Results

I. In vitro experiments

1. Effects on isolated perfused rabbit's heart:

- **Effect of losartan on isolated perfused rabbit's heart:**

It was noticed that losartan in increasing doses (1, 3, and 10 μg) did not produce any change in the amplitude of spontaneous contraction of isolated perfused rabbit's heart. However losartan in doses (30, 100, 300 and 1000 μg) produced inhibition of the force of spontaneous contraction of the isolated perfused rabbit's heart in dose related manner. This inhibition of the force of spontaneous contractions of the isolated perfused rabbit's heart was significant ($P < 0.05$) with the dose of 30μg with percentage of reduction 27.1%. Meanwhile, it was significant ($P < 0.01$) with the doses of 100μg and 300μg with percentage of reduction 39.4% and 57.1% respectively, and significant ($P < 0.001$) with the dose of 1000μg with percentage of reduction 71.1% compared to basal value (Table 1, Figs. 1, 4).

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

It was observed that losartan added in dose of 100 μg produced inhibitory effect on spontaneous rhythmic contractility of the isolated perfused rabbit's heart. This inhibitory effect of losartan was still present after blocking both nicotinic and muscarinic receptor by using nicotine large dose in a dose of 100 μg and atropine in a dose of 50 μg respectively (Fig. 5).

Angiotensin II (100ng) induced positive inotrpic effect, which was completely antagonized by 100 μg losartan (Fig. 6).

- **Effect of telmisartan on isolated perfused rabbit's heart:**

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 1000 μg) produced increase of the force of spontaneous contraction of the isolated perfused rabbit's heart. This increase in the force of contraction of isolated perfused rabbit's heart was significant ($P < 0.05$) with dose 30μg with percentage of increase 24.7% and significant ($P < 0.01$) with doses 100, 300, and 1000μg with percentage of increase 29.4% compared to basal value (Table 2, Fig. 2, 7).

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 ß-adrenergic receptor by using propranolol in a dose of 10μg (Fig. 8).

Moreover, angiotensin II adding in dose of 100ng induced positive inotropic effect, which was completely antagonized by 100 μg telmisartan (Fig. 8).

So, it was found that, losartan produced dose related inhibitory effect (negative inotropic effect), while telmisartan produced dose related stimulant effect (positive inotropic effect) of the force of spontaneous contraction of the isolated perfused rabbit's heart (Fig. 3, 4, 7).

Table (1): Effect of losartan in the amplitude of spontaneous contraction of isolated perfused rabbit's heart.

Dose of losartan µg	Amplitude of contraction before (cm)	Amplitude of contraction after (cm)	Percentage of reduction (%)	P
30	5.37±0.22	3.9 ± 0.37	27.1	< 0.05*
100		3.25 ± 0.18	39.4	< 0.01*
300		2.3 ± 0.33	57.1	< 0.001*
1000		1.55 ± 0.17	71.1	< 0.001*

Data represented as mean ± SEM of six experiments.

* Significant at $P < 0.05$ compared to control value.

Table (2): Effect of telmisartan in the amplitude of spontaneous contraction of isolated perfused rabbit's heart.

Dose of telmisartan µg	Amplitude of contraction before (cm)	Amplitude of contraction after (cm)	Percentage of increase (%)	P
30	4.25 ± 0.32	5.3 ± 0.42	24.7	< 0.05*
100		5.5 ± 0.44	29.4	< 0.01*
300		5.5 ± 0.44	29.4	< 0.01*
1000		5.5 ± 0.44	29.4	< 0.01*

Data represented as mean ± SEM of six experiments.

* Significant at $P < 0.05$ compared to control value.

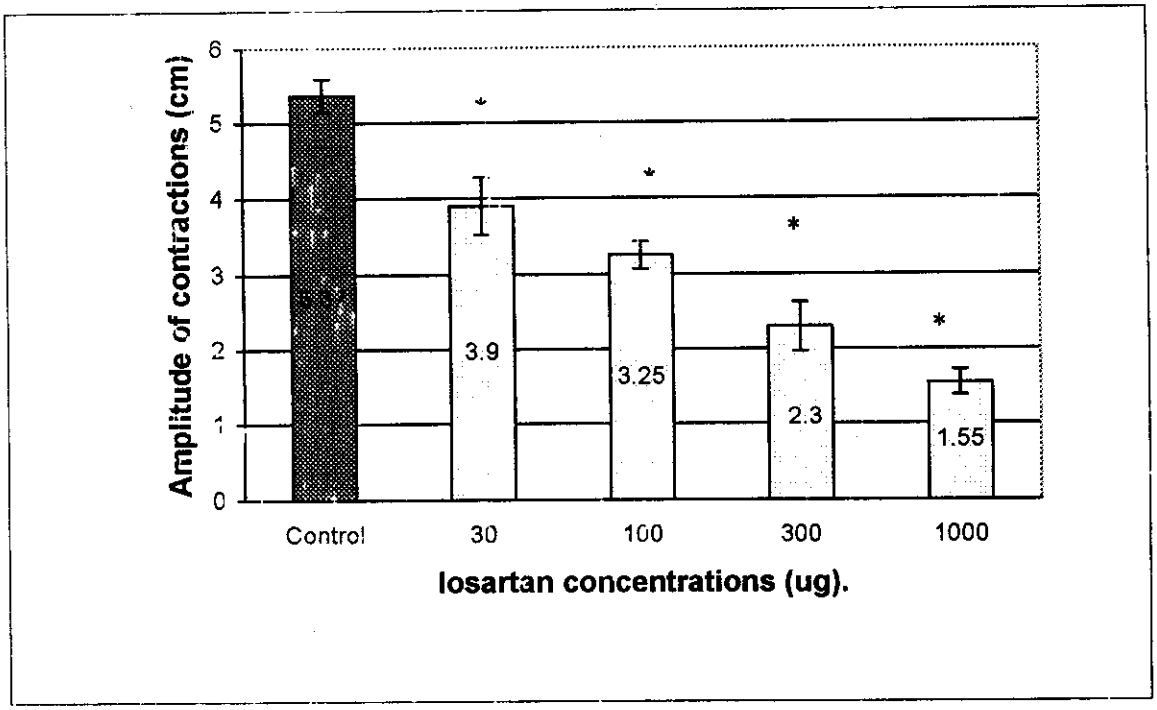
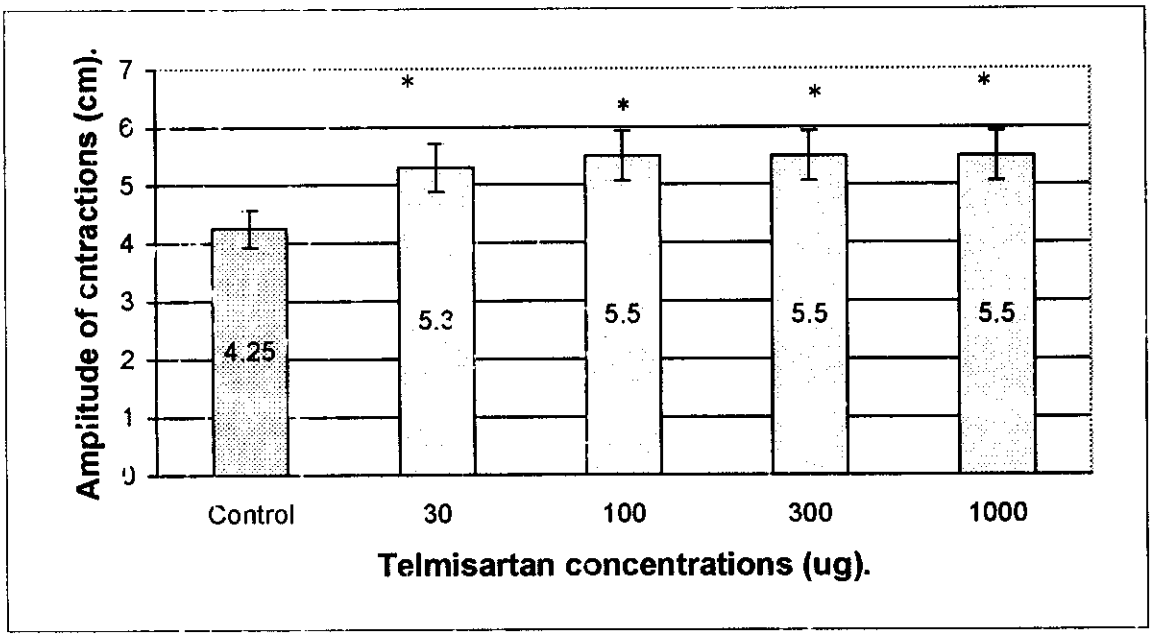


Figure (1): Histogram showing the inhibitory effect of losartan on the amplitude of spontaneous contraction of isolated perfused rabbit's heart.

* Significant at $P < 0.05$ compared to control value.



Figure(2): Histogram showing the stimulant effect of telmisartan on the amplitude of spontaneous contraction of isolated perfused rabbit's heart.

* Significant at $P < 0.05$ compared to control value.

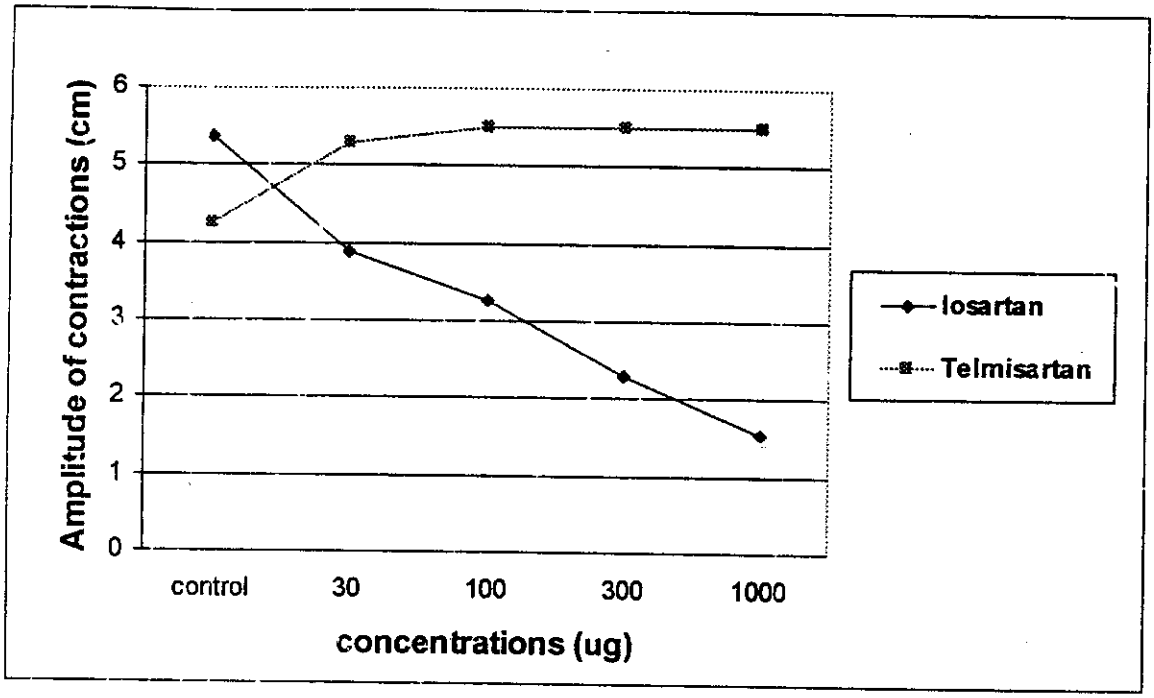


Figure (3): Histogram showing the effect of losartan versus telmisartan on the amplitude of spontaneous contractions of isolated perfused rabbit's heart.

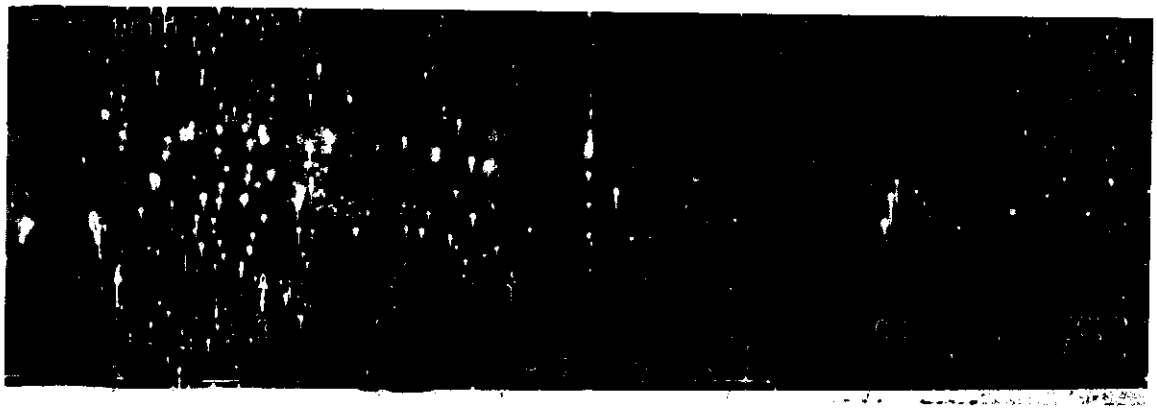


Figure (4): A record demonstrating the effect of gradually increasing concentrations of losartan on the isolated perfused rabbit's heart contractions.

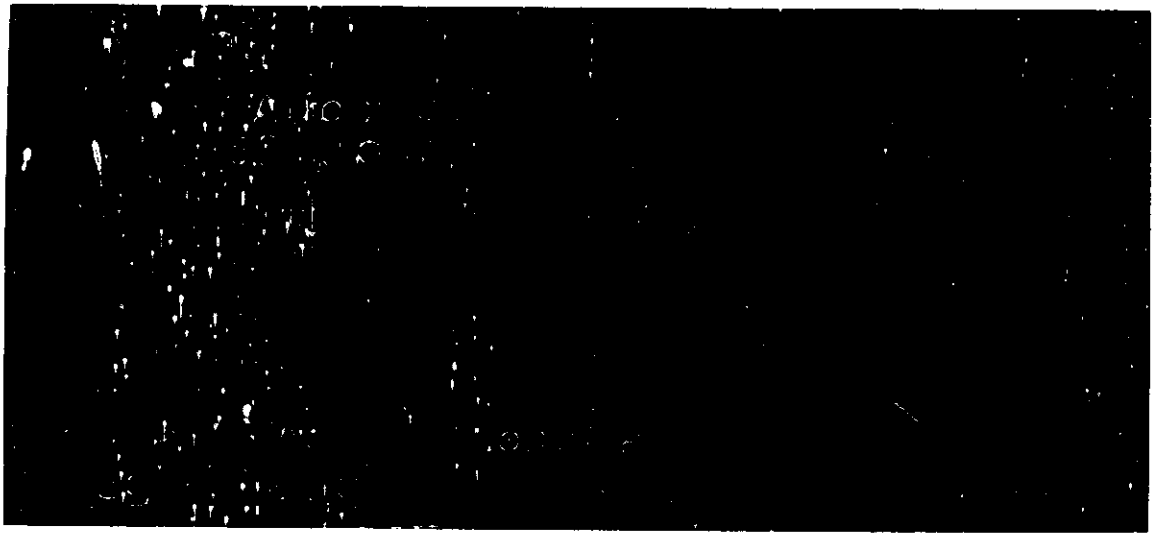


Figure (5): A record demonstrating the site of action of losartan on the isolated perfused rabbit's heart.

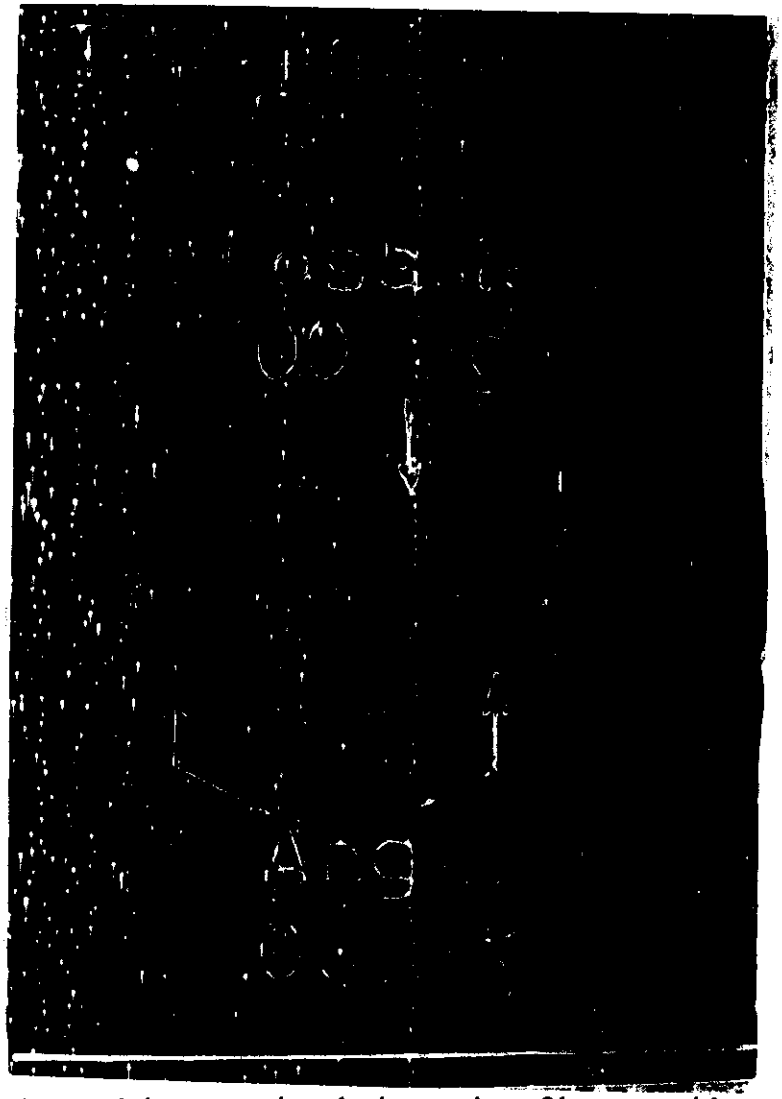


Figure (6): A record demonstrating the interaction of losartan with angiotensin II on the isolated perfused rabbit's heart.

Figure (7): A record demonstrating the effect of gradually increasing concentrations of telmisartan on the isolated perfused rabbit's heart contractions.

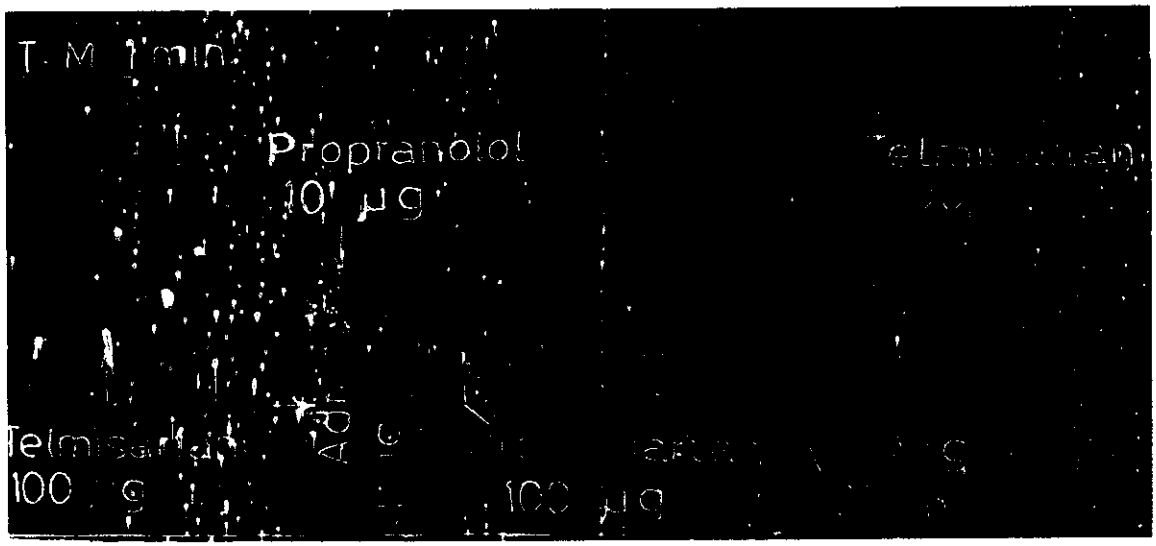


Figure (8): A record demonstrating the site of action of telmisartan on the isolated perfused rabbit's heart.

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

- **Effect of losartan on isolated rabbit's aortic spiral strip:**

It was observed that preincubation of gradually increasing doses of losartan (1, 3, 10 and 30 μg/ml bath) for 5 minutes before the addition of angiotensin II in a submaximal dose (5 ng/ml bath) produced significant reduction of the angiotensin II induced contractile response of the rabbit's aortic spiral strip. This reduction of the Ang II induced contractile response of the rabbit's aortic spiral strip is significant ($P < 0.01$) with dose 1 μg/ml bath with percentage of reduction of 12.44% and significant ($P < 0.001$) with doses 3, 10, 30 μg/ml bath with percentage of reduction of 48.02%, 70.27% and 87.11% respectively (Table 3, Figs. 9, 12).

As regards interaction of losartan with norepinephrine, it was observed that preincubation of gradually increasing doses of losartan (1, 3, 10, 30 and 100 μg/ml bath) for 5 minutes before the addition of norepinephrine in a submaximal dose (2 μg/ml bath) produced no change in the aortic strip response to norepinephrine (Figs. 13).

- **Effect of telmisartan on isolated rabbit aortic spiral strip:**

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 significant reduction of the Ang II induced contractile response of the rabbit's aortic spiral strip. This reduction of the Ang II induced contractile response of the rabbit's aortic spiral strip is significant ($P < 0.01$) with dose 1 μg/ml bath with percentage of reduction of 19.62% and significant ($P < 0.001$) with doses 3, 10, 30 μg/ml bath with percentage of reduction of 57.73%, 84.52% and 100% respectively (Table 4, Figs.10, 14).

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 bath) for 5 minutes before the addition of norepinephrine in a submaximal dose (2 μg/ml bath) produced no change in the aortic strip response to norepinephrine (Fig. 15).

As regards comparing the effect of telmisartan to that of losartan at doses (1, 3, 10 and 30μg/ml bath) on the reduction of the Ang II induced contractile response of the rabbit's aortic spiral strip, it was found that telmisartan was more potent than losartan and produced significant more reduction ($P < 0.05$) at the doses of 10 and 30 μg/ml bath (Table 5, Fig.11).

Table (3): Effect of losartan on angiotensin II-induced contractions of isolated rabbit's aortic spiral strip.

Losartan µg/ml bath	Level of contraction befor (cm)	Level of contraction after (cm)	Percentage of reduction %	P
1	6.83 ± 0.16	5.98 ± 0.22	12.44	< 0.01*
3		3.55 ± 0.21	48.02	< 0.001*
10		2.03 ± 0.18	70.27	< 0.001*
30		0.88 ± 0.23	87.11	< 0.001*

Data represented as mean ± SEM of six experiments.

* Significant at $P < 0.05$ compared to control value.