Results

I. In vivo experiments:

1. Effect of Arabic gum and carvedilol treatment on serum urea of nephrotoxic rats:

Intra-peritoneal injection of gentamicin (80mg/kg/day) for 8 consecutive days resulted in significant rise of serum urea ($P < 0.001$) from 34.516 ± 1.5 mg/dl in control group (group I) to 185 ± 9.9 mg/dl in nephrotoxic group (group II) (Table 3, Figure 4)..

Treatment of nephrotoxic rats with Arabic gum (1.5gm/ rat daily) orally for 3 days before and 8 days concurrently with gentamicin (group III) reduced serum urea significantly ($P < 0.001$) from 185 ± 9.9 mg/dl to 63.166 ± 5.58 mg/dl compared to nephrotoxic group (group II). (Table 3, Figure 4).

Treatment of nephrotoxic rats with carvedilol (2mg /kg body weight i.p. injection) for 3 days before and 8 days concurrently with gentamicin (group IV) reduced serum urea significantly ($P< 0.001$) from 185 ± 9.9 mg/dl to 78.5 ± 6.39 mg/dl compared to nephrotoxic group (group II) (Table 3, Figure 4).

Treatment of nephrotoxic rats with both carvedilol (2mg /kg body weight) and Arabic gum (1.5gm/ rat) for 3 days before and 8 days concurrently with gentamicin (group V) reduced serum urea significantly ($P< 0.001$) from 185 ± 9.9 mg/dl to 41.66 ± 3.05 mg/dl compared to nephrotoxic group (group II) (Table 3, Figure 4).

Comparing the result of arabic gum-treated group (group III) to that of carvedilol-treated group (group IV), there was no significant differences (P >0.05) between Arabic gum and carvedilol in their effect on serum urea (Table 3 , Figure 4).

Table (3): Effect of Arabic gum (1.5gm/rat orally) and carvedilol (2mg/kg BW i.p injection) 3 days before and 8 days concurrently with gentamicin on serum urea of nephrotoxic rats (n=6)

Parameters / Groups	Serum urea (mg/dl)
Control group	**34.516 ± 1.5**
Nephrotoxic group **Percent change (%)**	**185 ± 9.9*** **↑ > 100 %**
Arabic gum-treated nephrotoxic group **Percent change (%)**	**63.166 ± 5.58**** **↓ 65.31 %**
Carvedilol-treated nephrotoxic group **Percent change (%)**	**78.5 ±6.39 **#** **↓ 57.56 %**
Arabic gum and carvedilol-treated nephrotoxic group **Percent change (%)**	**41.66 ± 3.05**** **↓ 77.48 %**

Data represented as Mean ± SEM

*significant (p < 0. 001) compared to control group

**significant (p < 0. 001) compared to nephrotoxic group

insignificant (p > 0. 05) compared to Arabic gum-treated group

Comparing the result of Arabic gum-treated group (group III) to that of Arabic gum and carvedilol-treated group (group V), Arabic gum and carvedilol together were significantly more effective than Arabic gum alone in reducing serum urea (P <0.01) (Table 4 , Figure 4).

Comparing the result of carvedilol-treated group (group IV) to that of Arabic gum and carvedilol-treated group (group V), Arabic gum and carvedilol together were significantly more effective than carvedilol alone in reducing serum urea (P <0.001) (Table 4 , Figure 4).

Table (4):Table showing comparison between the effect of either Arabic gum (1.5gm/rat orally) or carvedilol (2mg/kg BW i.p injection) 3 days before and 8 days concurrently with gentamicin and two drugs together on serum urea of nephrotoxic rats (n=6)

Group / Serum urea	Arabic gum-treated group	Carvedilol-treated group	Arabic gum and carvedilol-treated group
(mg/dl) (M ± SE)	63.166 ± 5.58 ↓ 65.31 %	78.5 ± 6.39 ↓ 57.56 %	41.66 ±3.05 $+ ↓ 77.48 %

Data represented as Mean ± SEM

$ significant (p < 0. 01) compared to arabic gum-treated group

+ significant (p< 0. 001) compared to carvedilol-treated group

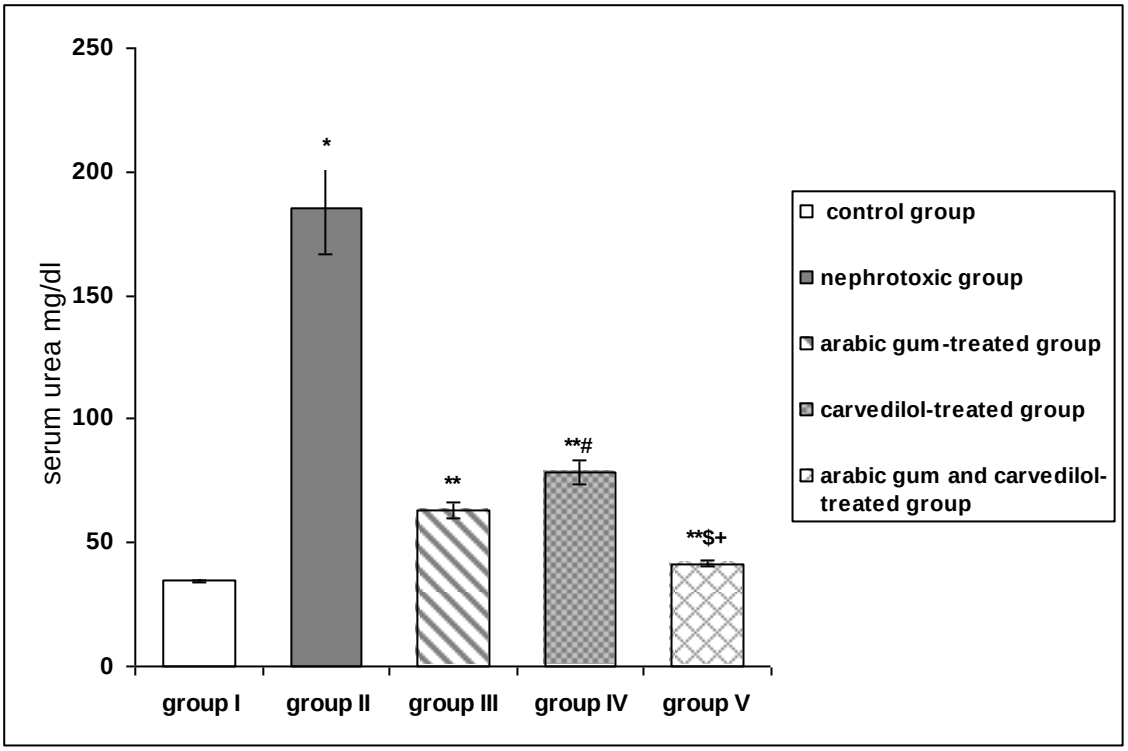


Figure (4): Histogram showing effect of Arabic gum (1.5gm/rat orally) and carvedilol (2mg/kg BW i.p injection) 3 days before and 8 days concurrently with gentamicin on serum urea of nephrotoxic rats in various groups.

***** significant (p < 0. 001) compared to control group
**significant (p < 0. 001) compared to nephrotoxic group
# insignificant (p > 0. 05) compared to Arabic gum-treated group
$ significant (p < 0. 01) compared to arabic gum-treated group
+ significant (p< 0. 001) compared to carvedilol-treated group

2. Effect of Arabic gum and carvedilol treatment on serum creatinine of nephrotoxic rats:

Intra-peritoneal injection of gentamicin (80mg/kg/day) for 8 consecutive days resulted in significant rise of serum creatinine (P < 0.001) from 0.49 ± .034 mg/dl in control group (group I) to 2.49 ± 0.23 mg/dl in nephrotoxic group (group II) (Table 5, Figure 5)..

Treatment of nephrotoxic rats with Arabic gum (1.5gm/ rat daily) orally for 3 days before and 8 days concurrently with gentamicin (group III) reduced serum creatinine significantly ($P < 0.001$) from 2.49 ± 0.23 mg/dl to 0.78 ± 0.047 mg/dl compared to nephrotoxic group (group II). (Table 5, Figure 5).

Treatment of nephrotoxic rats with carvedilol (2mg /kg body weight i.p. injection) for 3 days before and 8 days concurrently with gentamicin (group IV) reduced serum creatinine significantly ($P< 0.001$)from 2.49 ± 0.23 mg/dl to 0.966 ± 0.095 mg/dl compared to nephrotoxic group (group II) (Table 5, Figure 5).

Treatment of nephrotoxic rats with both carvedilol (2mg /kg body weight) and Arabic gum (1.5gm/ rat) for 3 days before and 8 days concurrently with gentamicin (group V) reduced serum creatinine significantly ($P< 0.001$) from 2.49 ± 0.23 mg/dl to 0.533 ± 0.033 mg/dl compared to nephrotoxic group (group II) (Table 5, Figure 5).

Comparing the result of Arabic gum-treated group (group III) to that of carvedilol-treated group (group IV), there was no significant differences ($P >0.05$) between Arabic gum and carvedilol in their effect on serum creatinine (Table 5, Figure 5).

Table (5): Effect of Arabic gum (1.5gm/rat orally) and carvedilol (2mg/kg BW i.p injection) 3 days before and 8 days concurrently with gentamicin on serum creatinine of nephrotoxic rats (n=6)

Parameters / Groups	Serum creatinine (mg/dl)
Control group	**0.49 ± 0.034**
Nephrotoxic group Percent change (%)	**2.49 ± 0.23* ↑ > 100 %**
Arabic gum-treated nephrotoxic group Percent change (%)	**0.78 ± 0.047** ↓ 68.67 %**
Carvedilol-treated nephrotoxic group Percent change (%)	**0.966 ± 0.095**# ↓ 61.20 %**
Arabic gum and carvedilol-treated nephrotoxic group Percent change (%)	**0.533 ± 0.033** ↓ 78.59 %**

Data represented as Mean ± SEM

***** significant (p < 0. 001) compared to control group

**significant (p < 0. 001) compared to nephrotoxic group

insignificant (p > 0. 05) compared to Arabic gum-treated group

Comparing the result of Arabic gum-treated group (group III) to that of Arabic gum and carvedilol-treated group (group V), Arabic gum and carvedilol together were significantly more effective than Arabic gum alone in reducing serum creatinine (P <0.001) (Table 6 , Figure 5).

Comparing the result of carvedilol-treated group (group IV) to that of Arabic gum and carvedilol-treated group (group V), Arabic gum and carvedilol together were significantly more effective than carvedilol alone in reducing serum creatinine (P <0.001) (Table 6, Figure 5).

Table (6): Table showing comparison between the effect of either Arabic gum (1.5gm/rat orally) or carvedilol (2mg/kg BW i.p injection) 3 days before and 8 days concurrently with gentamicin and two drugs together on serum creatinine of nephrotoxic rats (n=6)

Group / Serum creatinine	Arabic gum-treated group	Carvedilol-treated group	Arabic gum and carvedilol-treated group
(mg/dl) (M ± SE)	0.78 ± 0.047 ↓ 68.67 %	0.966 ± 0.095 ↓ 61.20 %	0.533 ± 0.033 $+ ↓ 78.59 %

Data represented as Mean ± SEM

$significant (p < 0. 001) compared to Arabic gum-treated group

+ significant (p <0.001) compared to carvedilol-treated group

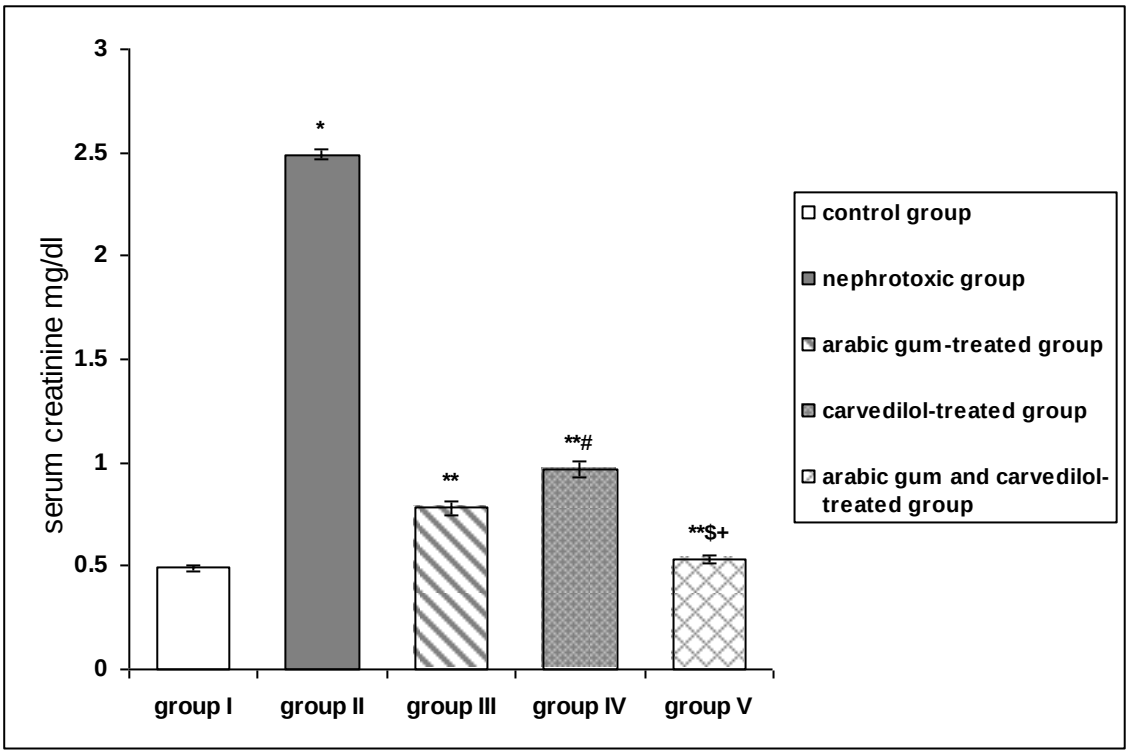


Figure (5): Histogram showing effect of Arabic gum (1.5gm/rat orally) and carvedilol (2mg/kg BW i.p injection) 3 days before and 8 days concurrently with gentamicin on serum creatinine of nephrotoxic rats in various groups.

***** significant (p < 0. 001) compared to control group

**significant (p < 0. 001) compared to nephrotoxic group

insignificant (p > 0. 05) compared to Arabic gum-treated group

$ significant (p < 0. 001) compared to Arabic gum-treated group

\+ significant (p <0.001) compared to carvedilol-treated group

3. Effect of Arabic gum and carvedilol treatment on oxidative activity of nephrotoxic rats:

Intra-peritoneal injection of gentamicin (80mg/kg/day) for 8 consecutive days resulted in significant rise of MDA (P < 0.001) from

2.366 ± .0.189 µmol/ml in control group (group I) to 7.88 ± 0.39 µmol/ml in nephrotoxic group (group II) (Table 7, Figure 6)..

Treatment of nephrotoxic rats with Arabic gum (1.5gm/ rat daily) orally for 3 days before and 8 days concurrently with gentamicin (group III) reduced MDA significantly ($P < 0.001$) from 7.88 ± 0.39 µmol/ml to 4.8 ± 0.45 µmol/ml compared to nephrotoxic group (group II). (Table 7, Figure 6).

Treatment of nephrotoxic rats with carvedilol (2mg /kg body weight i.p. injection) for 3 days before and 8 days concurrently with gentamicin (group IV) reduced MDA significantly ($P< 0.05$) from 7.88 ± 0.39 µmol/ml to 5.85 ± 0.62 µmol/ml compared to nephrotoxic group (group II) (Table 7, Figure 6).

Treatment of nephrotoxic rats with both carvedilol (2mg /kg body weight) and Arabic gum (1.5gm/ rat) for 3 days before and 8 days concurrently with gentamicin (group V) reduced MDA significantly ($P< 0.001$) from 7.88 ± 0.39 µmol/ml to 3 ± 0.096 µmol/ml compared to nephrotoxic group (group II) (Table 7, Figure 6).

Comparing the result of Arabic gum-treated group (group III) to that of carvedilol-treated group (group IV), there was no significant differences ($P >0.05$) between Arabic gum and carvedilol in their effect on MDA (Table 7, Figure 6).

Table (7): Effect of Arabic gum (1.5gm/rat orally) and carvedilol (2mg/kg BW i.p injection) 3 days before and 8 days concurrently with gentamicin on MDA of nephrotoxic rats (n=6)

Parameters / Groups	MDA (µmol/ml)
Control group	**2.366 ± 0.189**
Nephrotoxic group **Percent change (%)**	**7.88 ± 0.39*** **↑ > 100 %**
Arabic gum-treated nephrotoxic group **Percent change (%)**	**4.8 ± 0.45**** **↓ 39.08 %**
Carvedilol-treated nephrotoxic group **Percent change (%)**	**5.85 ± 0.62**#** **↓ 25.76 %**
Arabic gum and carvedilol-treated nephrotoxic group **Percent change (%)**	**3 ± 0.096**** **↓ 61.92 %**

Data represented as Mean ± SEM

***** significant (p < 0. 001) compared to control group

**significant (p < 0. 001) compared to nephrotoxic group

insignificant (p > 0. 05) compared to Arabic gum-treated group

Comparing the result of Arabic gum-treated group (group III) to that of Arabic gum and carvedilol-treated group (group V), Arabic gum and carvedilol together were significantly more effective than Arabic gum alone in reducing MDA ($P < 0.01$) (Table 8 , Figure 6).

Comparing the result of carvedilol-treated group (group IV) to that of Arabic gum and carvedilol-treated group (group V), Arabic gum and carvedilol together were significantly more effective than carvedilol alone in reducing MDA ($P < 0.001$) (Table 8, Figure 6).

Table (8): Table showing comparison between the effect of either Arabic gum (1.5gm/rat orally) or carvedilol (2mg/kg BW i.p injection) 3 days before and 8 days concurrently with gentamicin and two drugs together on MDA of nephrotoxic rats (n=6)

Group / MDA	Arabic gum-treated group	Carvedilol-treated group	Arabic gum and carvedilol-treated group
(umol/ml) (M ± SE)	**4.8 ± 0.45 ↓ 39.08 %**	**5.85 ± 0.62 ↓ 25.76 %**	**3 ± 0.096$^{\$+}$ ↓ 61.92 %**

Data represented as Mean ± SEM (n = 6)

$ significant (p < 0. 01) compared to arabic gum-treated group

+ significant (p < 0. 001) compared to carvedilol-treated group

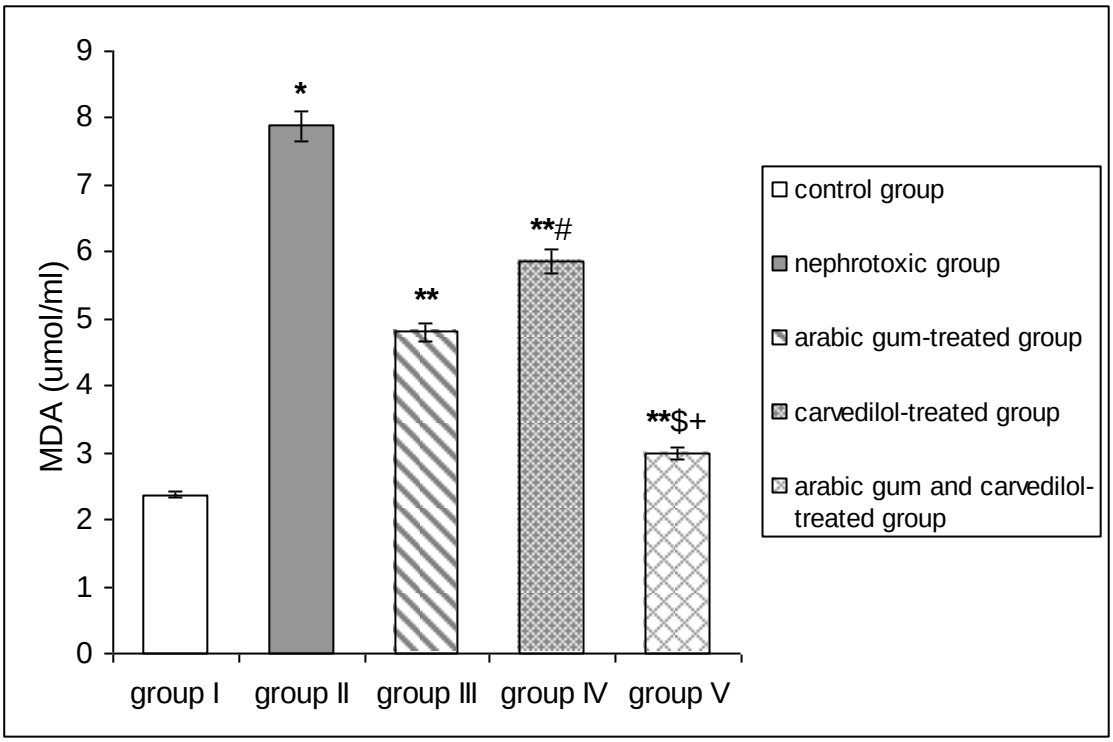


Figure (6): Histogram showing the effect of Arabic gum (1.5gm/rat orally) and carvedilol (2mg/kg BW i.p injection) 3 days before and 8 days concurrently with gentamicin on MDA of nephrotoxic rats in various groups.

***** significant (p < 0. 001) compared to control group

**significant (p < 0. 001) compared to nephrotoxic group

insignificant (p > 0. 05) compared to Arabic gum-treated group

$ significant (p < 0. 01) compared to arabic gum-treated group

\+ significant (p < 0. 001) compared to carvedilol-treated group

4- Histopathological evaluation of the kidney:

Histological examination of a cut section of the kidney of control group (group I) showed that normal collecting tubules lined by one layer

of cuboidal epithelial cells , normal proximal convoluted tubules and normal distal convoluted tubules (Figure 7).

In nephrotoxic group (group II); there were accumulation of inflammatory cells in interstitial tissue which indicat marked interstitial nephritis with tubular necrosis and desquamation of tubular epithelial cells (Figure 8).

In Arabic gum-treated nephrotoxic group (group III), Arabic gum treatment markedly decreased the swelling of glomeruli , cloudy swelling of tubular epithelium with mild interstitial nephritis (Figure 9).

Carvedilol-treated nephrotoxic group (group IV) showed cloudy swelling of tubular epithelial cells with mild interstitial nephritis (Figure 10).

Arabic gum and carvedilol-treated nephrotoxic group (group V) showed marked decrease in glomerular swelling with slightly vacuolated but otherwise normal tubular cells (Figure 11)

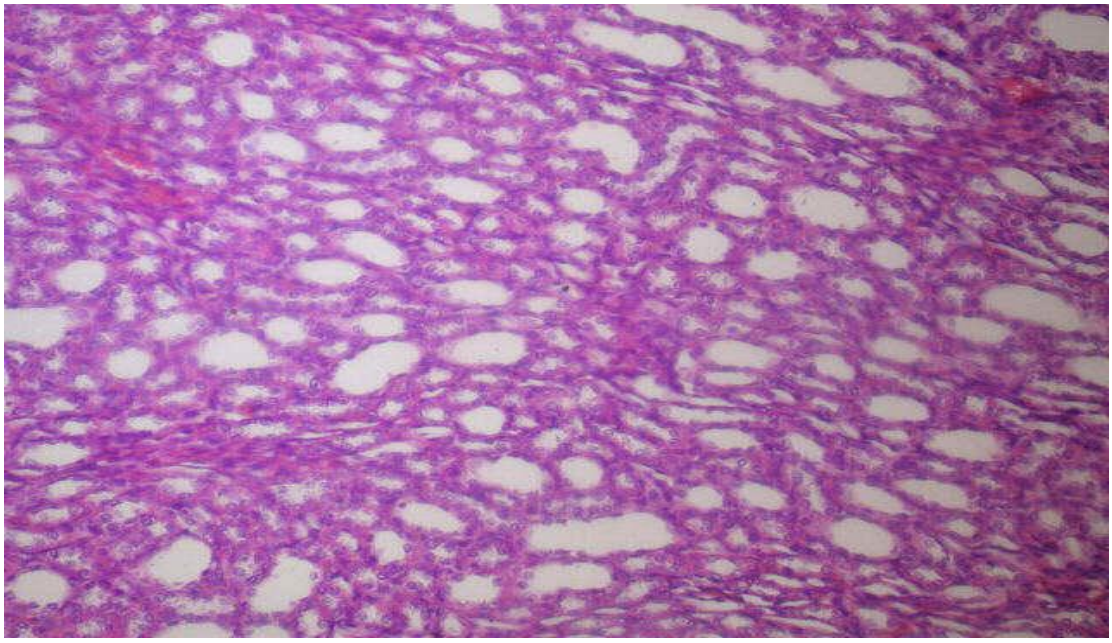


Figure (7) A photomicrograph of a cut section in the kidney of a control rat (group I) showing normal renal tubules lined by one layer of cuboidal epithelial cells.

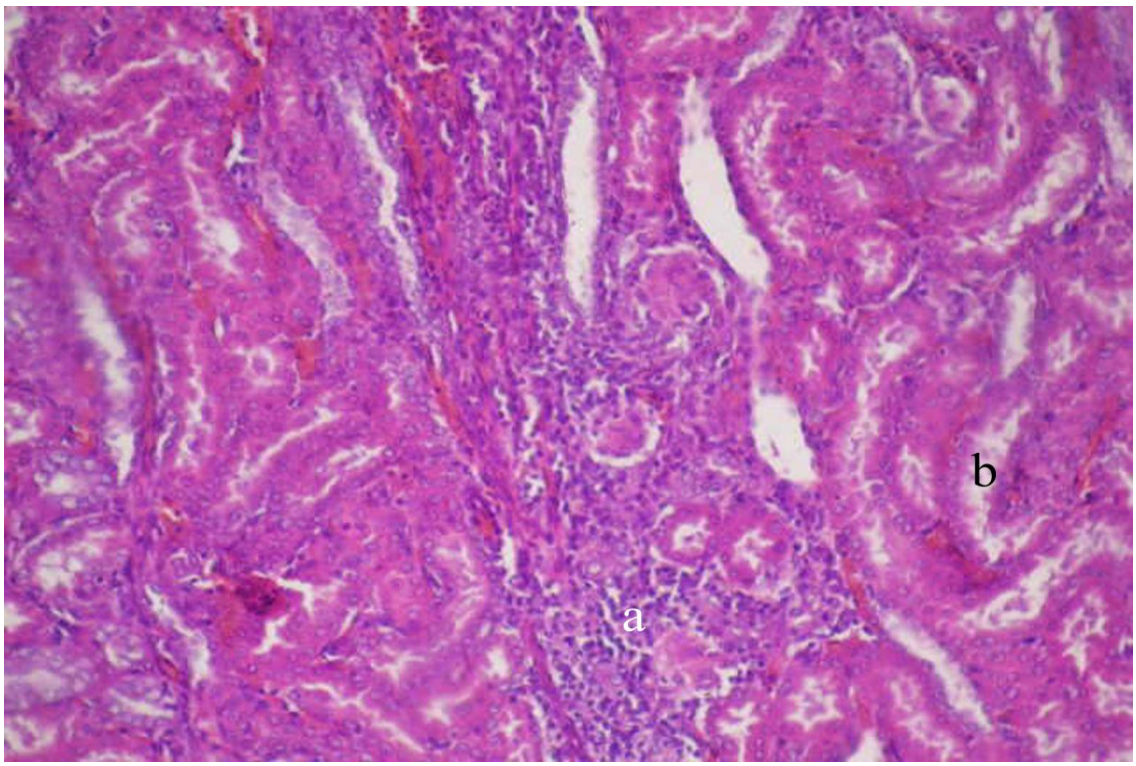


Figure (8) A photomicrograph of a cut section in the kidney of a nephrotoxic rat (group II) showing (a) marked interstitial nephritis with (b) tubular necrosis and desquamation of tubular epithelial cells.

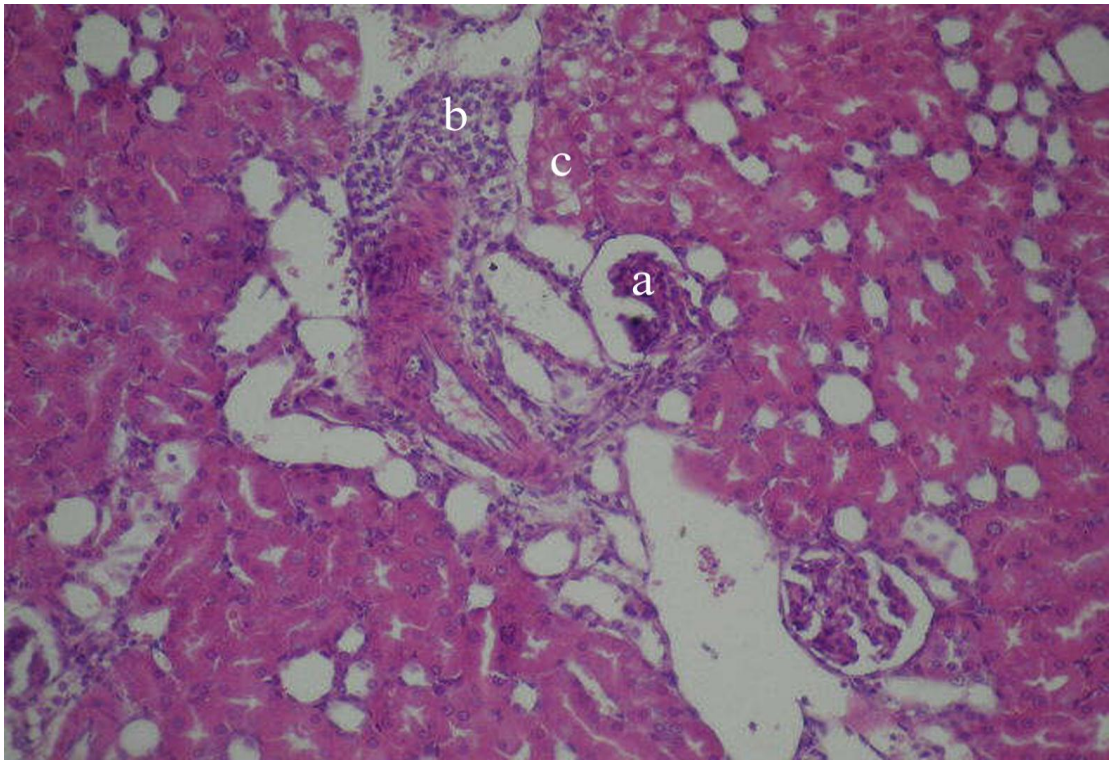


Figure (9) A photomicrograph of a cut section in the kidney of an Arabic gum-treated rat (group III) showing (a)markedly decreased the swelling of glomeruli , (b) cloudy swelling of tubular epithelium with (c) mild interstitial nephritis.

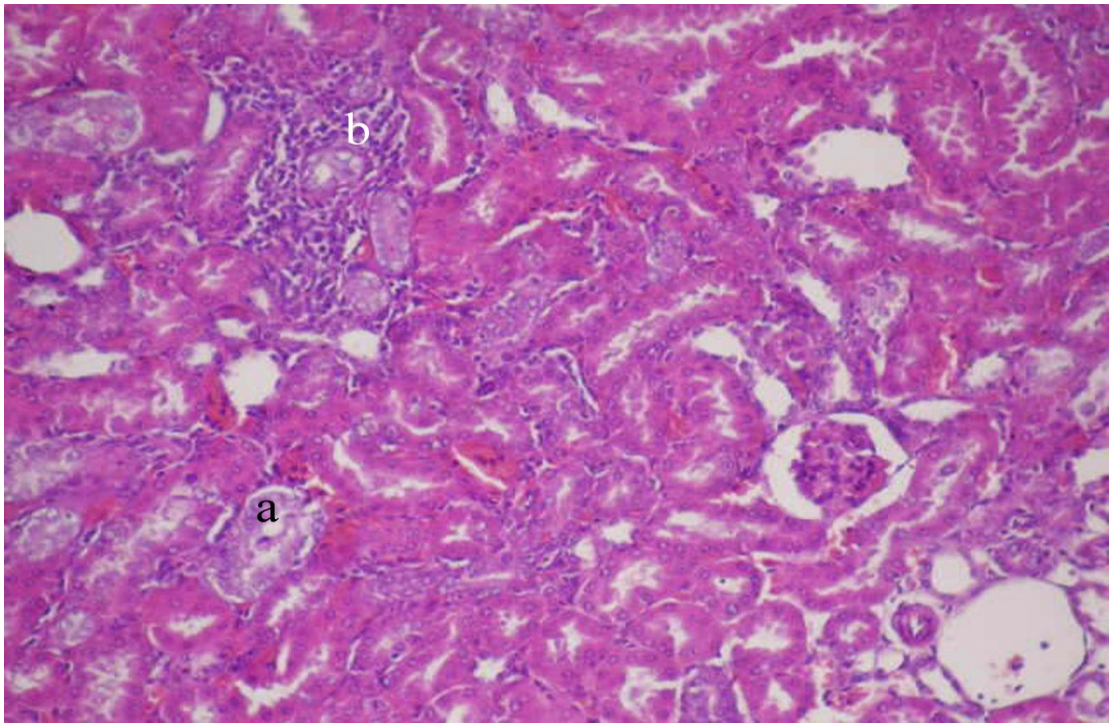


Figure (10) A photomicrograph of a cut section in the kidney of a carvedilol-treated rat (group IV) showing (a) cloudy swelling of tubular epithelial cells with (b) mild interstitial nephritis.

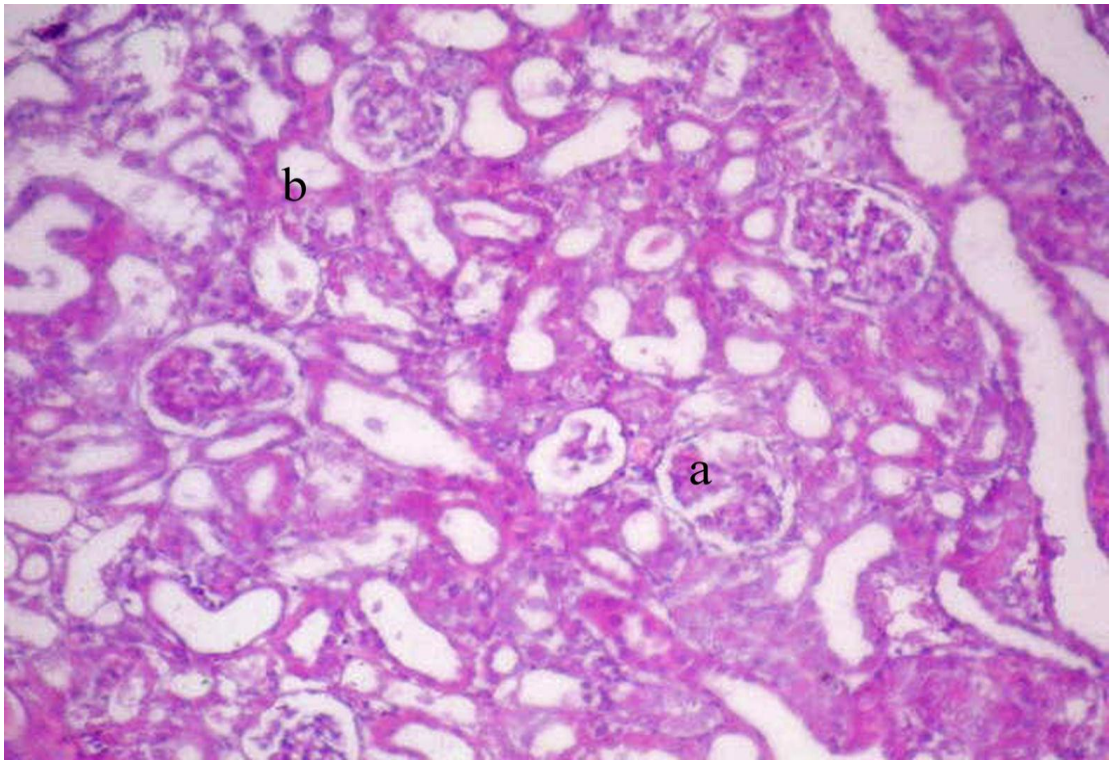


Figure (11) A photomicrograph of a cut section in the kidney of an arabic gum and carvedilol-treated rat (group V) showing (a) marked decrease in glomerular swelling with (b) normal tubular cells.

II. In vitro experiments:

1. Effects on isolated perfused rabbit's jejunum:

- **Effect of Arabic gum on isolated perfused rabbit's jejunum:**

It was observed that addition of Arabic gum in different dose levels (30, 100, 300, and 1000 μg/ml bath) produced statistically significant ($P < 0.05$) dose related stimulation of rhythmic contraction of rabbit's jejunum with percentage increase of 30.85 %, 51.52%, 72.18% and 73.55% respectively. Addition of higher dose (1000 μg/ml bath) also produced a stimulatory effect with an amplitude similar to that of the previous dose used (300 μg/ml bath) . (Table 9, Figures 12, 13).

- **Site of action of Arabic gum on isolated perfused rabbit's jejunum:**

It was observed that blocking of muscarinic, nicotinic, histaminic and serotonergic receptors did not affect the stimulatory action of Arabic gum (100 ug/ml bath). This indicates that Arabic gum did not act through the muscarinic, nicotinic, histaminic nor serotonergic receptors (Figures 14,15,16,17).

Table (9):Effects of gradually increasing doses of arabic gum (dose-response curve) on mean ± SE on the amplitude of spontaneous rhythmic contraction {cm} of isolated perfused rabbit's jejunum (N=6).

	Control	30 ug	100ug	300ug	1000 ug
Amplitude of contraction (cm) M ± SE	3.63 ± 1.2	4.75 ± 0.6*	5.50 ± 0.7*	6.25 ± 0.5*	6.30 ± 0.5*
Percentage of maximum response%		↑ 30.85	↑ 51.52	↑ 72.18	↑ 73.55

* Significant (P < 0.05) compared to the control.

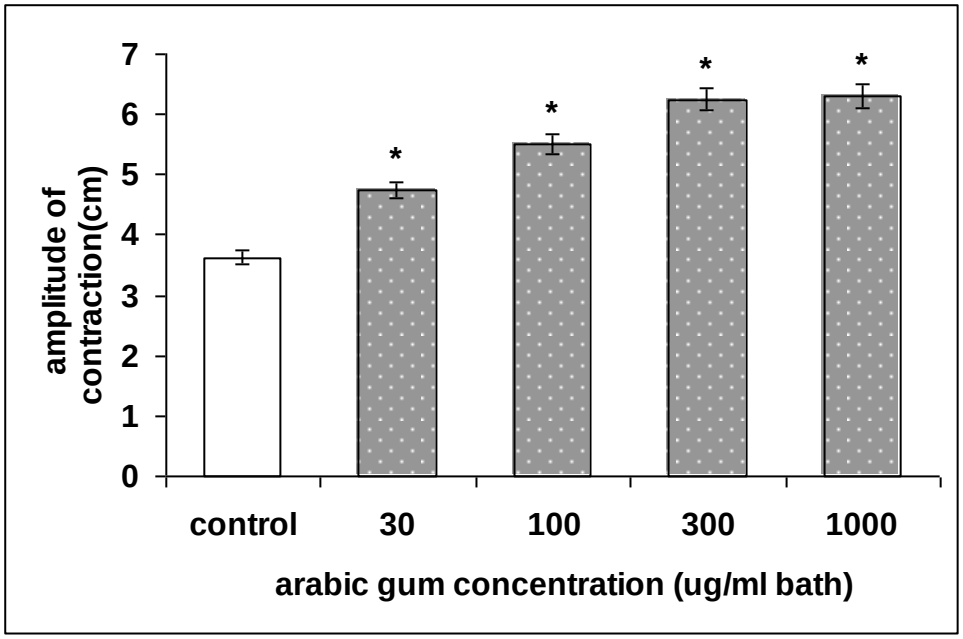


Figure (12): A histogram showing the effects of gradually increasing doses of Arabic gum (dose-response curve) on amplitude of spontaneous rhythmic contraction of isolated perfused rabbit's jejunum.

* Significant (P < 0.05) compared to the control.

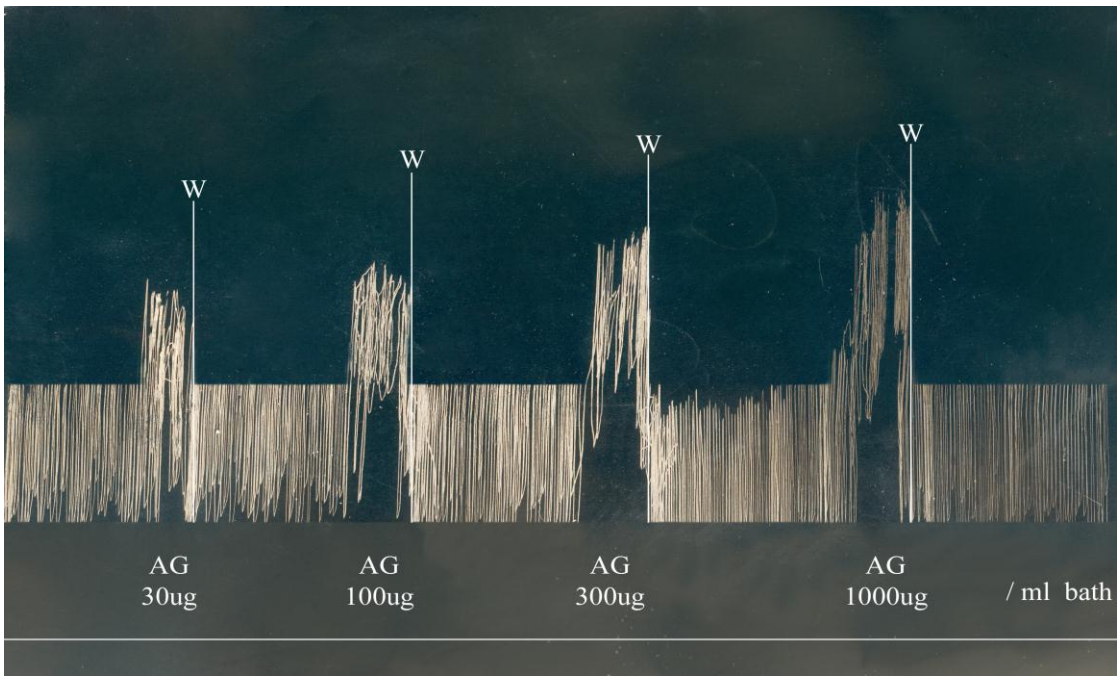


Figure (13): A record demonstrating the effect of Arabic gum on isolated perfused rabbit's jejunum.

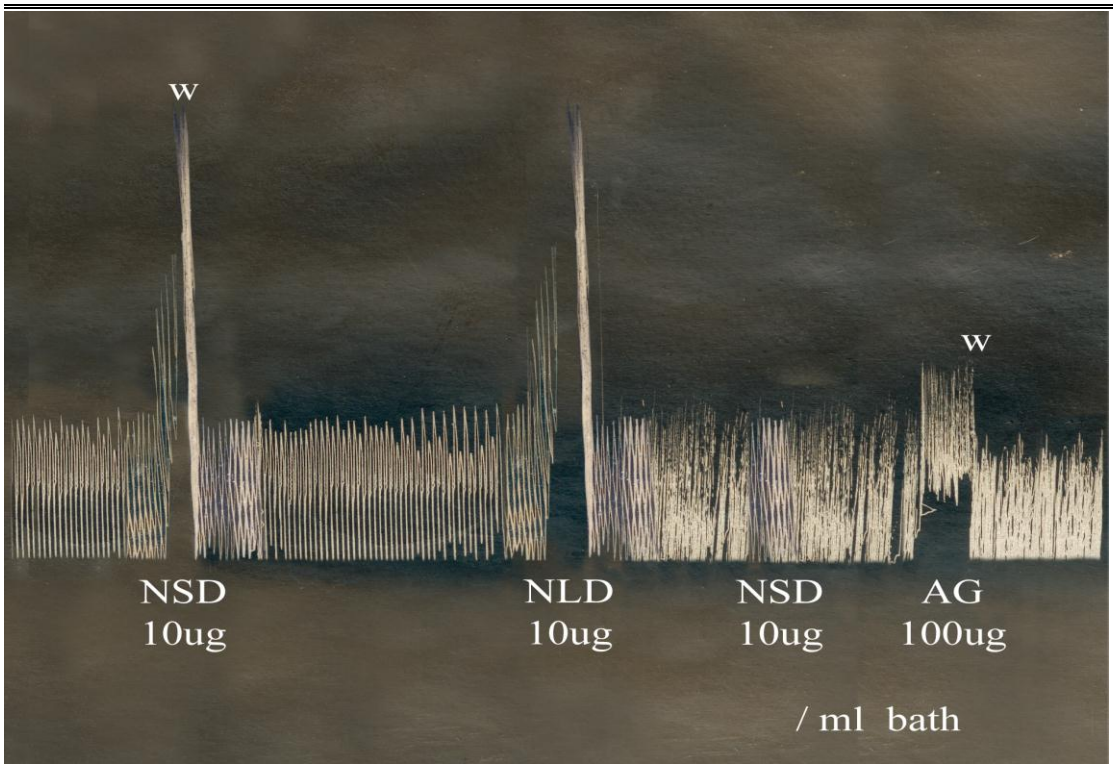


Figure (14): A record demonstrating the site of action of Arabic gum on isolated perfused rabbit's jejunum. (Nicotinic receptor).

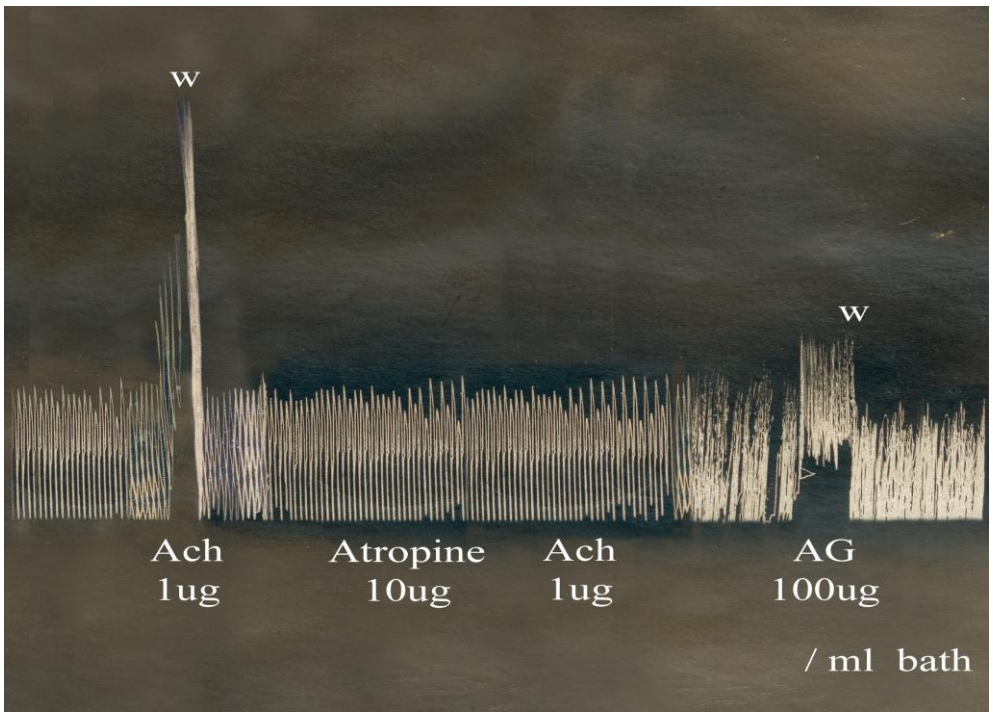


Figure (15): A record demonstrating the site of action of Arabic gum on isolated perfused rabbit's jejunum. (Muscarinic receptor).

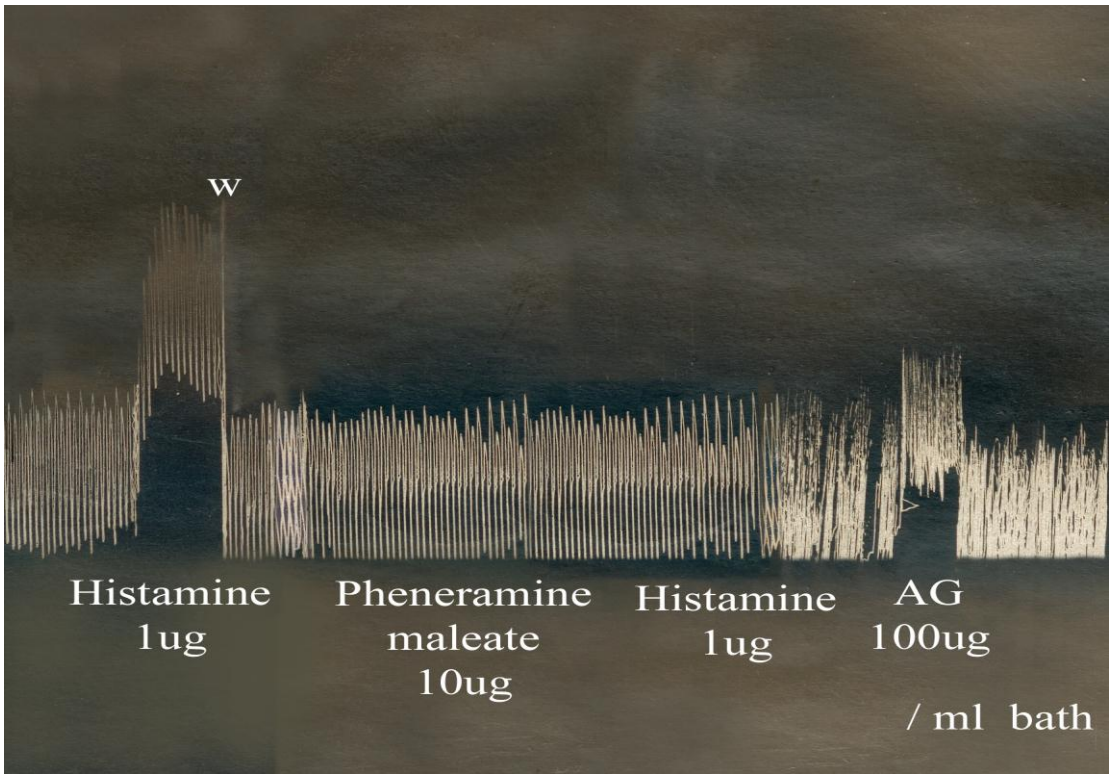


Figure (16): A record demonstrating the site of action of arabic gum on isolated perfused rabbit's jejunum (Histaminic receptor).

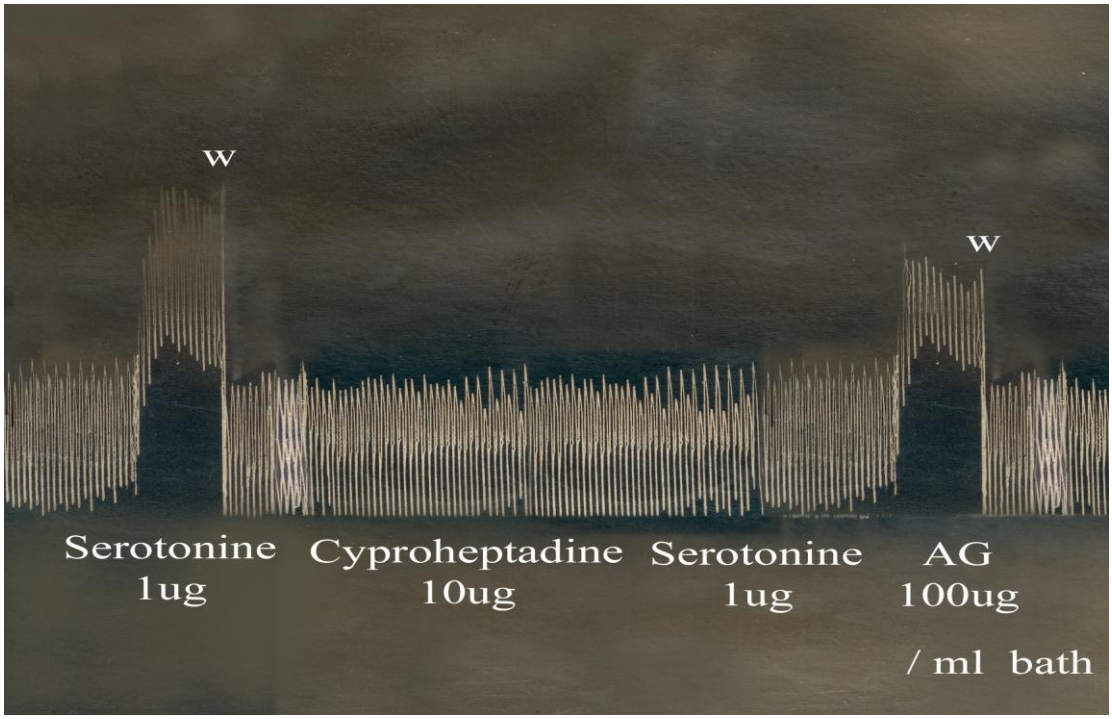


Figure (17): A record demonstrating the site of action of arabic gum on isolated perfused rabbit's jejunum (Serotonergic receptor).

- **Effect of carvedilol on isolated perfused rabbit's jejunum:**

It was observed that addition of carvedilol in different dose levels (2, 4, 8, 16, 32 and 64 µg/ml bath) produced no change in rhythmic contraction of rabbit's jejunum (Figure 18).

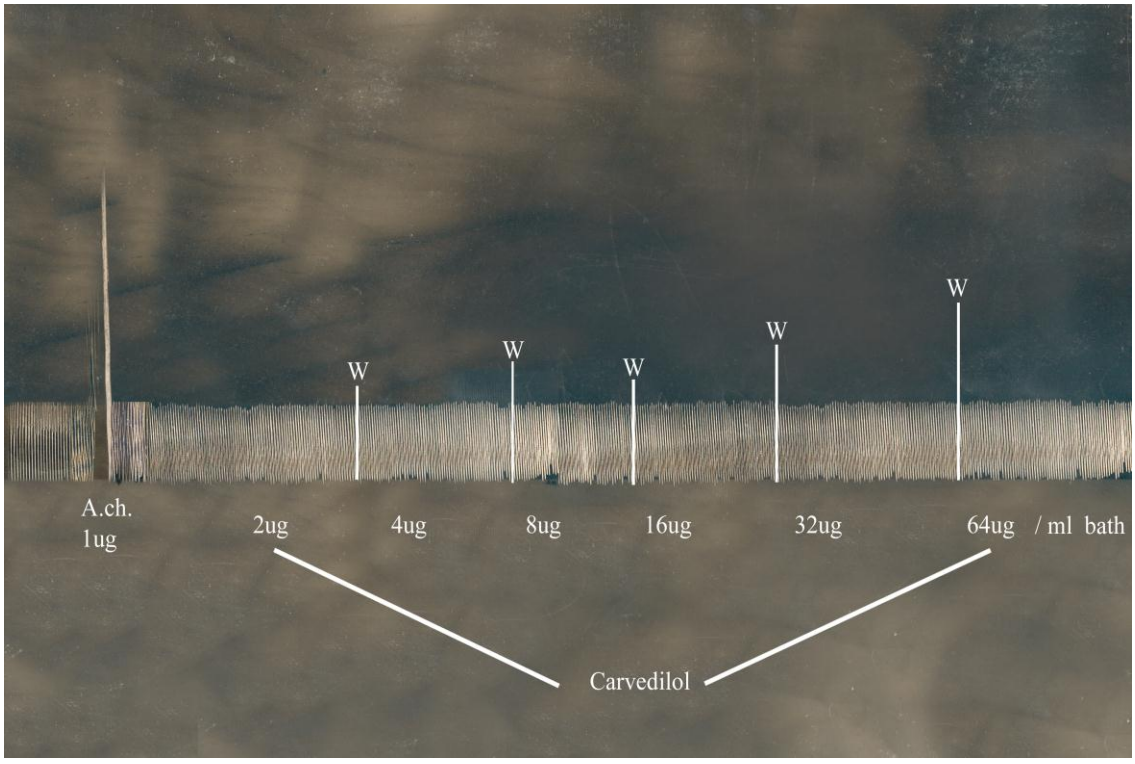


Figure (18): A record demonstrating the effect of carvedilol on isolated perfused rabbit's jejunum.

2. Effects on isolated perfused rabbit's heart:

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

It was noticed that Arabic gum in increasing doses (30, 100, 300, and 1000 µg/ bath) produced no change in the force of spontaneous contraction of isolated perfused rabbit's heart.(Figure 19)

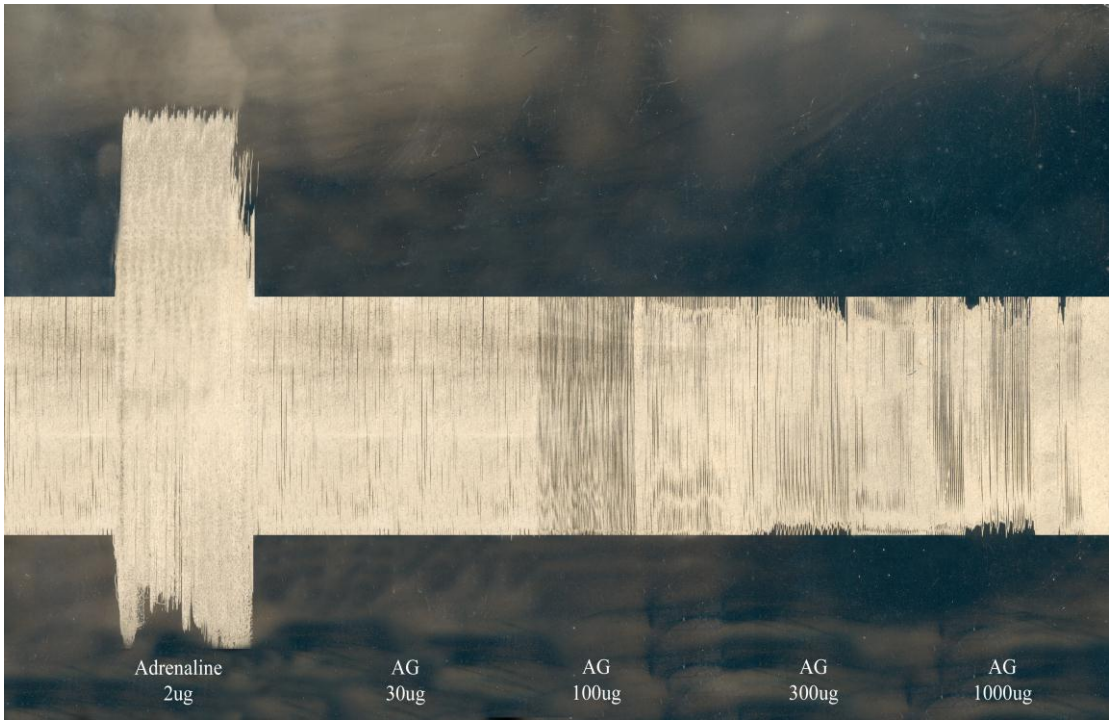


Figure (19): A record demonstrating the effect of Arabic gum on isolated perfused rabbit's heart.

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

It was noticed that carvedilol in increasing doses (2, 4, 8, 16, 32 and 64 μg/ bath) produced no change in the force of spontaneous contraction of isolated perfused rabbit's heart.(Figure 20)

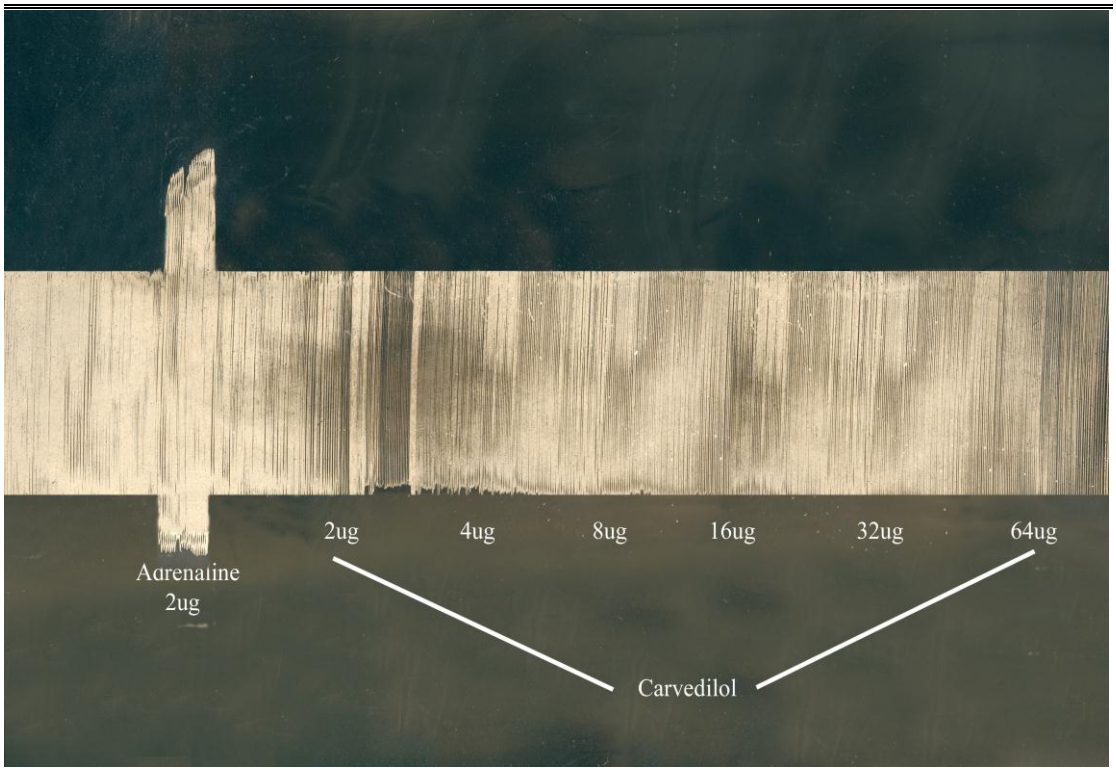


Figure (20): A record demonstrating the effect of carvedilol on isolated perfused rabbit's heart.

3. Effects on isolated perfused rabbit's auricle:

- **Effect of Arabic gum on isolated perfused rabbit's auricle:**

It was observed that addition of Arabic gum in different dose levels (30, 100, 300, and 1000 μg/ ml bath) produced statistically significant ($P < 0.001$) dose related decrease in heart rate of rabbit's auricle with percentage decrease of 16.39 %, 39.34% ,52.46% and 54.09% respectively. (Table 10, Figures 21,22).

- **Site of action of Arabic gum on isolated perfused rabbit's auricle:**

It was observed that blocking of muscarinic receptor did not affect the inhibitory action of Arabic gum (100 ug/ml bath). This indicates that Arabic gum did not act through the muscarinic receptor (Figure 23).

Table (10):Effects of gradually increasing doses of Arabic gum (dose-response curve) on mean ± SE of heart rate of isolated perfused rabbit's auricle (N=6).

	Control	30 ug	100ug	300ug	1000 ug
Heart rate/min M ± SE	91.5 ±2.9	76.5 ± 1.5*	55.5 ± 1.5*	43.5 ± 1.7*	42 ± 1.5*
Percentage of maximum response%		↓ 16.39	↓ 39.34	↓ 52.46	↓ 54.09

* Significant (P < 0.001) compared to the control.

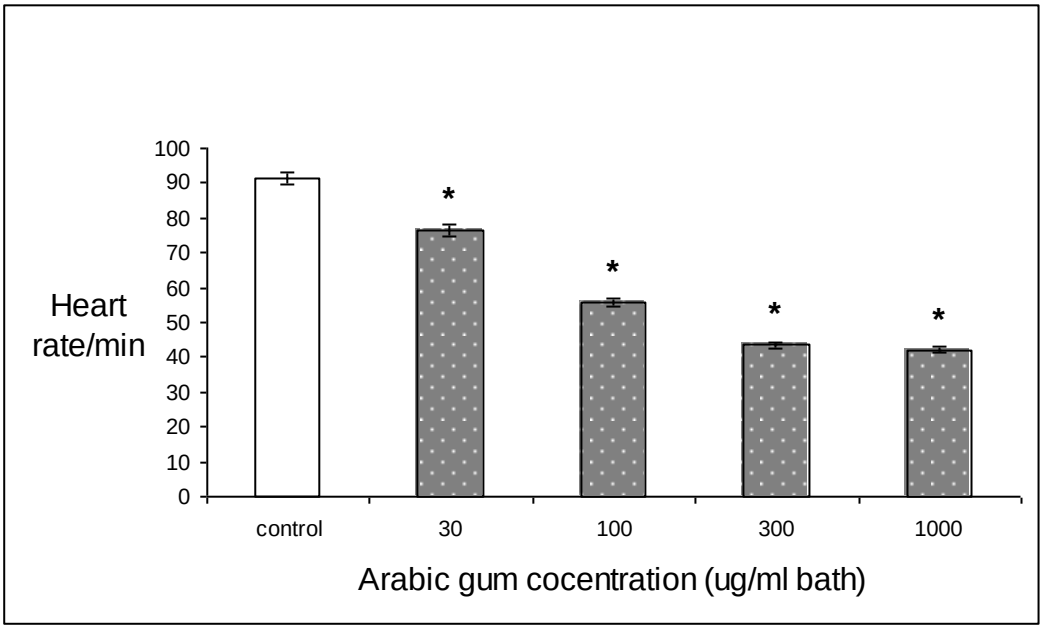


Figure (21): A histogram showing the effects of gradually increasing doses of Arabic gum (dose-response curve) on heart rate of isolated perfused rabbit's auricle.

* Significant (P < 0.001) compared to the control.

Figure (22): A record demonstrating the effect of Arabic gum on isolated perfused rabbit's auricle.

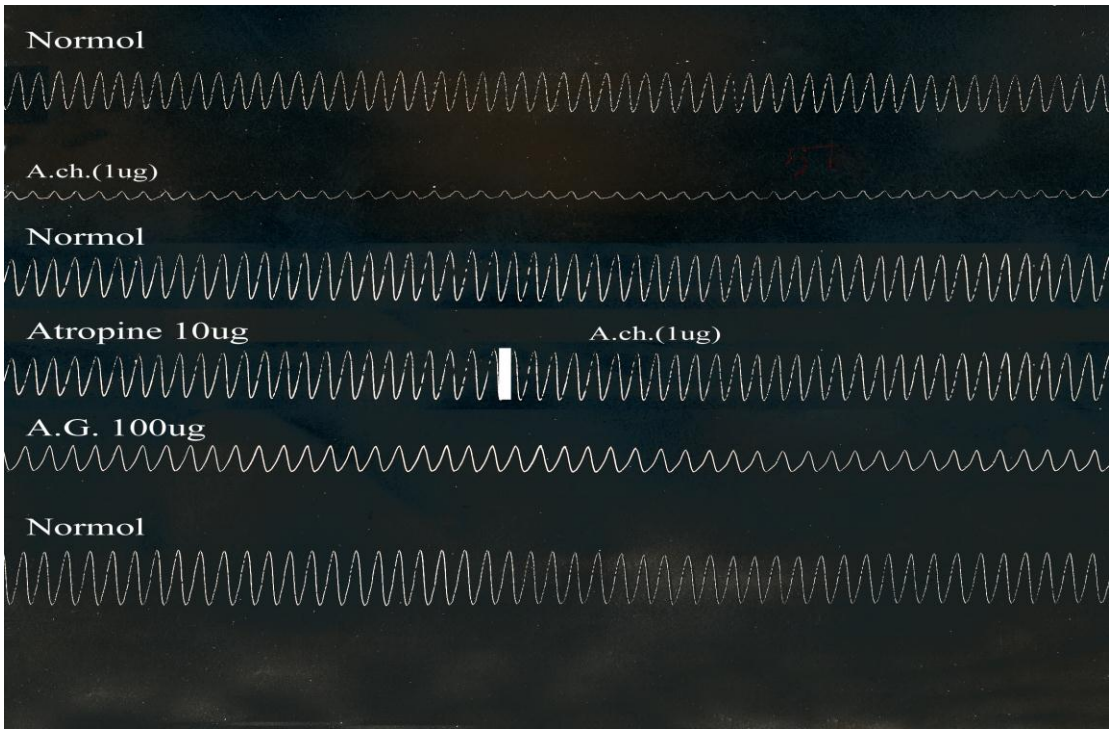


Figure (23): A record demonstrating the site of action of Arabic gum on isolated perfused rabbit's auricle. (Muscarinic receptor).

- **Effect of carvedilol on isolated perfused rabbit's auricle:**

It was observed that addition of carvedilol in different dose levels (2, 4 and 8 μg/ ml bath) produced statistically insignificant ($P > 0.05$) dose related decrease in heart rate of rabbit's auricle . However by increasing the dose of carvedilol (16, 32 and 64 μg/ ml bath) there is statistically significant ($P < 0.001$) dose related decrease in heart rate of rabbit's auricle with percentage decrease of 28.04 %, 38.09% and 39.68% respectively. (Table 11, Figures 24 ,25 a,b).

Table (11):Effects of gradually increasing doses of carvedilol (dose-response curve) on mean ± SE of heart rate of isolated perfused rabbit's auricle (N=6)

	Control	2 ug	4ug	8ug	16 ug	32 ug	64 ug
Heart rate/min M ± SE	94.5 ± 4.5	88.5 ± 4.5#	87 ± 1.7#	84.5 ± 5.1#	68 ± 4.7*	58.5 ± 6.6*	57 ± 5.2*
Percentage of maximum response %		↓ 6.34	↓ 7.93	↓ 10.58	↓ 28.04	↓ 38.09	↓ 39.68

insignificant ($P > 0.05$) compared to the control.
* Significant ($P < 0.001$) compared to the control.

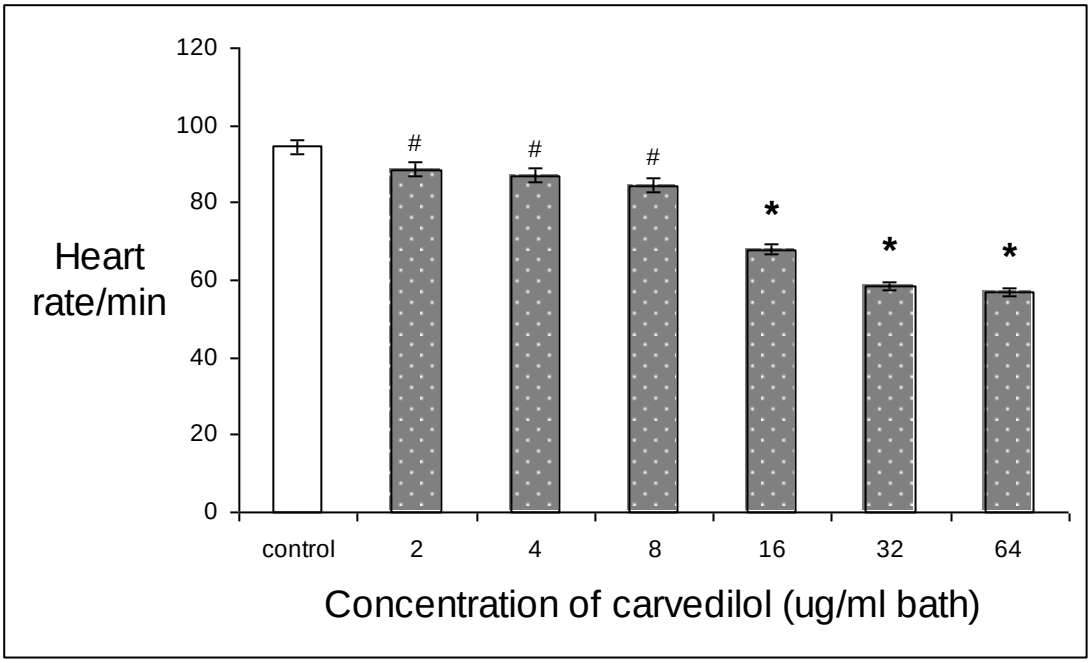


Figure (24): A histogram showing the effects of gradually increasing doses of carvedilol (dose-response curve) on heart rate of isolated perfused rabbit's auricle.

[#] insignificant (P > 0.05) compared to the control.
* Significant (P < 0.001) compared to the control.

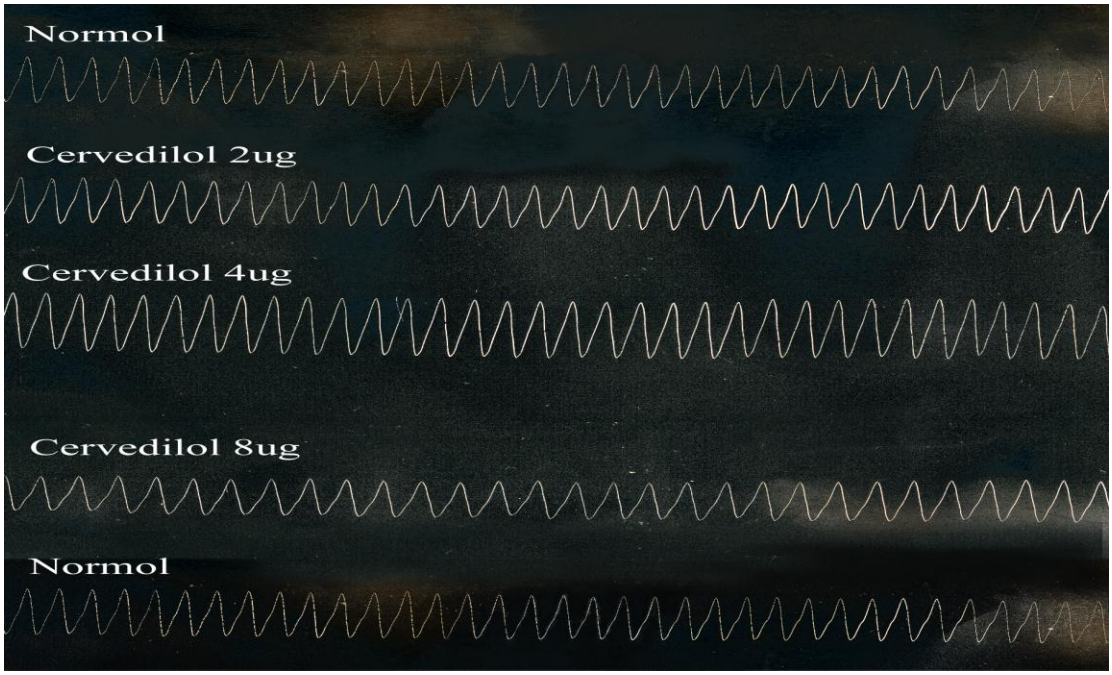
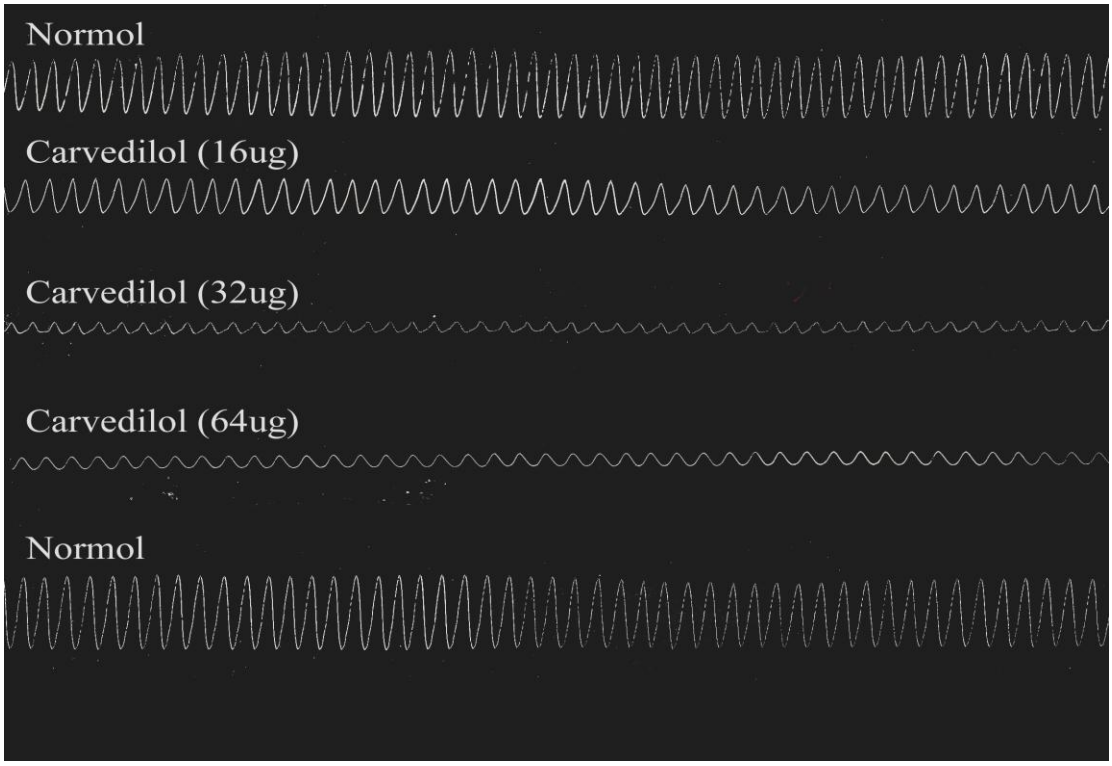


Figure (25 a): A record demonstrating the effect of carvedilol on isolated perfused rabbit's auricle.



Figure(25 b): A record demonstrating the effect of carvedilol on isolated perfused rabbit's auricle.

- **Effect of Arabic gum and carvedilol together on isolated perfused rabbit's auricle:**

It was observed that addition of Arabic gum (100 ug/ml bath) and carvedilol (16 ug/ml bath) together produced statistically significant ($P < 0.01$) decrease in heart rate of rabbit's auricle. Comparing effect of Arabic gum and carvedilol together to that of each drug alone , there is statistically insignificant ($P > 0.05$) decrease in heart rate of rabbit's auricle. (Table 12, Figures 26, 27).

Table (12): Table showing comparison between the effect of either Arabic gum or carvedilol and two drugs together on mean ± SE of heart rate of isolated perfused rabbit's auricle (N=6)

	Control	Arabic gum 100 ug	carvedilol 16ug	Arabic gum and carvedilol
Heart rate/min M ± SE	91.5 ± 2.9	55.5 ± 1.5*	68 ± 4.7*	54 ± 1.5*#
Percentage of maximum response%		↓ 39.34	↓ 25.68	↓ 40.98

* Significant ($P < 0.001$) compared to the control.
# insignificant ($P > 0.05$) compared to Arabic gum and carvedilol each one alone.

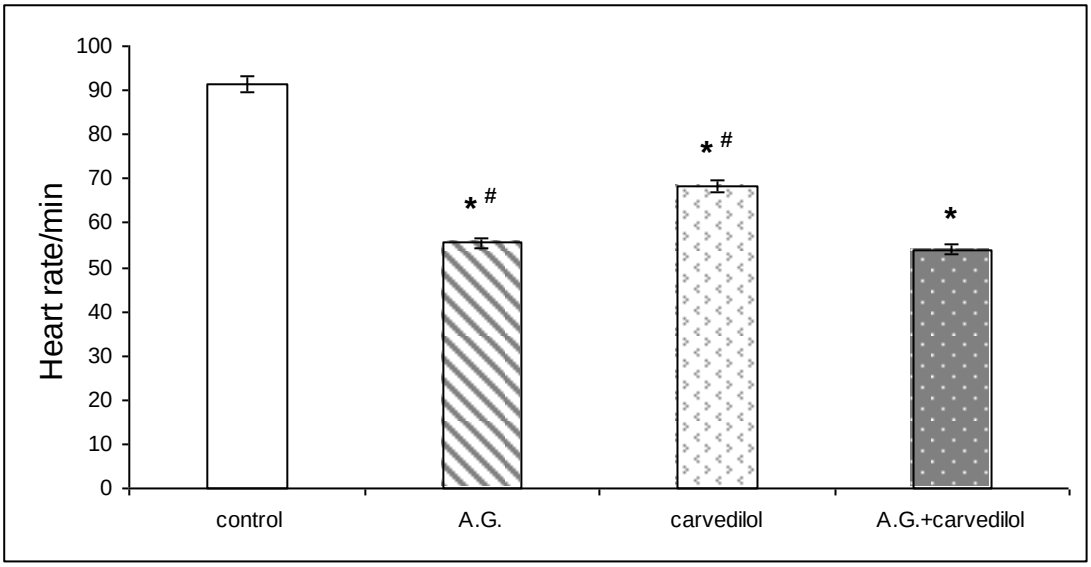


Figure (26): A histogram showing the effects of Arabic gum, carvedilol and two drugs together on heart rate of isolated perfused rabbit's auricle.

* Significant ($P < 0.001$) compared to the control.
# insignificant ($P > 0.05$) compared to Arabic gum and carvedilol each one alone.

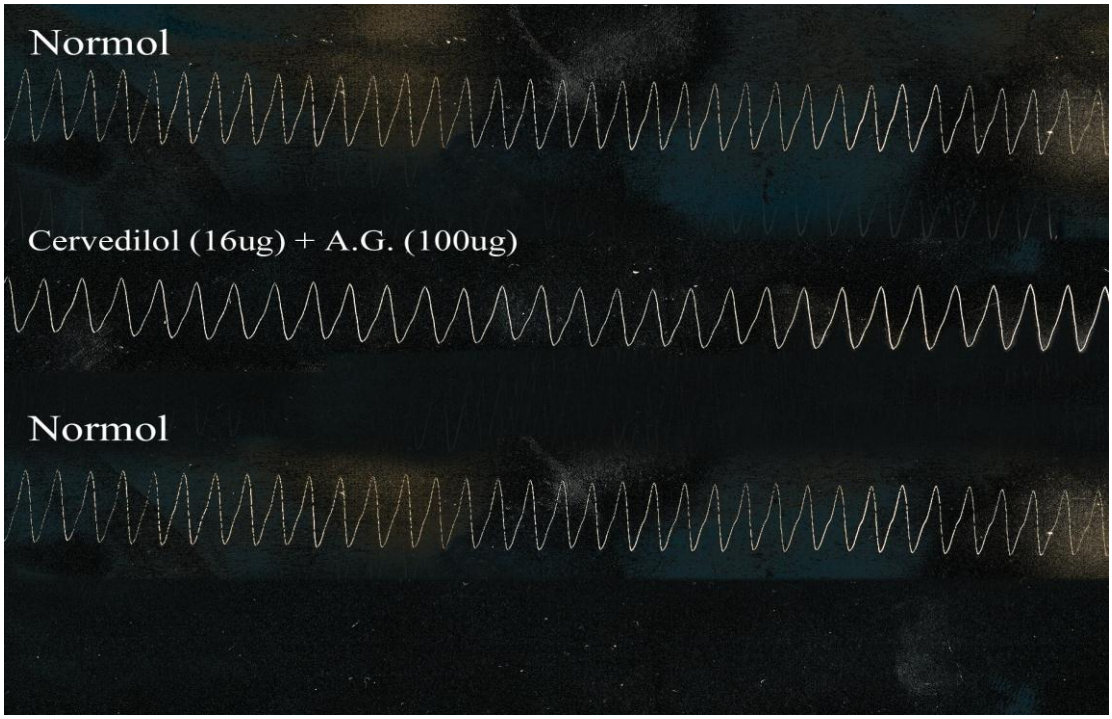


Figure (27): A record demonstrating the effect of Arabic gum and carvedilol together on isolated perfused rabbit's auricle.