ($p < 0.05$) compared to control group

significant ($p < 0.05$) compared to metabolic syndrome- induced group

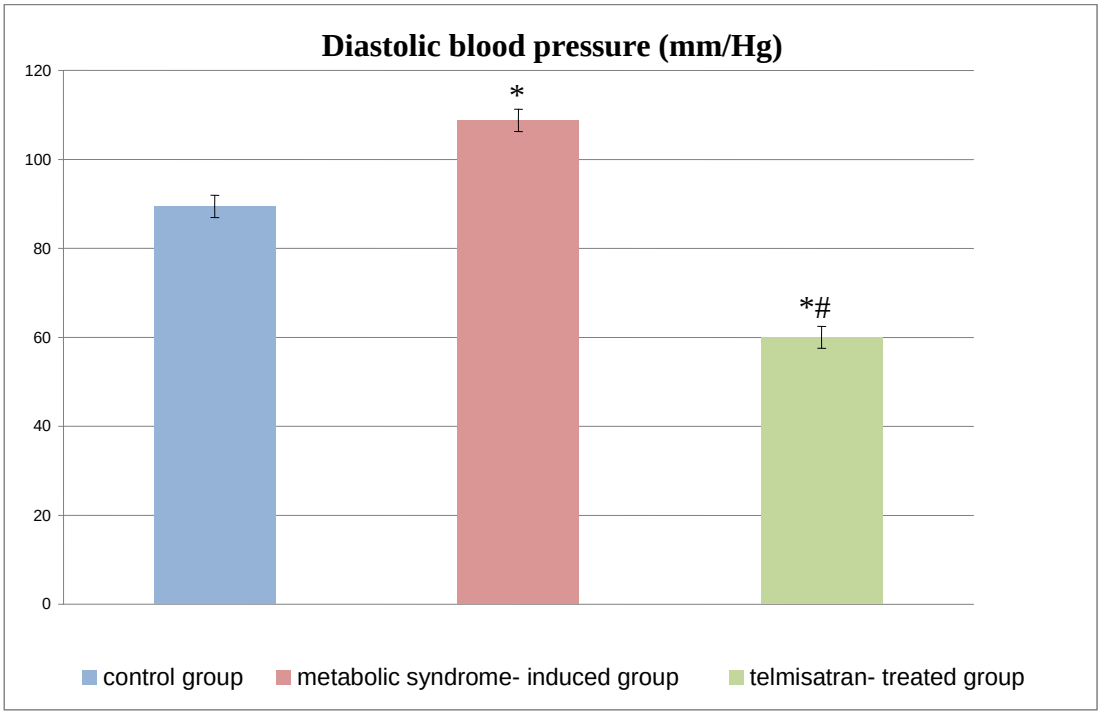


Figure (14): Histogram showing effect of telmisartan (5mg/kg/day) for 2 weeks on diastolic blood pressure in experimentally induced metabolic syndrome (by administration of 10%L-fructose solution in drinking water for 5 weeks).

Data are presented as mean ± SEM

***** significant ($p < 0.05$) compared to control group

significant ($p < 0.05$) compared to metabolic syndrome- induced group.

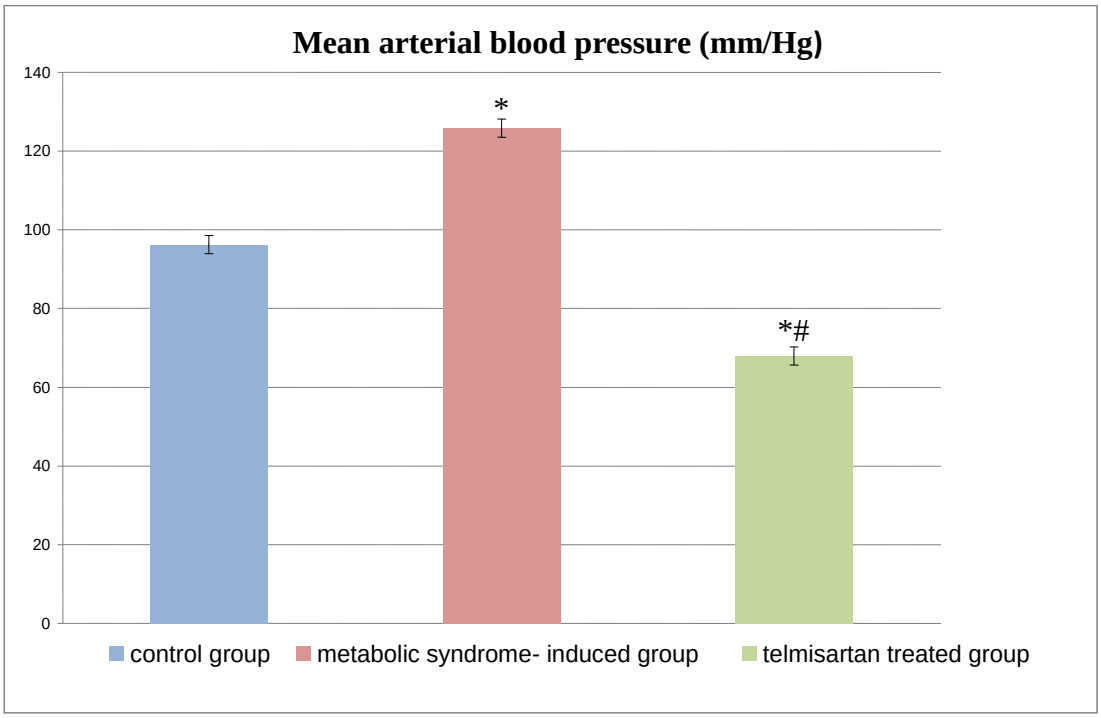


Figure (15): Histogram showing effect of telmisartan (5mg/kg/day) for 2weeks on mean blood pressure in experimentally induced metabolic syndrome (by administration of 10%L-fructose solution in drinking water for 5 weeks).

Data are presented as mean ± SEM

***** significant ($p < 0.05$) compared to control group

$^{\#}$ significant ($p < 0.05$) compared to metabolic syndrome- induced group.

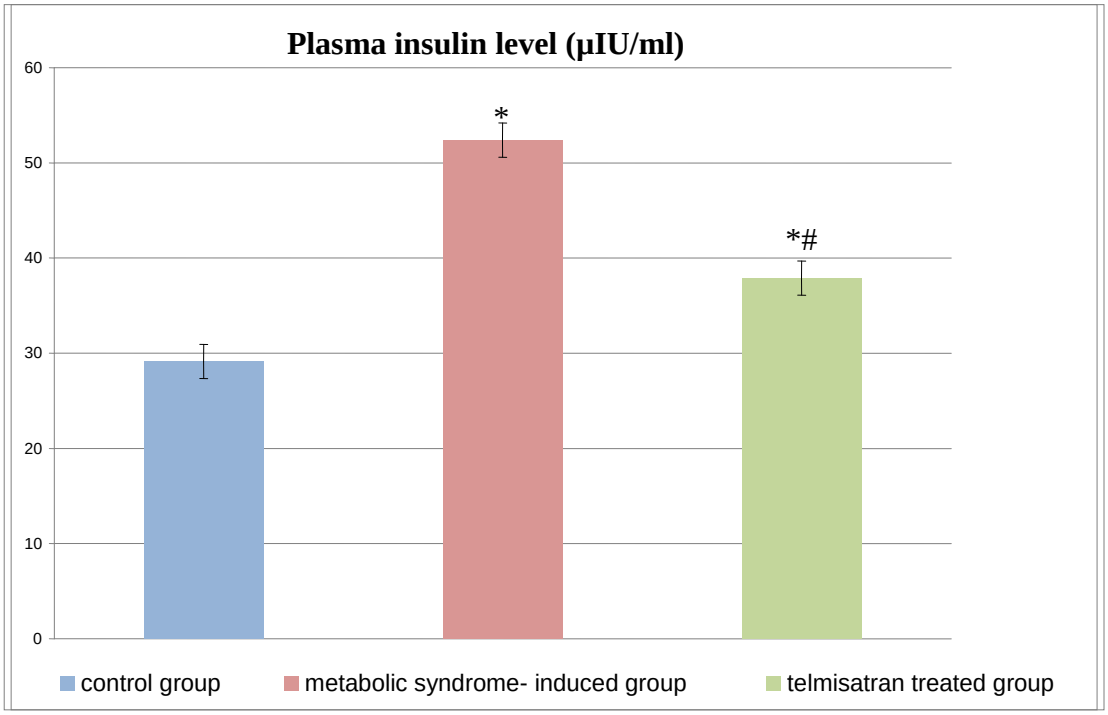


Figure (16): Histogram showing effect of telmisartan (5mg/kg/day) for 2weeks on plasma insulin level in experimentally induced metabolic syndrome (by administration of 10%L-fructose solution in drinking water for 5 weeks).

Data are presented as mean ± SEM

***** significant ($p < 0.05$) compared to control group

significant ($p < 0.05$) compared to metabolic syndrome- induced group.

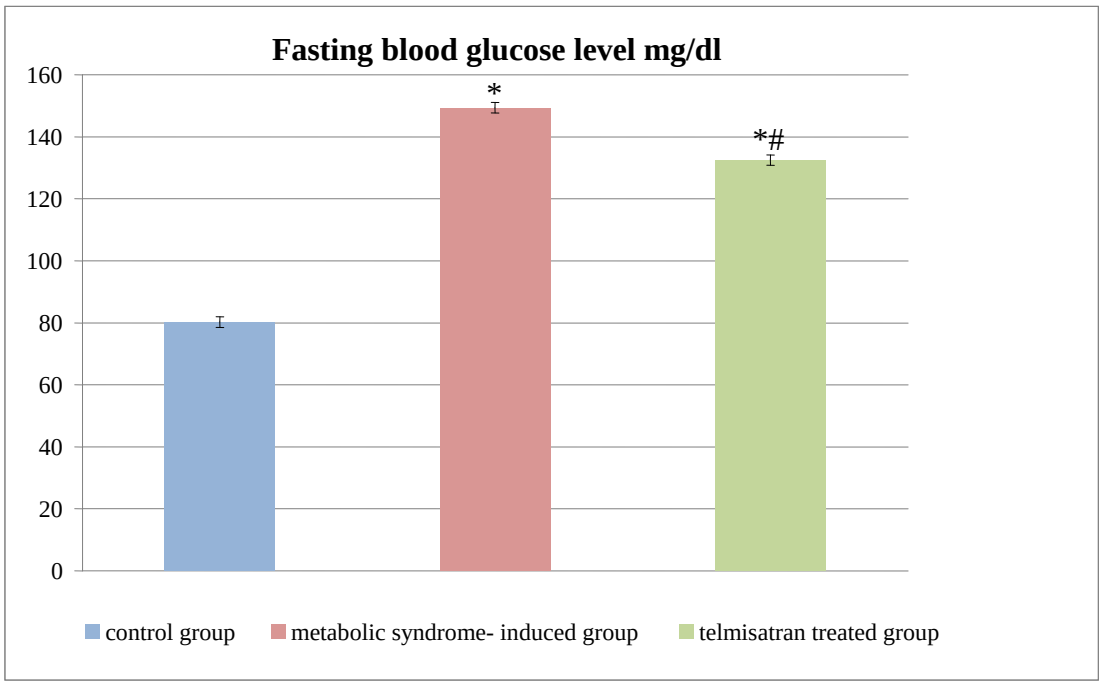


Figure (17): Histogram showing effect of telmisartan (5mg/kg/day) for 2weeks on fasting blood glucose level in experimentally induced metabolic syndrome (by administration of 10%L-fructose solution in drinking water for 5 weeks).

Data are presented as mean ± SEM

***** significant ($p < 0.05$) compared to control group

significant ($p < 0.05$) compared to metabolic syndrome- induced group.

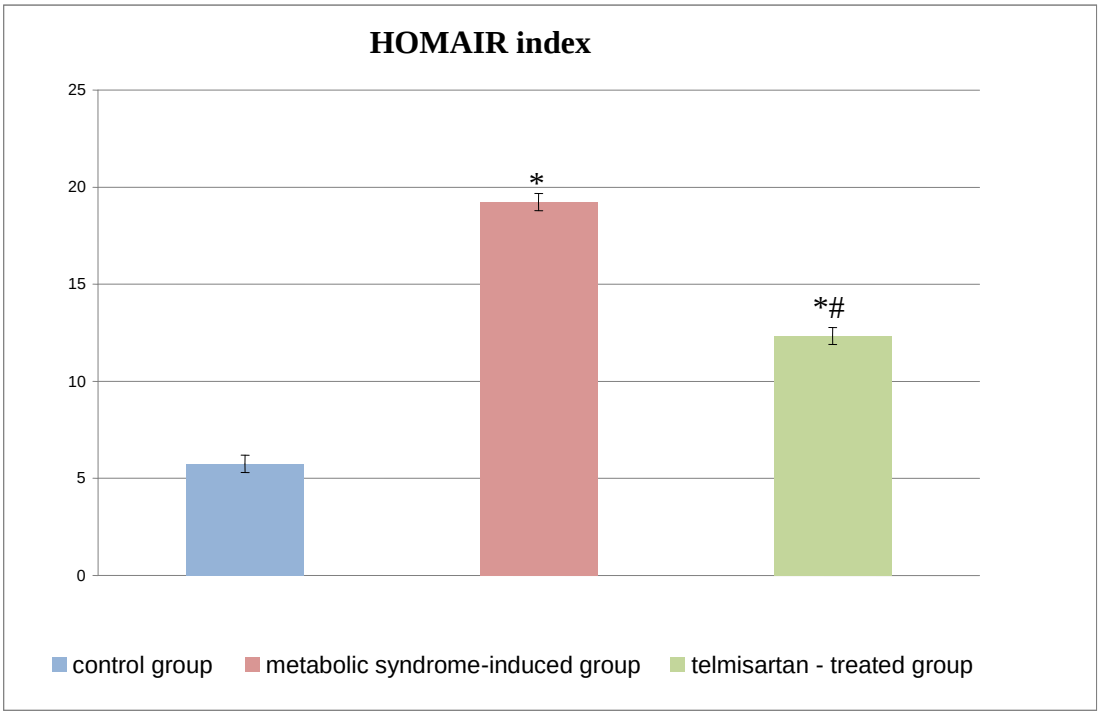


Figure (18): Histogram showing effect of telmisartan (5mg/kg/day) for 2weeks on HOMA-IR index in experimentally induced metabolic syndrome (by administration of 10%L-fructose solution in drinking water for 5 weeks).

Data are presented as mean ± SEM

***** significant ($p < 0.05$) compared to control group

$^{\#}$ significant ($p < 0.05$) compared to metabolic syndrome- induced group.

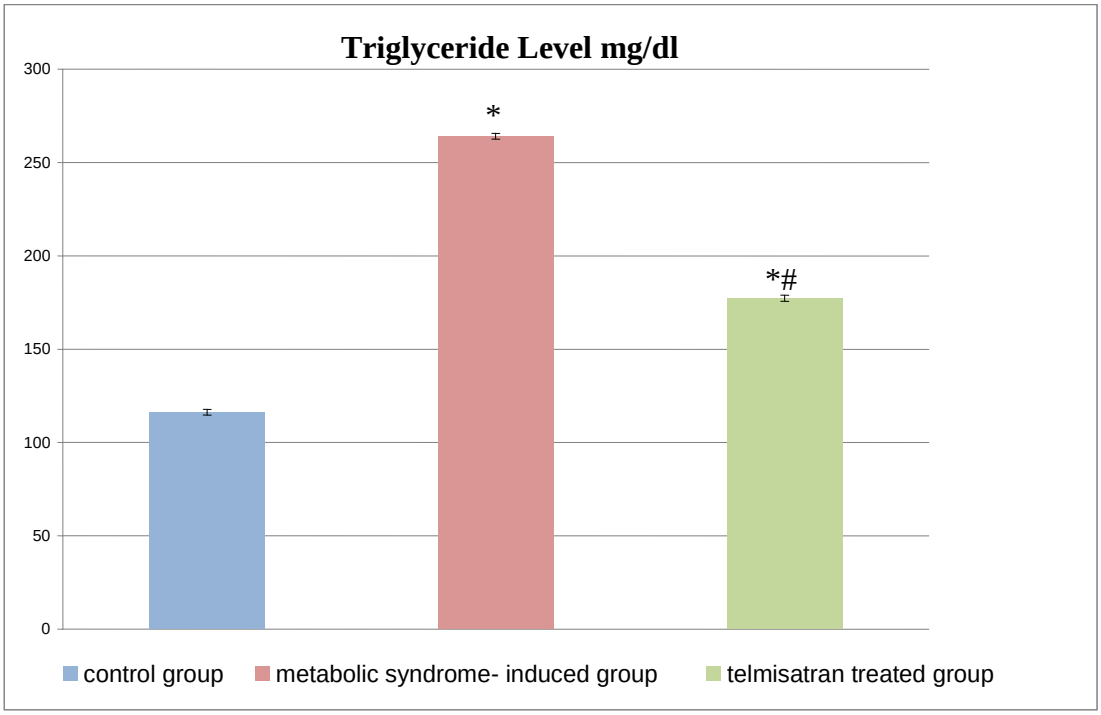


Figure (19): Histogram showing effect of telmisartan (5mg/kg/day) for 2weeks on triglyceride level in experimentally induced metabolic syndrome (by administration of 10%L-fructose solution in drinking water for 5 weeks).

Data are presented as mean ± SEM

***** significant ($p < 0.05$) compared to control group

\# significant ($p < 0.05$) compared to metabolic syndrome- induced group.

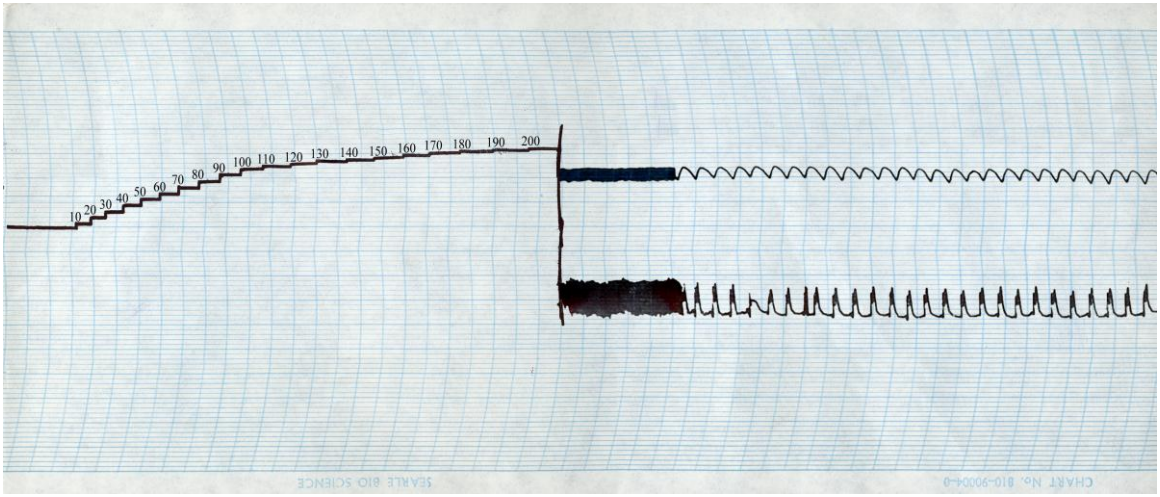


Figure (20): Blood pressure tracing of control normal rat (group I). (A typical trace of 8 seprate experiments).

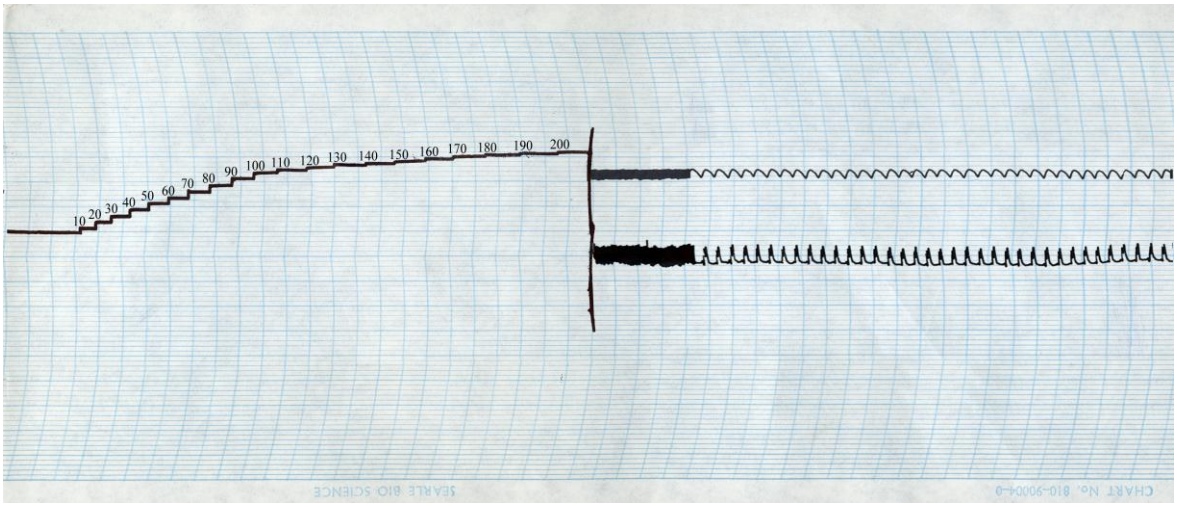


Figure (21): Blood pressure tracing of Vehicle group (group II). (A typical trace of 8 seprate experiments).

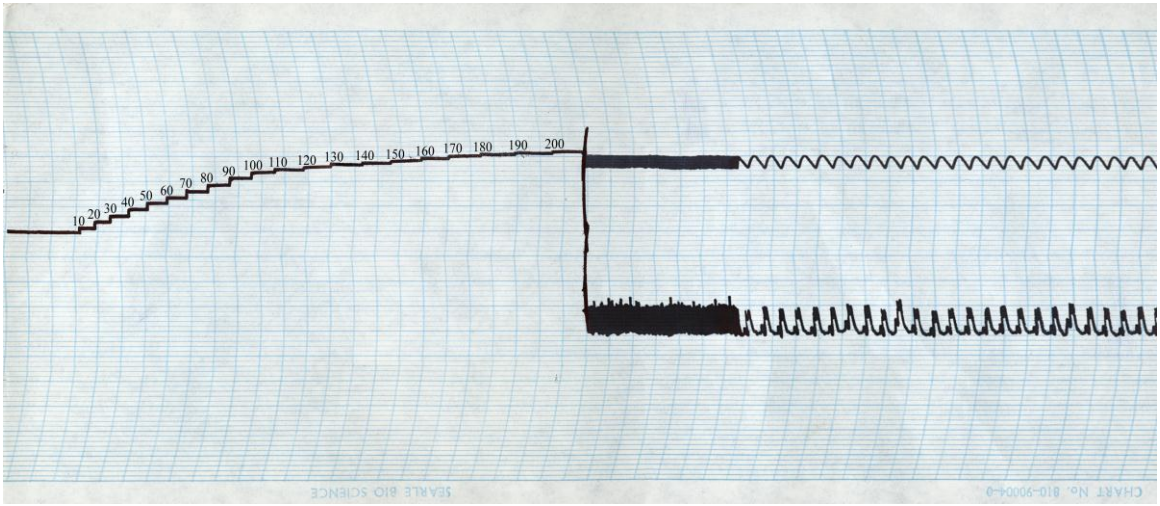


Figure (22): Blood pressure tracing of fructose- induced hypertension in metabolic syndrome group

(A typical trace of 8 seprate experiments).

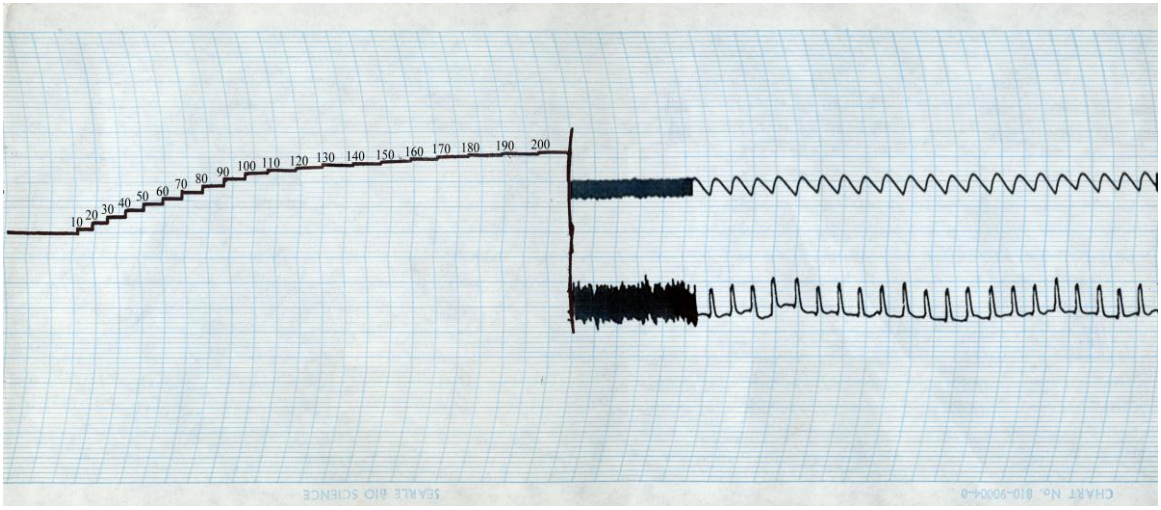


Figure (23): Blood pressure tracing of telmisartan-treated group.

(A typical trace of 8 seprate experiments).

2. The effects of telmisartan administration in a dose of (5 mg/kg/day) for 2 weeks on arterial blood pressure, lipid profiles, histopathology of aorta in DOCA-salt hypertensive hypercholesterolemia-induced group:

It should be mentioned that there was no significant difference between the vehicle group (group II) which received 0.5% Carboxy-methyl cellulose and the control group (group I) so all statistical analysis was done in comparison to the control group (group I).

2-1.The effect on arterial blood pressure

A- Systolic blood pressure :

Administration of a suspension of deoxycorticosterone acetate (DOCA) in olive oil at weekly intervals in a dose of (50mg/kg) subcutaneously combined with a solution of 1% sodium chloride solution containing 0.2% KCI and 2% glucose in the drinking water for a period of 6 weeks resulted in significant rise ($P < 0.001$) of SBP from 110.22±1.34 mmHg in control group (group I) to 166.25±2.75mm Hg in DOCA- salt hypertensive hypercholesterolemic group (group III). In DOCA –salt hypertensive hypercholesterolemic treated group with telmisartan in a dose of 5 mg/kg/day for 2weeks(group IV) there was significant decrease ($P < 0.001$) of SBP to 87.50±1.62 mm Hg compared to non treated group (group III). Comparing the result of the treated group (group IV) to that of control group (group I), there was significant differences ($P < 0.001$) between the two groups(Table 8, Fig.24,31,32,33,34)

B-Diastolic blood pressure:

Regarding the diastolic blood pressure it was 87.95±1.47 mm Hg in control group (group I) , and there was significant increase ($P < 0.001$)

of DBP to121.25±4.40 mmHg in DOCA- salt hypertensive hypercholesterolemic group (group III)compared to control group . Telmisartan -treated group (5mg/kg /day) for 2weeks (group IV) showed significant decrease ($P < 0.001$) of DBP to 66.88±4.62mm Hg compared to(group III). Also there was significant ($P < 0.001$) difference between (group IV) and (group I). (Table 8, Fig.25,31,32,33,34)

***c-Mean arterial blood pressure*:**

By calculating the mean arterial blood pressure it was 95.88±1.32mm Hg in control group (group I).In DOCA- salt hypertensive hypercholesterolemic group (group III) MBP increased significantly($P < 0.001$) to a mean of 136.25±1.80mm Hg compared to control group. In telmisartan-treated group (group IV) MBP was significantly ($P < 0.001$) decrease to a mean of 73.75±0.39 mm Hg. There was also significant ($P < 0.001$) difference between telmisartan-treated group and control group (Table 8, Fig.26,31,32,33,34).

Table (8): Effect of telmisartan (5 mg/kg/day) treatment for 2 weeks on arterial blood pressure in DOCA–salt hypertensive hypercholesterolemia in rats .

Parameter / Groups	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Mean arterial blood pressure (mmHg)
Control group	110.22± 1.34	87.95 ± 1.47	95.88 ± 1.32
Vehicle group	111.12± 0.23	89.90± 0.05	97.03 ± 1.12
DOCA –salt hypertensive hypercholesterolemic - induced group	166.25 ± 2.75*	121.25 ±1.40*	136.25 ± 1.80*
Percent change (%)	↑ 60.2%	↑47.7	↑ 41.4
telmisartan-treated group	87.50 ± 1.62* #	66.88 ± 1.62* #	73.75 ± 0.39* #
Percent change (%)	↓ 47.9	↓44.8	↓ 45.8

Data represented as Mean ± SEM (n = 8)

* significant ($p < 0.05$) compared to control group

significant ($p < 0.05$) compared to DOCA–salt hypertensive hypercholesterolemic-induced group.

2-2.The effect on lipid profiles:

High fat diet supplementation (2% cholesterol) for 6 weeks resulted in significant rise ($P < 0.001$) of total cholesterol from 91.07± 0.51 mg/dl in control group (group I) to 202.55 ± 4.26 mg/dl in hypertensive hypercholesterolemic group (group III)& significant rise ($P < 0.001$) of triglyceride from 118.45 ± 3.044 mg/dl in control group to 196.41 ± 2.93 mg/dl in hypercholesterolemic group (group III) & significant rise ($P < 0.001$) of LDL from26.75±1.04 mg/dl in control group to143.47±4.06 mg/dl in hypercholesterolemic group (group III) and finally significant decrease of HDL ($P < 0.001$) from 41.08 ±0.72mg/dl

in control group to 19.80±0.57mg/dl in hypertensive hypercholesterolemic group (group III). (Table 9, Fig.27,28,29,30).

- **Total cholesterol:**

Treatment of hypercholesterolemic rats in (group IV) with telmisartan (5mg/kg/day) oral for 2weeks reduced total cholesterol significantly ($P < 0.01$) to 133.55 ± 2.78 mg/dl compared to (group III). comparing the treated group (group IV) and control group (group I) there was significant($P < 0.01$) difference in between. (Table 9, Fig.27).

- **Triglyceride:**

Telmisartan -treated group (group IV) showed reduction of triglyceride level significantly ($P < 0.001$) from 196.41 ± 2.93 mg/dl to 147.41 ± 1.57 mg/dl compared to non treated group (group III). There was also significant difference ($P < 0.05$) difference between telmisartan -treated group (group IV) 147.41 ± 1.57 mg/dl and control group (group I)118.45 ± 3.044 mg/dl. (Table 9, Fig.28).

- **Low density lipoprotein(LDL):**

Treatment the rats with telmisartan in (group IV) resulted in significantly ($P < 0.05$) decrease of LDL from 143.47±4.06mg/dl to 77.46±2.68 mg/dl compared to hypercholesterolemic non treated group (group III). In comparison there was significant ($P < 0.05$) difference between telmisartan treated group and control group. (Table 9, Fig.29).

- **High density lipoprotein(HDL):**

Treatment of (group IV) with telmisartan increased HDL significantly ($P < 0.05$) from 19.80 ± 0.57mg/dl to 26.59 ± 0.61 mg/dl compared to non treated group (group III). Comparing telmisartan treated group and control group there was significant ($P < 0.05$) difference in between**.** (Table 9, Fig.30).

Table (9): Effect of telmisartan (5 mg/kg/day) treatment on lipid profiles in DOCA –salt hypertensive hypercholesterolemia in rats .

Parameter / Group	Total cholesterol(mg/dl)	Triglyceride (mg/dl)	LDL (mg/dl)	HDL (mg/dl)
Control group	91.07 ± 0.51	118.45 ± 3.04	26.75 ± 1.04	41.08 ± 0.72
Vehicle group	92.12± 0.37	118.80± 1.57	27.01± 0.51	41.32 ± 1.02
DOCA–salt hypertensive hypercholesterolemic induced group.	202.55±4.26*	196.41±2.93*	143.47±4.06*	19.80±0.57*
Percent change	↑>100%	↑ 69.01	↑ >100%	↓53.6
Telmisartan- treated group.	133.55 ± 2.78*#	147.41±1.57*#	77.46±2.86*#	26.59± 0.61*#
Percent change	↓34.1%	↓24.9%	↓ 45.9%	↑ 34.3

Data represented as Mean ± SEM (n = 8)

* significant ($p < 0.05$) compared to control group

significant ($p < 0.05$) compared to DOCA–salt hypertensive hypercholesterolemic induced group

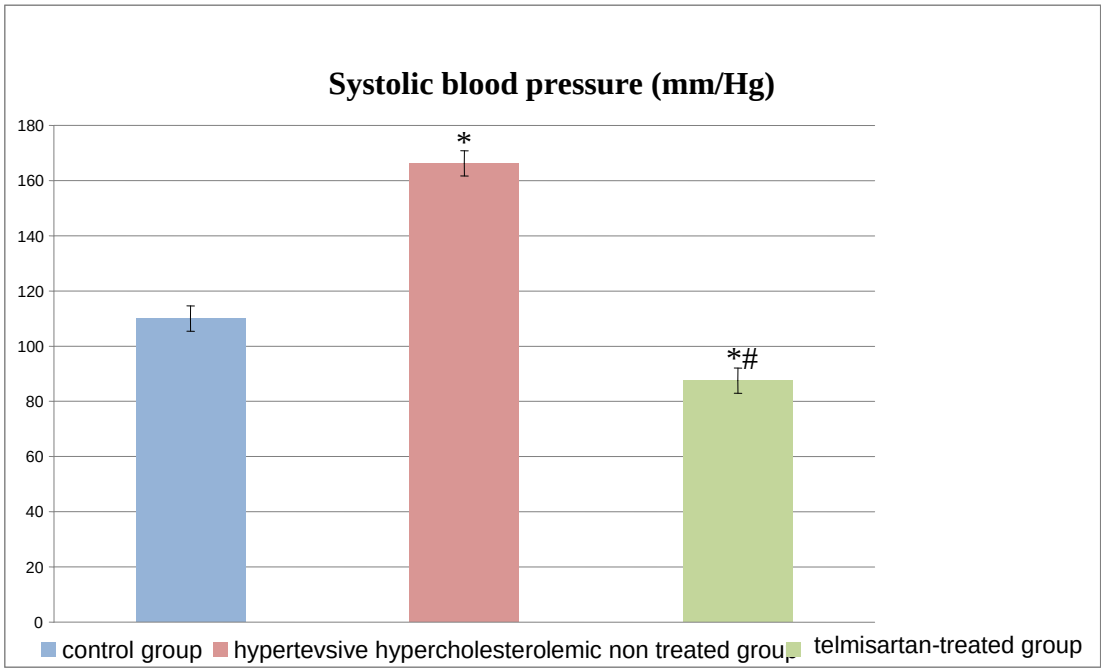


Figure (24): Histogram showing effect of telmisartan (5mg/kg/day) for 2 weeks on systolic blood pressure in experimentally induced hypertensive hypercholesterolemia (by given a suspension of (DOCA) in olive oil at weekly intervals in a dose of (50mg/kg) subcutaneously + fed standard chow supplemented with 2% cholesterol for a period of 6 weeks).

Data are presented as mean ± SE

***** significant ($p < 0.05$) compared to control group

\# significant ($p < 0.05$) compared to DOCA–salt hypertensive hypercholesterolemic induced group

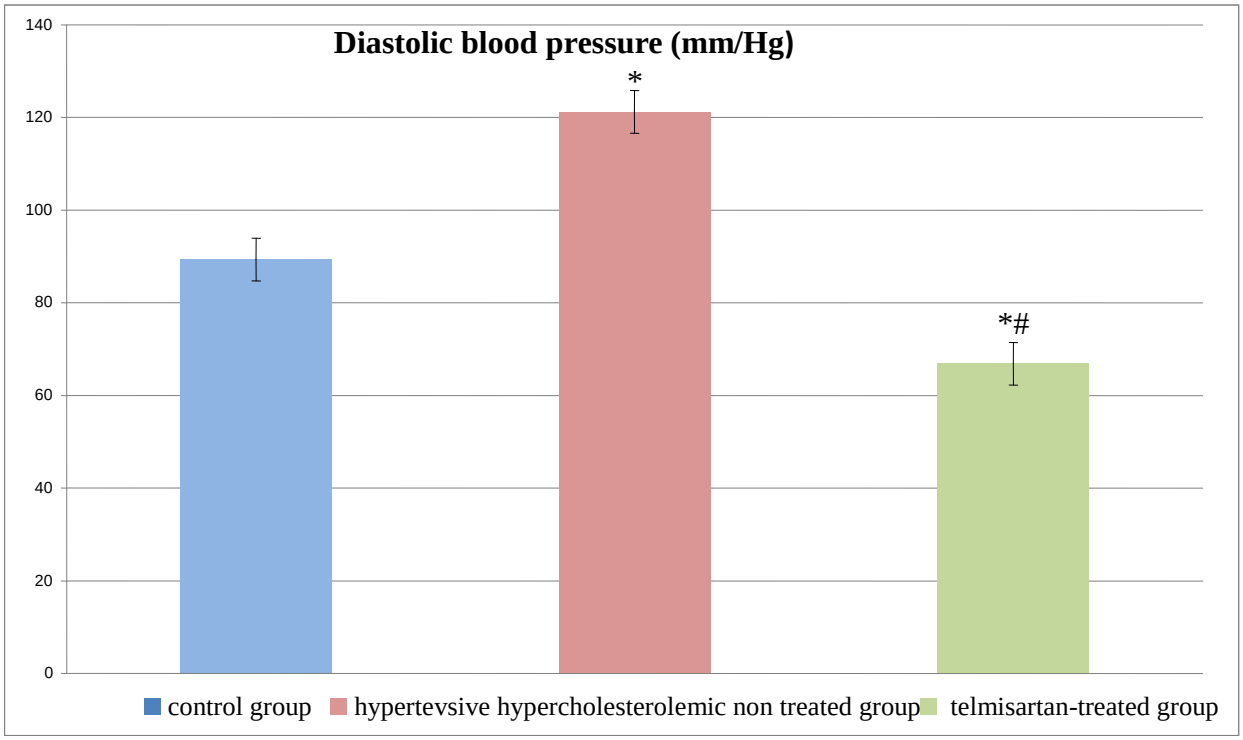


Figure (25): Histogram showing effect of telmisartan (5mg/kg/day) for 2 weeks on diastolic blood pressure in experimentally induced hypertensive hypercholesterolemia (by given a suspension of (DOCA) in olive oil at weekly intervals in a dose of (50mg/kg) subcutaneously + fed standard chow supplemented with 2% cholesterol for a period of 6 weeks).

Data are presented as mean ± SE

***** significant ($p < 0.05$) compared to control group

\# significant ($p < 0.05$) compared to DOCA–salt hypertensive hypercholesterolemic induced group

.

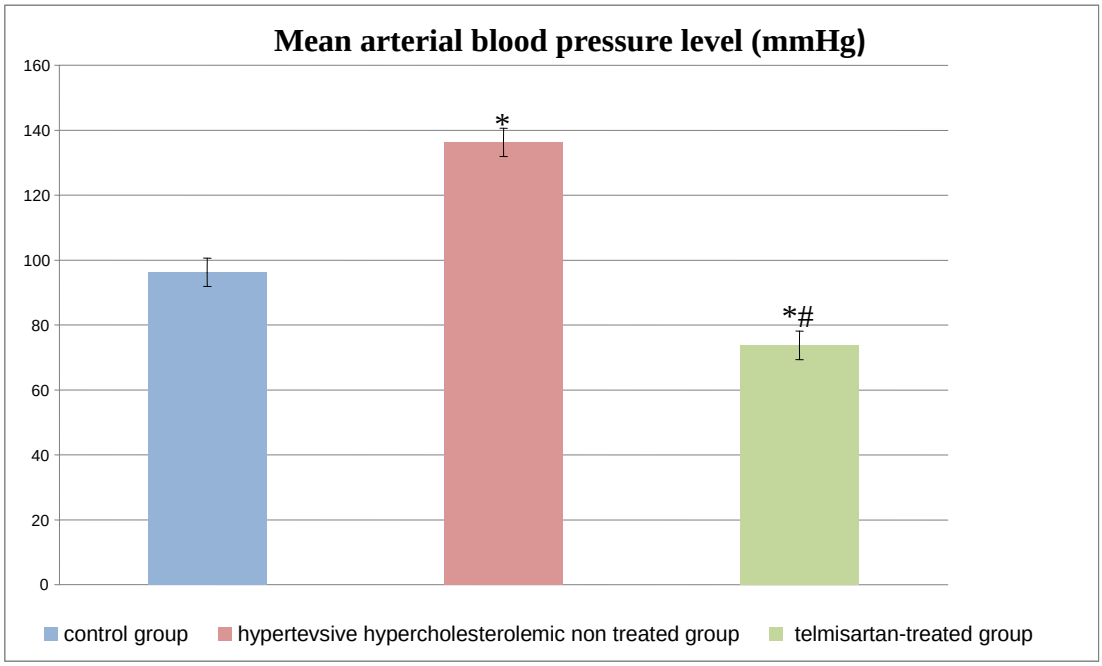


Figure (26): Histogram showing effect of telmisartan (5mg/kg/day) for 2 weeks on mean blood pressure in experimentally induced hypertensive hypercholesterolemia (by given a suspension of (DOCA) in olive oil at weekly intervals in a dose of (50mg/kg) subcutaneously + fed standard chow supplemented with 2% cholesterol for a period of 6 weeks).

Data are presented as mean ± SE

***** significant ($p < 0.05$) compared to control group

\# significant ($p < 0.05$) compared to DOCA–salt hypertensive hypercholesterolemic induced group

.

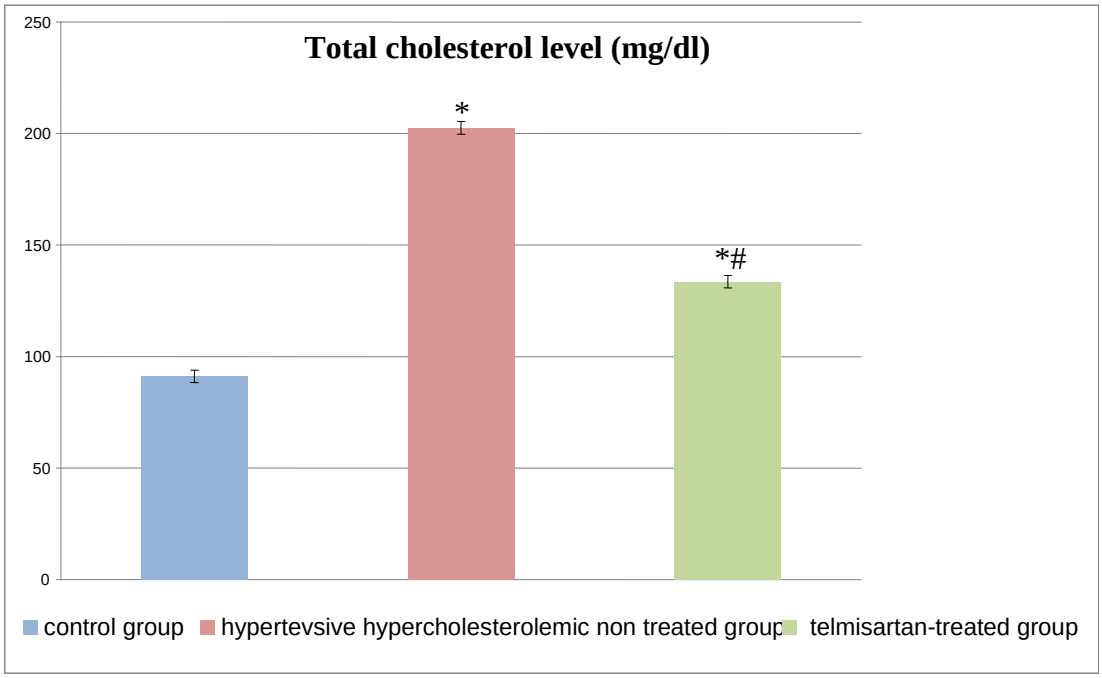


Figure (27): Histogram showing effect of telmisartan (5mg/kg/day) for 2 weeks on serum total cholesterol level in experimentally induced hypertensive hypercholesterolemia (by given a suspension of (DOCA) in olive oil at weekly intervals in a dose of (50mg/kg) subcutaneously + fed standard chow supplemented with 2% cholesterol for a period of 6 weeks).

Data are presented as mean ± SE

***** significant ($p < 0.05$) compared to control group

significant ($p < 0.05$) compared to DOCA–salt hypertensive hypercholesterolemic induced group

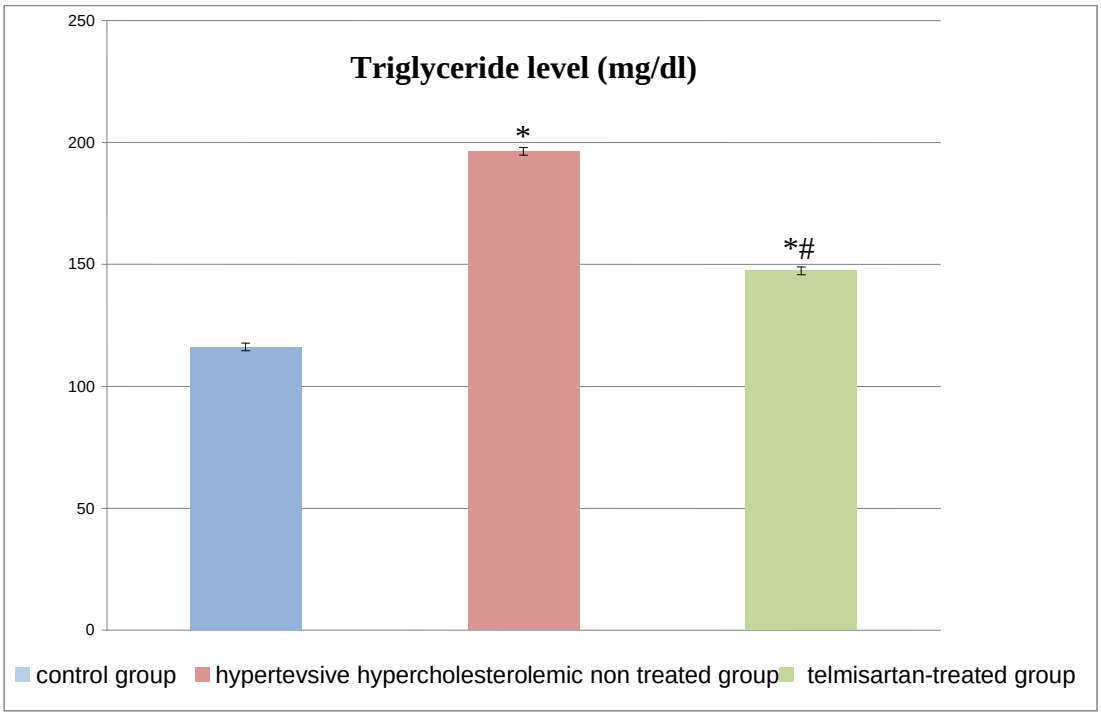


Figure (28): Histogram showing effect of telmisartan (5mg/kg/day) for 2 weeks on serum triglyceride level in experimentally induced hypertensive hypercholesterolemia (by given a suspension of (DOCA) in olive oil at weekly intervals in a dose of (50mg/kg) subcutaneously + fed standard chow supplemented with 2% cholesterol for a period of 6 weeks).

Data are presented as mean ± SE

***** significant ($p < 0.05$) compared to control group

\# significant ($p < 0.05$) compared to DOCA–salt hypertensive hypercholesterolemic induced group

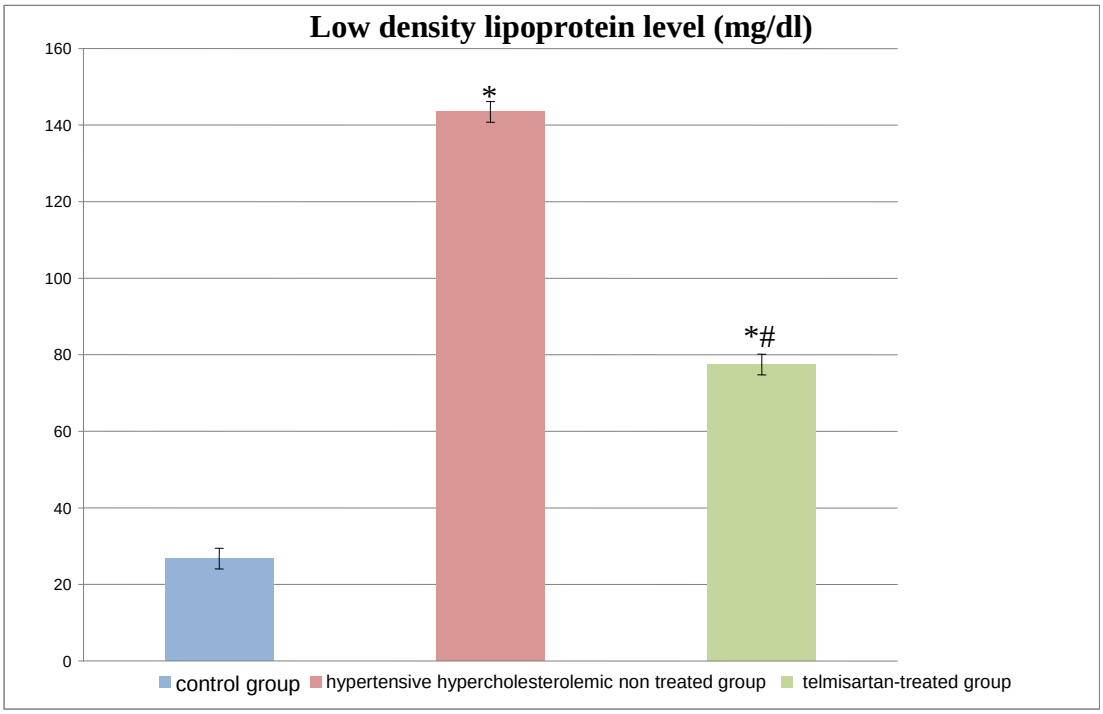


Figure (29): Histogram showing effect of telmisartan (5mg/kg/day) for 2 weeks on low density lipoprotein cholesterol level (LDL-C) in experimentally induced hypertensive hypercholesterolemia (by given a suspension of (DOCA) in olive oil at weekly intervals in a dose of (50mg/kg) subcutaneously + fed standard chow supplemented with 2% cholesterol for a period of 6 weeks).

Data are presented as mean ± SE

***** significant ($p < 0.05$) compared to control group

\# significant ($p < 0.05$) compared to DOCA–salt hypertensive hypercholesterolemic induced group

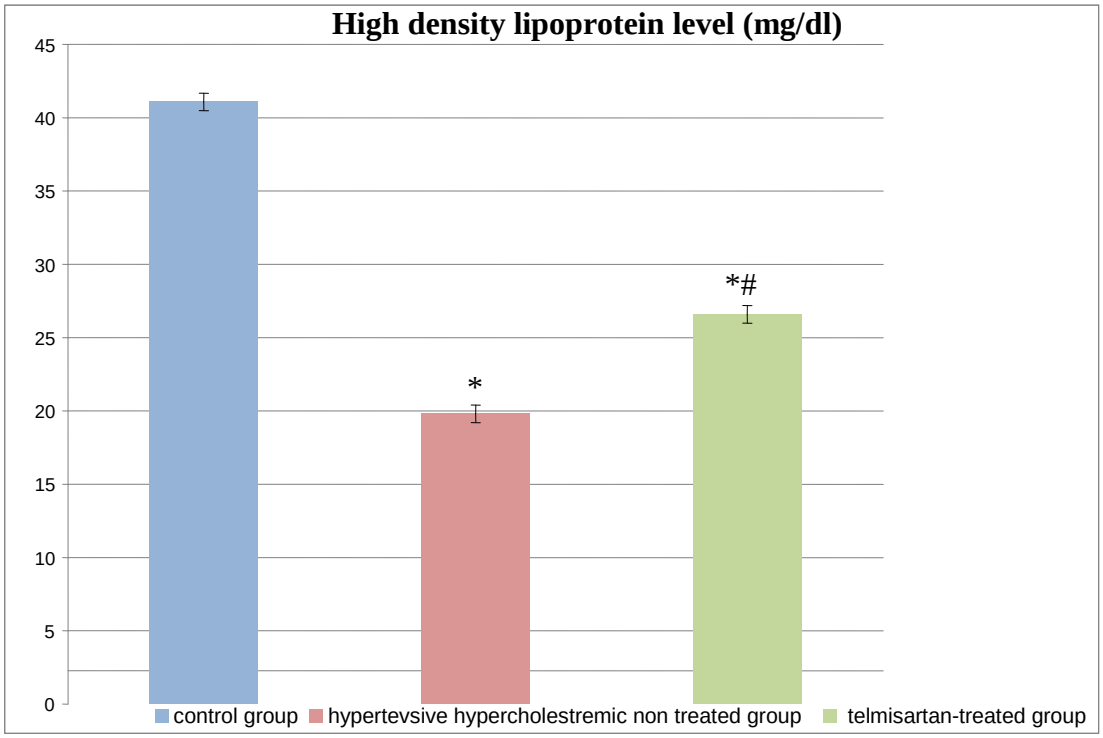


Figure (30): Histogram showing effect of telmisartan (5mg/kg/day) for 2 weeks on Low density lipoprotein cholesterol (LDL-C)level in experimentally induced hypertensive hypercholesterolemia (by given a suspension of (DOCA) in olive oil at weekly intervals in a dose of (50mg/kg) subcutaneously + fed standard chow supplemented with 2% cholesterol for a period of 6 weeks).

Data are presented as mean ± SE

***** significant ($p < 0.05$) compared to control group

\# significant ($p < 0.05$) compared to DOCA–salt hypertensive hypercholesterolemic induced group

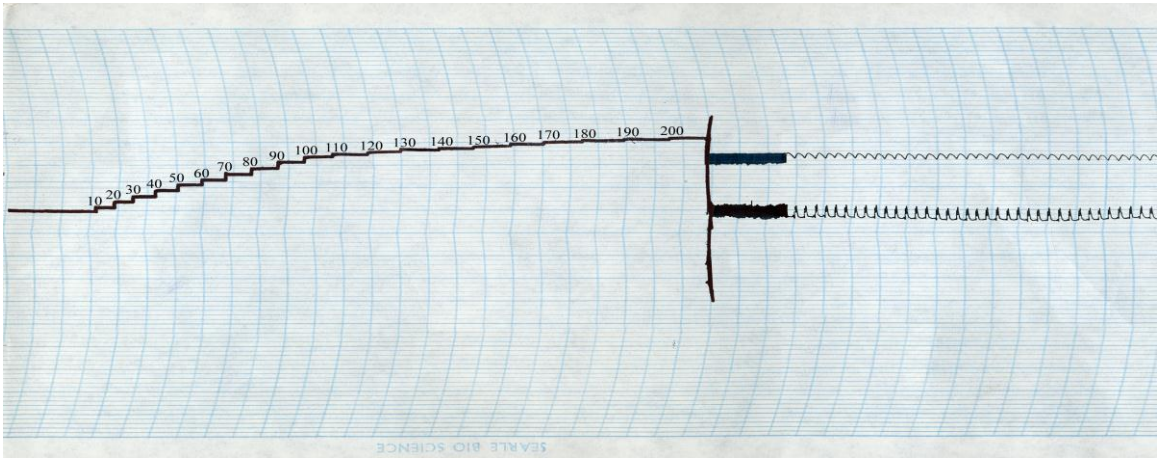


Figure (31): Blood pressure tracing of control normal rat
(A typical trace of 8seprate experiments**)**

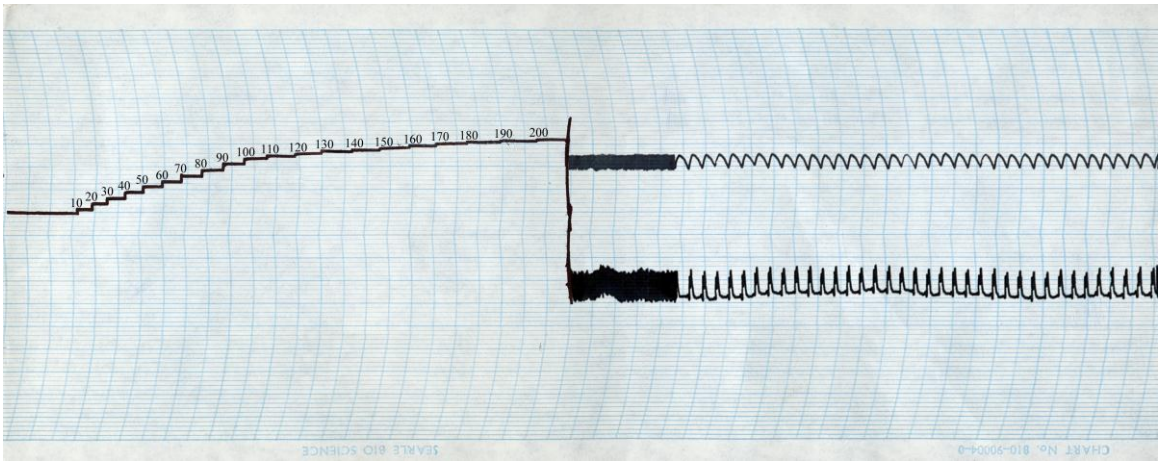


Figure (32): Blood pressure tracing of vehicle group.
(A typical trace of 8 seprate experiments**)**

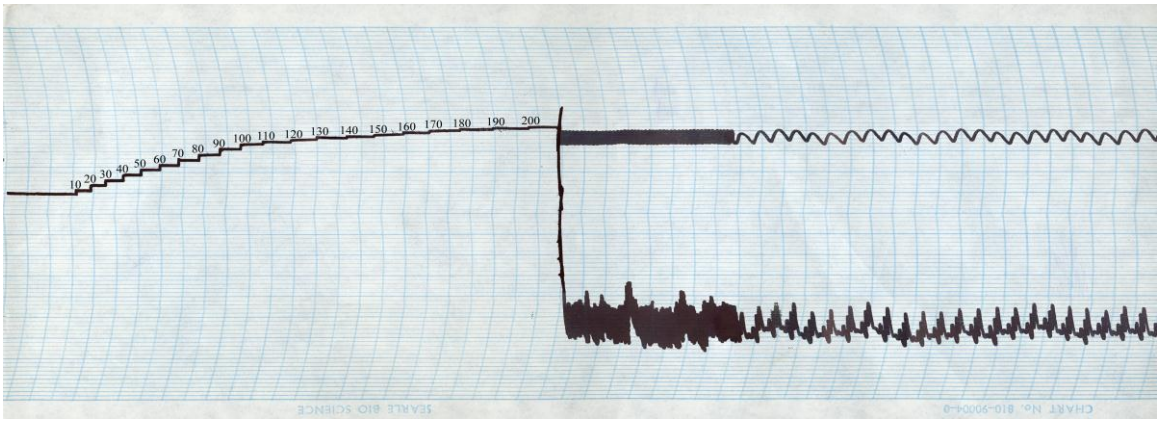


Figure (33): Blood pressure tracing of DOCA-salt induced hypertension in hypertensive hypercholesterolemic group.

(A typical trace of 8 seprate experiments)

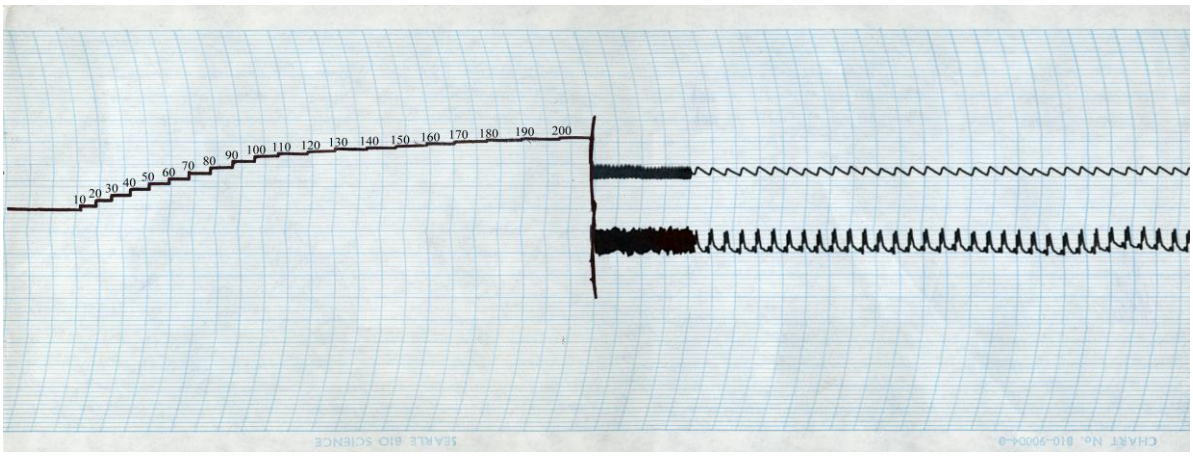


Figure (34): Blood pressure tracing of telmisartan treated rat.

(A typical trace of 8 seprate experiments)

2-3- Histopathological evaluation of the aorta:

Histological examination of a cut section of the aorta of control group (group I) and the vehicle group (group II) showed that the wall of the aorta consists of a tunica intima, tunica media, and tunica adventitia. The tunica intima consists of an endothelial coat of flattened squamous cells resting on a complete basal lamina and is supported by a subendothelial loose connective tissue.

The tunica media consists largely of elastic, concentric laminae and variable amounts of smooth muscle cells. The tunica adventitia contains bundles of collagen fibers and a few elastic fibers, both of which have a loose, helical arrangement (Fig.35,36).

In hypercholesterolemic group (group III); there were focal ulcerated endothelial cells of the intima and formation of needle- like (spindle shaped) cholesterol clefts"fatty streaks" in the subintimal tissue (Fig.37) with collection of foamy histocytes, fat globules. The media and adventitia showed fibrosis and inflammatory cell infiltration (Fig.38)

In telmisartan-treated group (group IV), telmisartan treatment markedly decreased the size of needle- like (spindle shaped) cholesterol clefts, also decreased the foamy and inflammatory cell infiltration. No regeneration of the endothelial cells of the intima was observed (Fig.39)

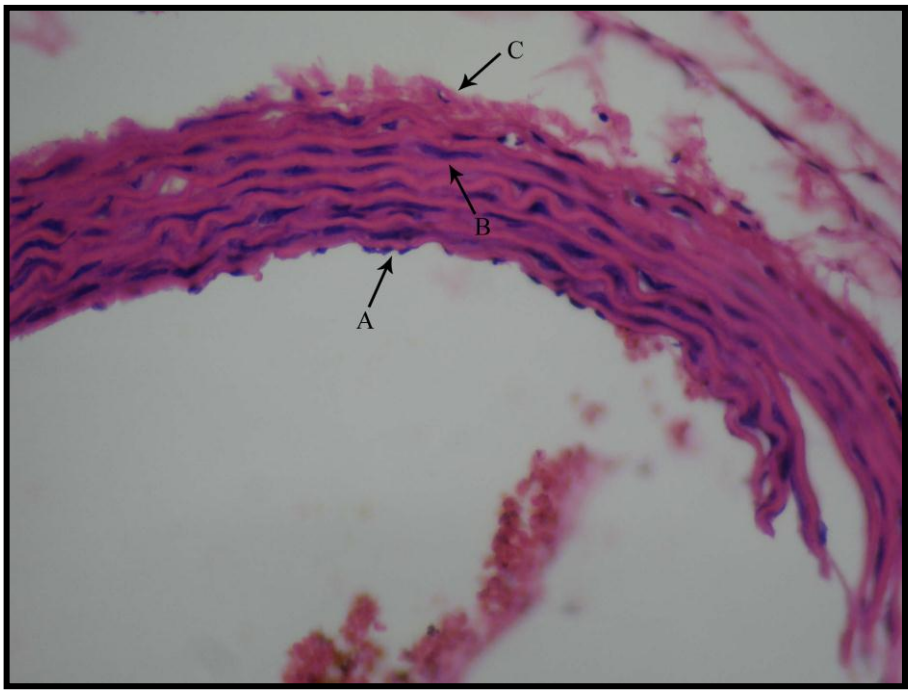


Figure (35): A photomicrograph of a cut section in the aorta of a control rat (group I) showing A)intact flat endothelial cell lining B) elastic media C)well fitted adventitia. (H & E x 400).

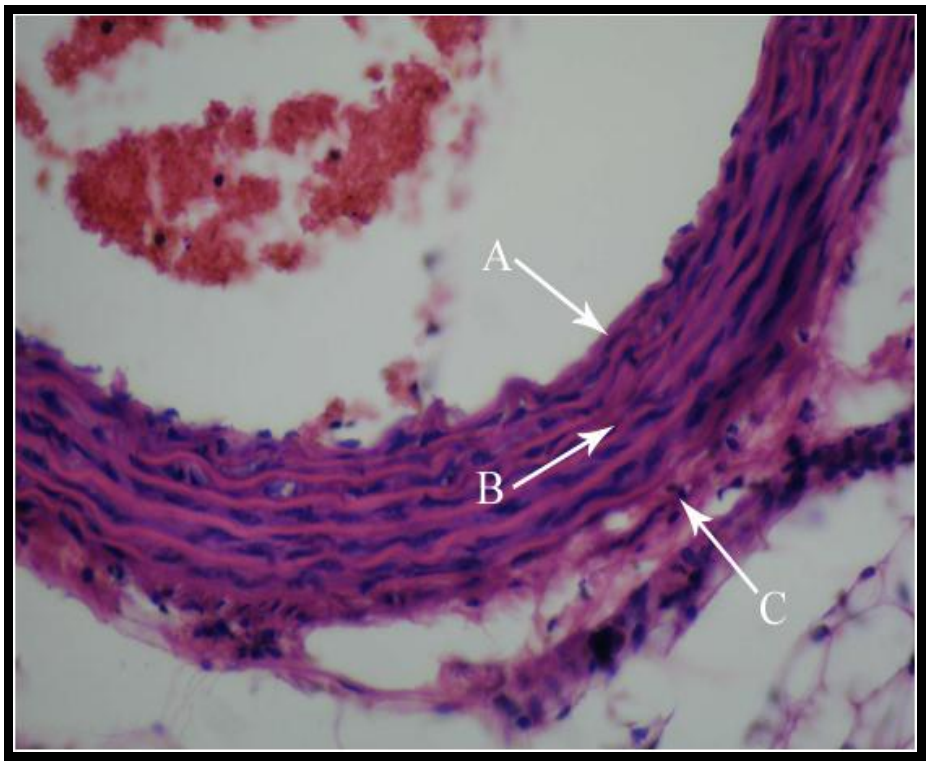


Figure (36): A photomicrograph of a cut section in the aorta of a rat of vehicle group (group II) showing A)intact flat endothelial cell lining B) elastic media C)well fitted adventitia. (H & E x 400).

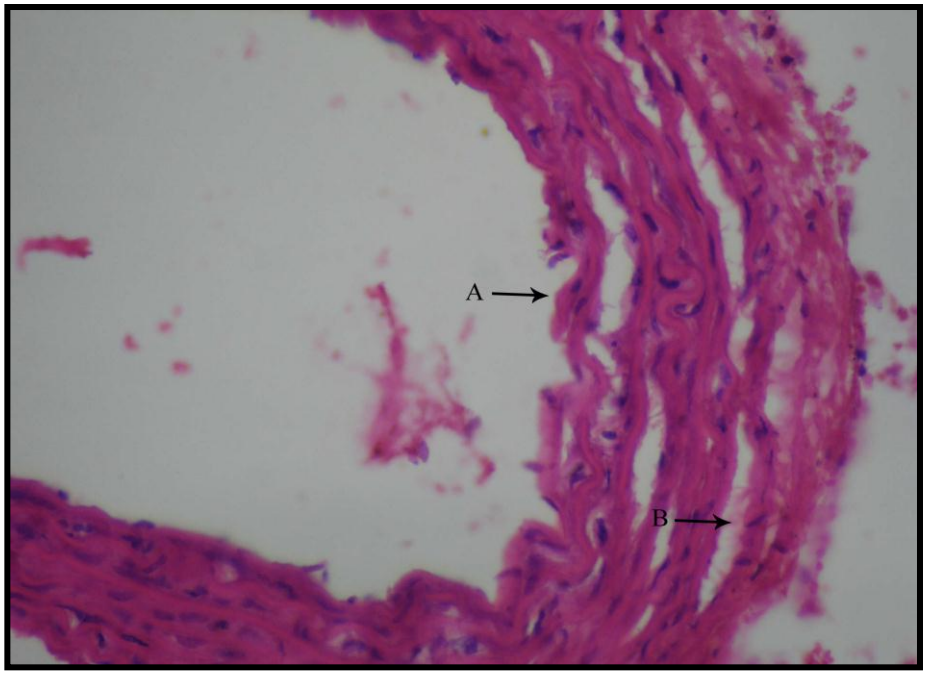


Figure (37): A photomicrograph of a cut section in the aorta of a hypercholesterolemic rat (group III) showing A)ulcerated endothelial cells of the intima B)formation of (spindle shaped) cholesterol clefts with degeneration. (H x & E x 400)

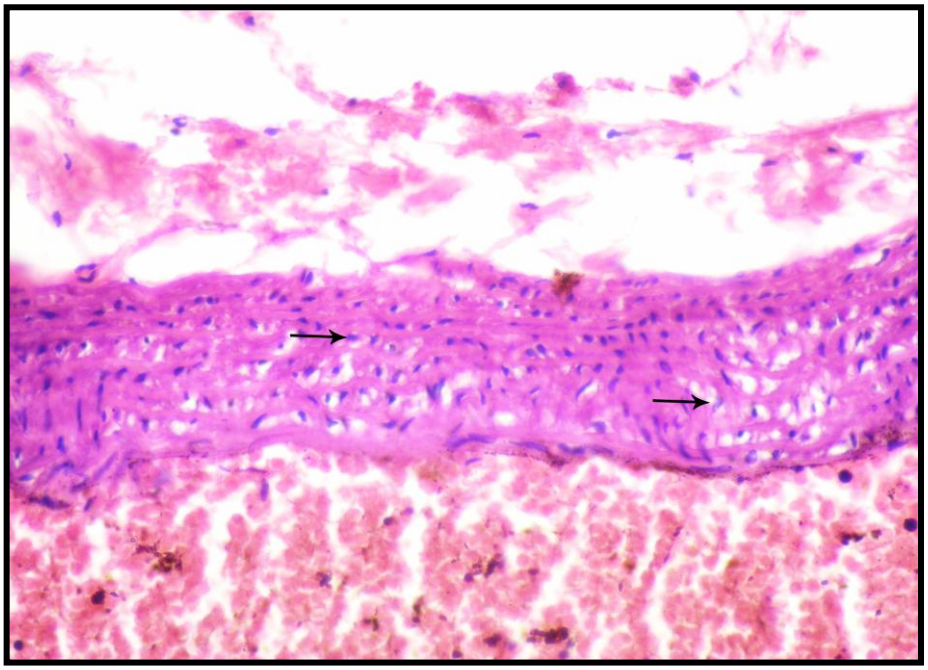


Figure (38): A photomicrograph of a cut section in the aorta of a hypercholesterolemic rat (group III) showing the intima with collection of foamy histocytes and fat globules. The media and adventitia showed fibrosis and inflammatory cell infiltration. (H x & E x 400)

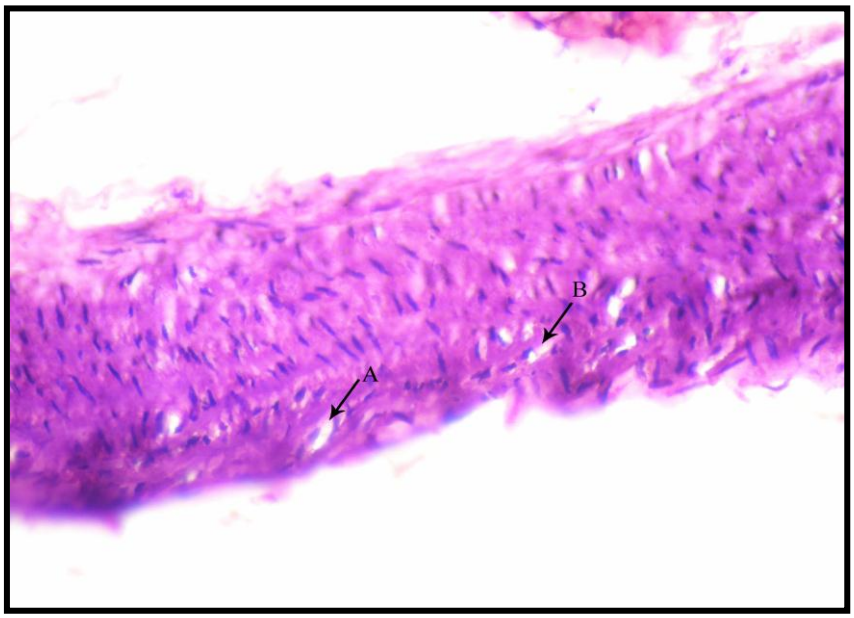


Figure (39): A photomicrograph of a cut section in the aorta of a rat of telmisartan treated group (groupIV) showing A)marked decrease of the size of fatty streaks, B) slightly decrease of the number of the foamy and the inflammatory cell. No Regeneration of the endothelial cells of the intima was observed. (H x & E x 400).

B.IN VITRO EXPERIMENTS:

1. Effects on isolated perfused rabbit's heart:

It was observed that methanol which used as organic solvent for telmisartan has no effect on the isolated heart in an increasing dose (1,3, 10,30,100,300,1000 μg)(Fig. 41)

It was observed that telmisartan in doses (1,3, and 10 μg) did not produce any change in the amplitude of contraction of isolated perfused rabbit's heart. However telmisartan in doses (30, 100, 300, and 1000μg) produced increase of the force of spontaneous contraction of the isolated perfused rabbit's heart. (Table 10, Fig.42).

Table (10): The effect of telmisartan in the amplitude of spontaneous contraction of isolated perfused rabbit's heart (n=6).

Dose of telmisartan (μg)	Amplitude of contraction before adding telmisartan (cm)	Amplitude of contraction after adding telmisartan (cm)
30	4.48±0.47	4.87±0.29*
100		4.98±0.31*
300		5.10±0.27*
1000		5.15±0.28*

* Data represented as Mean ± SEM of six experiments.

* Significant compared to control value (before adding telmisartan) at $P < 0.05$.

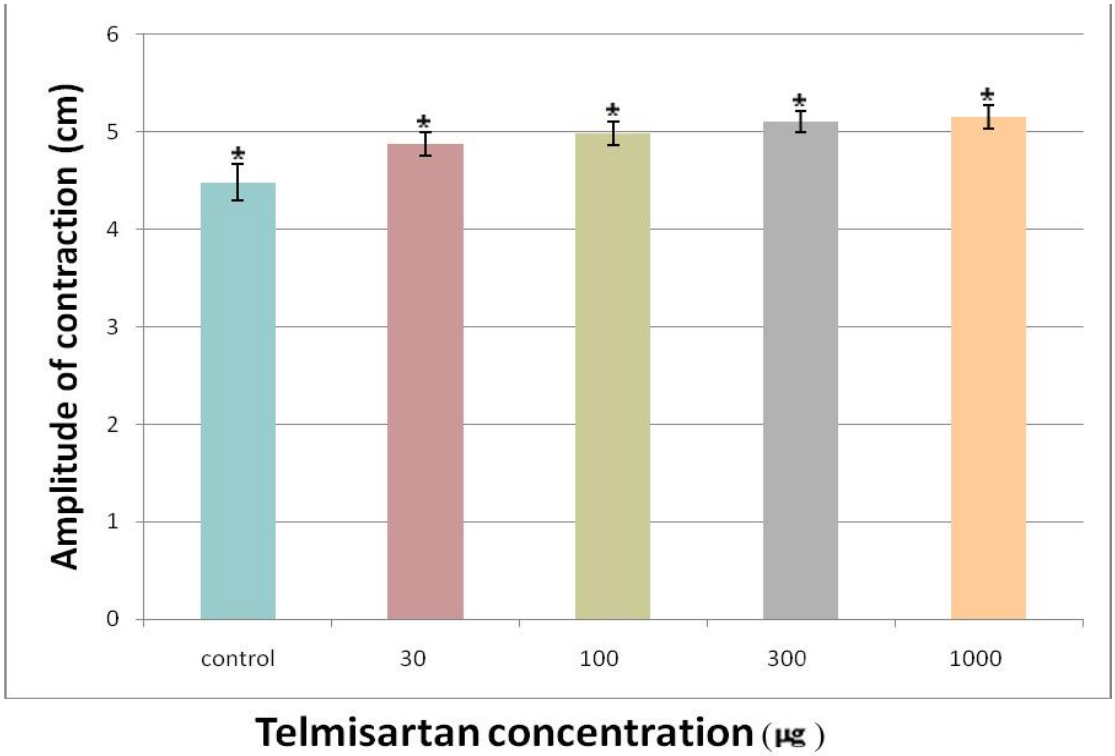


Figure (40): Histogram showing the stimulant effect of telmisartan on the amplitude of spontaneous contraction of isolated perfused rabbit's heart.

***** significant ($p < 0.05$) compared to control value (before adding telmisartan) .

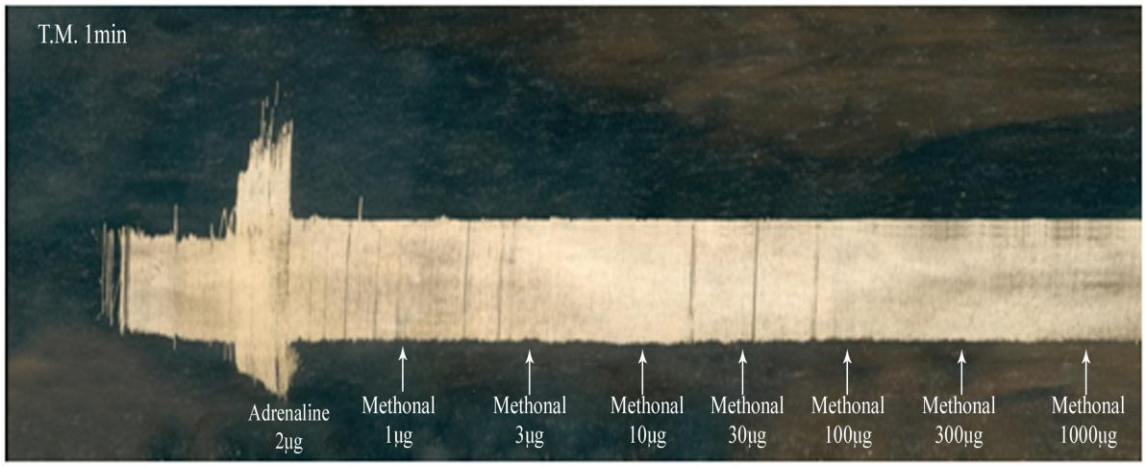


Figure (41): A record demonstrating the effect of gradually increasing concentrations of methanol on the isolated perfused rabbit's heart contractions.

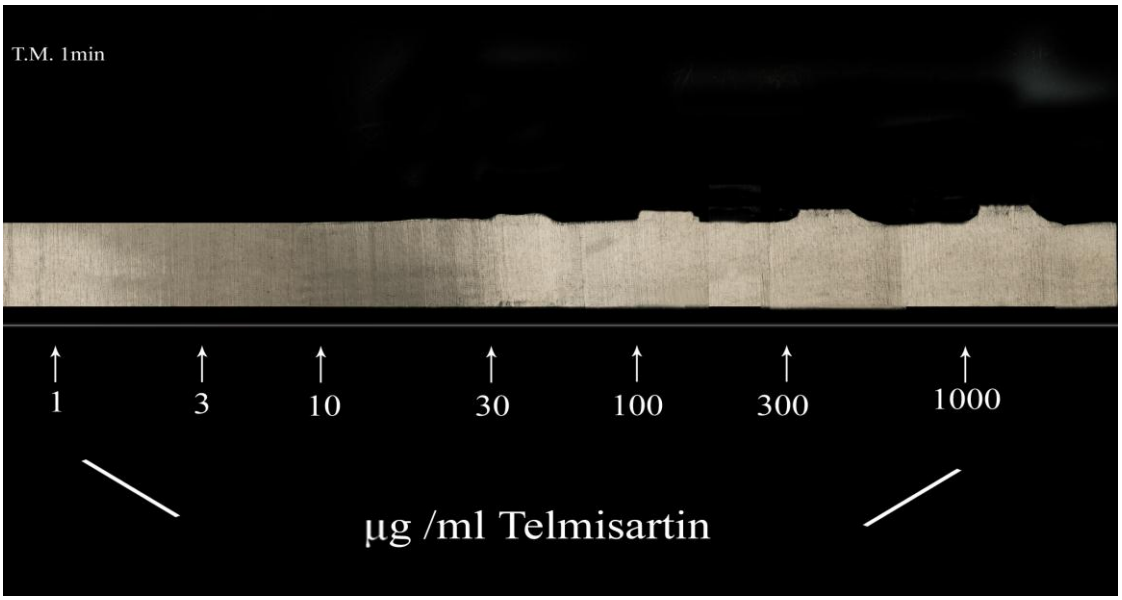
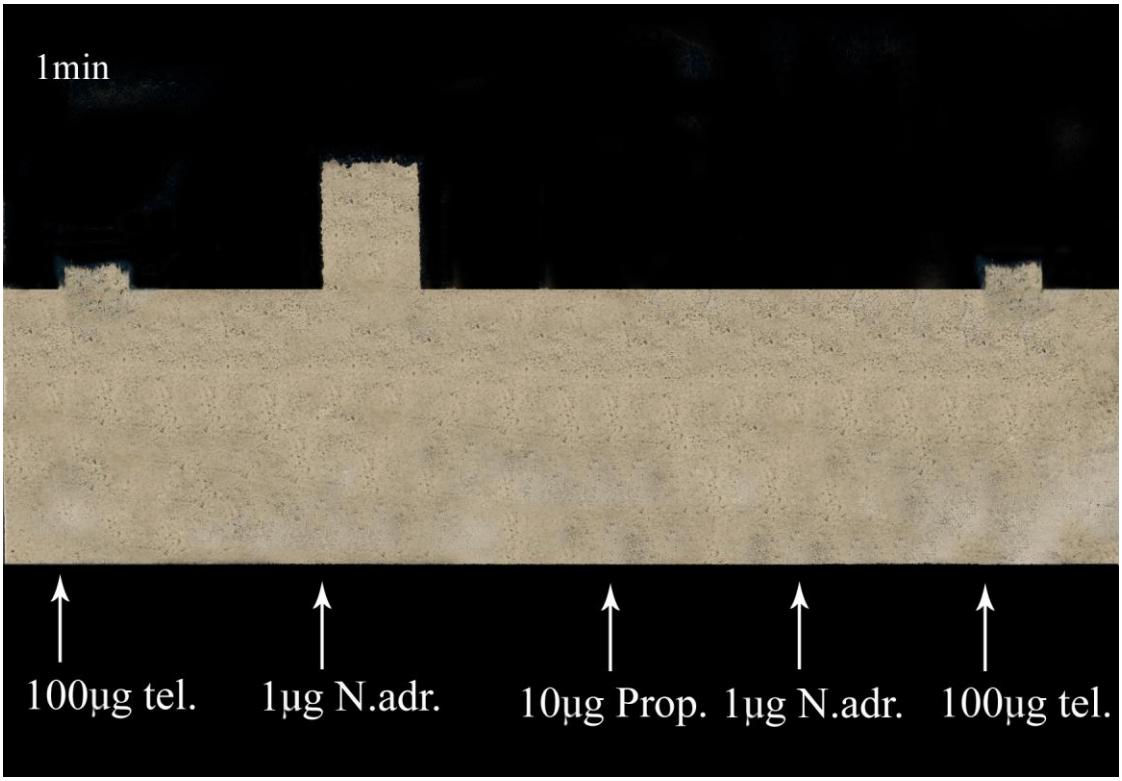


Figure (42): A record demonstrating the effect of gradually increasing concentrations of telmisartan on the isolated perfused rabbit's heart contractions.

Site of action of telmisartan on isolated perfused rabbit's heart:

It was observed that this positive inotropic effect of telmisartan was still present after blocking of β-adrenergic receptor by using propranolol in a dose of 10μg (Fig.43).

Moreover, angiotensin II adding in dose of 100ng induced positive inotropic effect, which was completely antagonized by 100 μg telmisartan (Fig. 44).



.

Figure(43): A record demonstrating the site of action of telmisartan on the isolated perfused rabbit's heart.

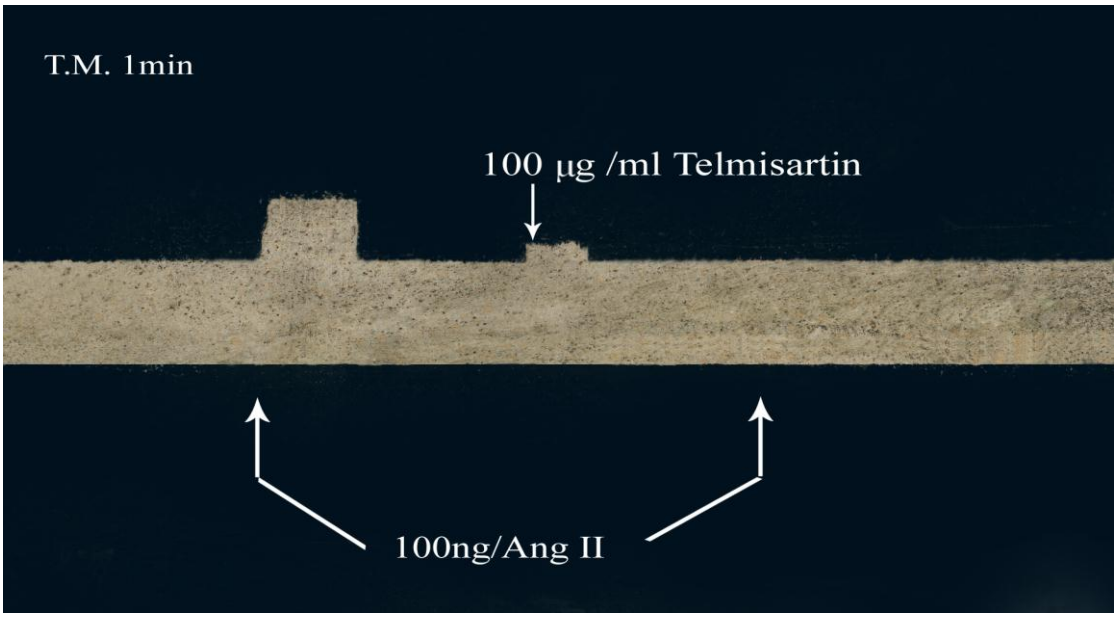


Figure (44): A record demonstrating the interaction of telmisartan with angiotensin II on the isolated perfused rabbit's heart.

2. Effects on isolated rabbit's aortic spiral strip:

It was observed that preincubation of gradually increasing doses of methanol in a dose of (1,3,10 30,100μg/ml) for 5 minutes before the addition of Ang II in a submaximal dose (5 ng/ml) and norepinephrine in a submaximal dose (2 μg/ml)had no effect in the aortic strip response to Ang II and norepineophrine respectively (Fig 46,47).

It was observed that preincubation of gradually increasing doses of telmisartan (1,3,10 and 30 μg/ml) for 5 minutes before the addition of Ang II in a submaximal dose (5 ng/ml) produced signficiant reduction of the Ang II induced contractile response of the rabbit's aortic spiral strip. This reduction of the Ang II inducd contractile response of the rabbit's aortic spiral strip is significant ($P < 0.01$) with dose 1 μg/ml bath and significant ($P < 0.001$) with doses (3,10,30 μg/ml) (Table 11, Fig.48).

As regards interaction of telmisartan with norepinephrine, it was observed that preincubation of gradually increasing doses of telmisartan (1, 3,10, 30 and 100 μg/ml) for 5 minutes before the addition of norepinephrine in a submaximal dose (2 μg/ml) produced no change in the aortic strip response to norepineophrine (Fig.49)

Table (11): The effect of telmisartan on angiotensin II-induced contractions on isolated rabbit's aortic spiral strip (n=6).

Telmisartan μg/ml	Level of contraction before adding telmisartan(cm)	level of contraction after adding telmisartan(cm)
1	6.70 ± 1.4	4.60± 0.58*
3		3.20± 0.75*
10		2.52± 0.57*
30		0*

* Data represented as Mean ± SEM of six experiments.

* Significant compared to control value (before adding telmisartan)at $P< 0.05$.

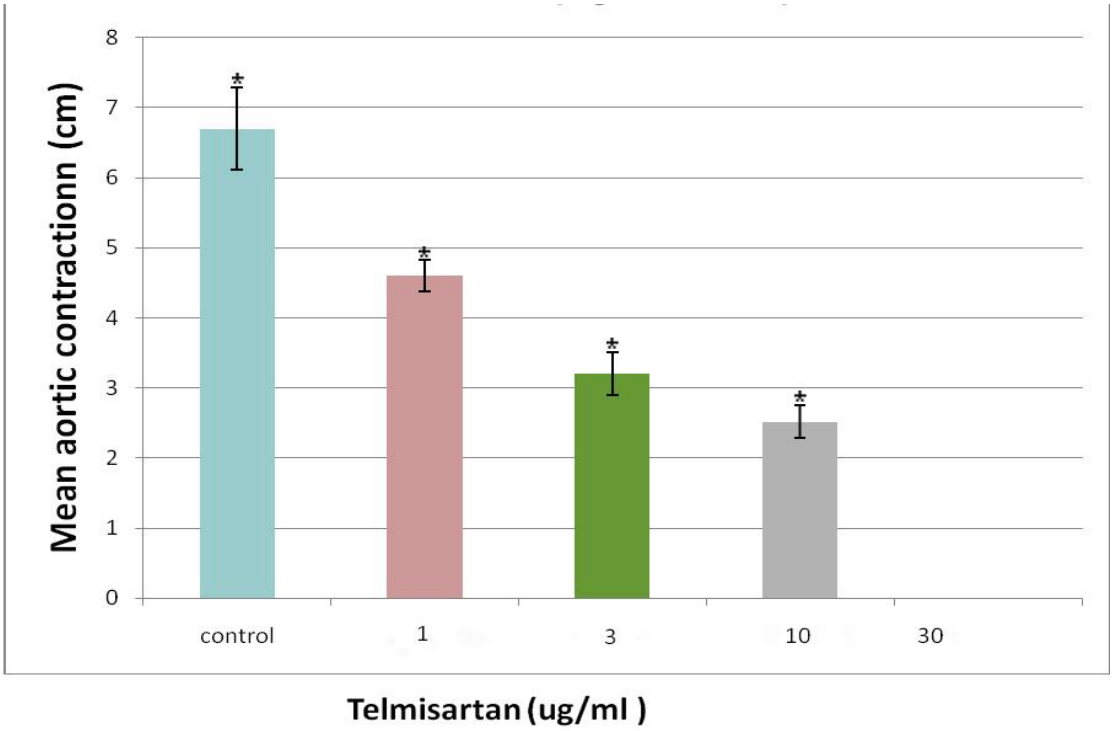


Figure (45): Histogram showing the effect of telmisartan on angiotensin II-induced contraction of isolated rabbit's aortic spiral strip.

***** significant ($p < 0.05$) compared to control value (before adding telmisartan).

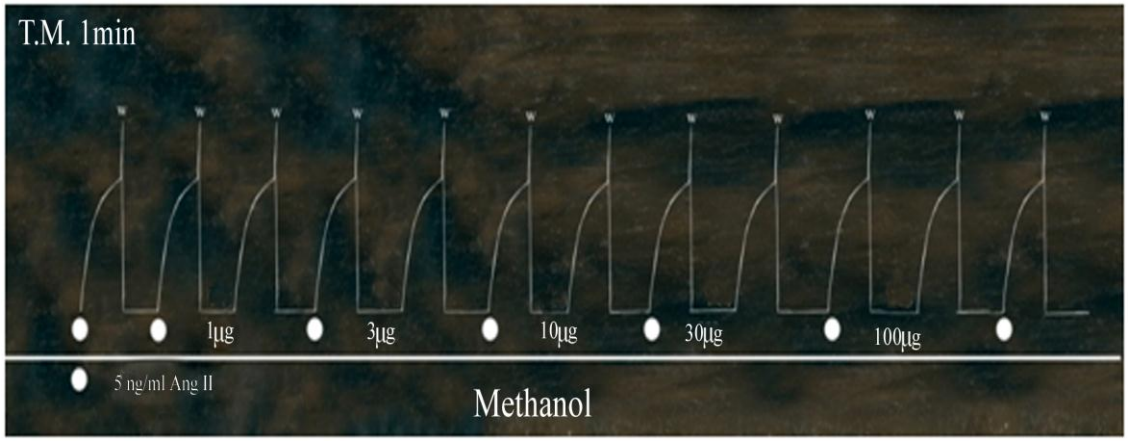


Figure (46): A record demonstrating the effect of methanol on the angiotensin II- induced contractions of isolated rabbit's aortic spiral strip.

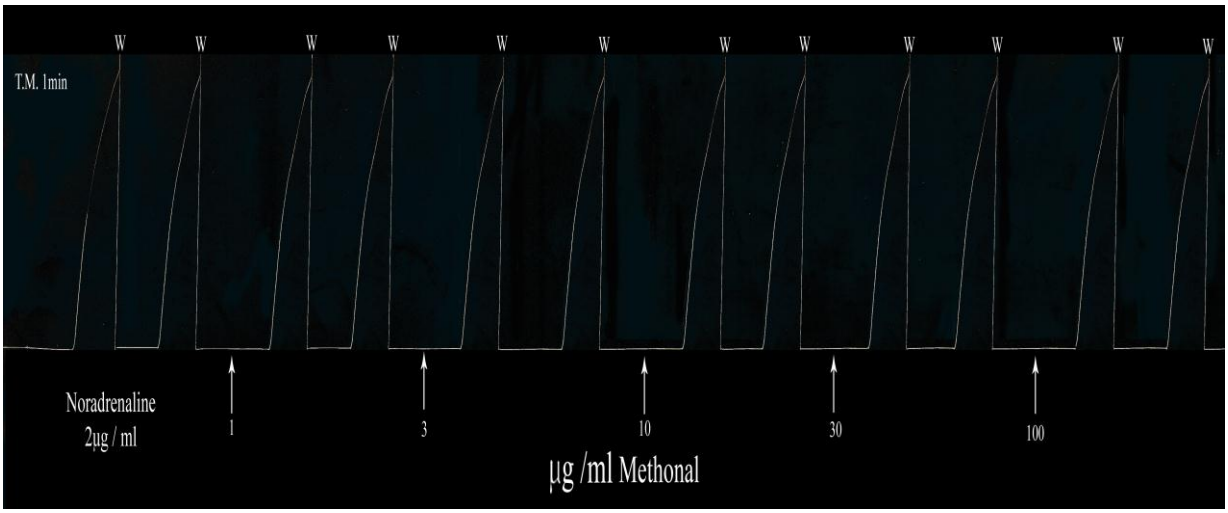


Figure (47): A record demonstrating the effect of methanol on the norepinephrine induced contractions of isolated rabbit's aortic spiral strip.

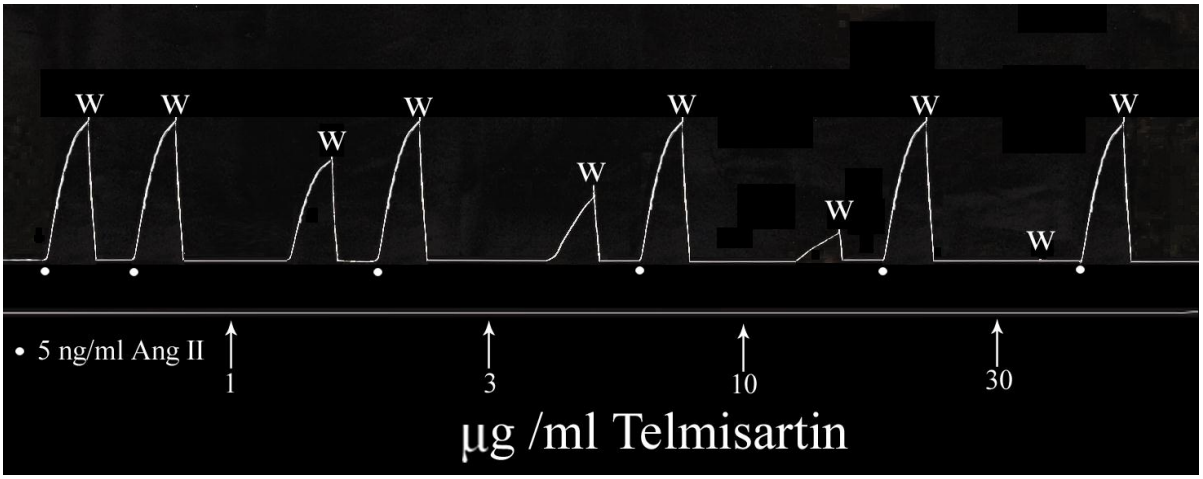


Figure (48): A record demonstrating the effect of telmisartan on the angiotensin II- induced contractions of isolated rabbit's aortic spiral strip.

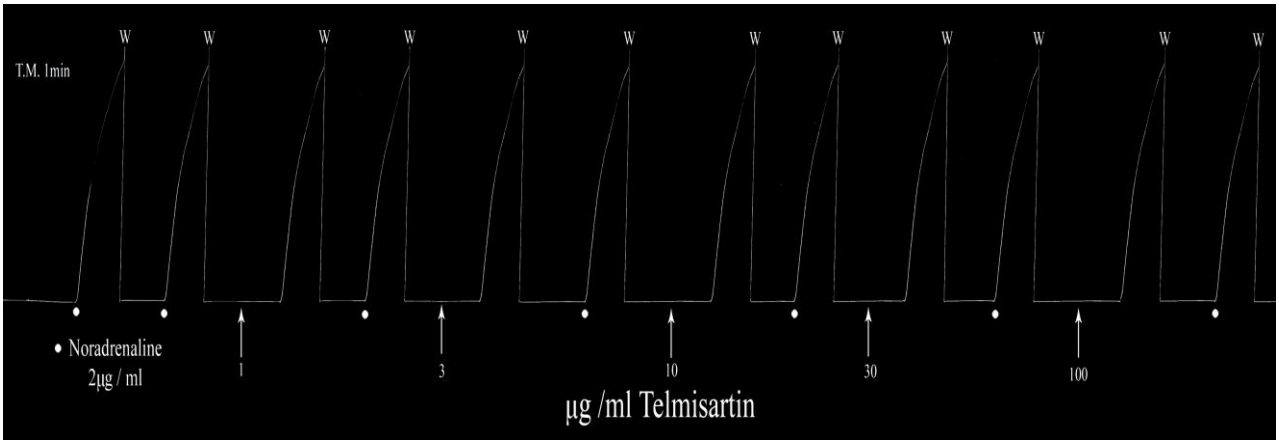


Figure (49): A record demonstrating the effect of telmisartan on the norepinephrine induced contractions of isolated rabbit's aortic spiral strip.