RESULTS

Results

I-Acute Toxicity Study

The results of this study were statistically analyzed and arranged in tables (1-4) and graphically illustrated in histograms (1-4) with figures (1-12) showing chromosomal and histopathological changes.

1- Weight, behavior, concentration, and number of deaths:

There were no detectable c hanges in weight between control and etodolac and meloxicam treated groups. Rats showed normal activity, normal feeding rate, and there were no morphological abnormalities. Rats were alert and showed normal movements. There is no reported death in acute toxicity study.

2-Chromosomal Study

Etodolac produced a very highly significant increase ($p<0.001$) in the percentage of chromatid fragment (CF), chromatid deletion(CD) and total number of structural anomalies (TSA) as regard (total with gap &total without gap structural abnormalities) when compared with those in control group. While produced a non significant increase in the percentage of chromatid gap(CG) ($P>0.05$), chromatid break (CB)($P>0.05$), chromatid separation(CS) ($P>0.05$), polyploidy (PP) ring chromosome (RC), centric fusion (CeF), and sticky chromosomes (SC), when compared with those of control group.

Meloxicam produced a very highly significant increase ($p<0.001$) in the percentage of chromatid fragment (CF), chromatid deletion(CD) and total number of structural abnormalities (TSA) as regard (total with gap &total without gap structural abnormalities) when compared with those in control group. While produced a non significant increase in the percentage of chromatid gap(CG) ($P>0.05$), chromatid break (CB) ($P>0.05$), chromatid separation(CS) ($P>0.05$), polyploidy (PP), ring chromosome (RC), centric

fusion (CsF), and sticky chromosomes (SC), when compared with those of control group.

Comparison between etodolac and meloxicam treated groups: There was a non significant difference (P>0.05) between etodolac and meloxicam treated groups after 24 hours as regard all changes.

3- Hepatic changes.

3-A. Biochemical changes:

Etodolac induced a very highly significant increase (P<0.001) in serum AST, and ALP, and a significant increase (P<0.05) in ALT, and bilirubin when compared with those in control rats.

Meloxicam treated rats showed a very highly significant increase (P<0.001) in serum ALT, AST, and ALP. While showed a highly significant increase (P<0.01) in bilirubin when compared with those in control rats.

Comparison between etodolac and meloxicam treated groups

Meloxicam showed a very highly significant increase (P<0.001) in serum ALT, a significant increase (P<0.05) in AST, but a non significant increase (P>0.05) in serum bilirubin as compared with those of etodolac treated rats. While etodolac showed a very highly significant increase (P<0.001) in serum ALP as compared with those of meloxicam treated rats.

3-B. Histopathological changes:

Control Group

Histopathological examination of the liver of the control group showed normal architecture in all rats in the form of hepatocytes arranged in hepatic figures radiating from central vein. Hepatocytes are polygonal in shape; cytoplasm is acidophilic with one or more rounded nuclei. Portal canal with normal vessels present at some angles of hepatic lobules.

Etodolac Treated group

The histopathological changes in the rats' liver showed moderate hepatic lesions due to acute intoxication with etodolac including, dilatation and congestion of the central vein and sinusoids, dilatation of portal venules, lymphocytic infiltration of portal tract, hydropic degeneration of hepatocytes .

Meloxicam treated group

The histopathological changes in the rats' liver showed moderate hepatic lesions due to acute intoxication with meloxicam including, dilatation and congestion of the central vein and sinusoids, dilatation of portal venules and lymphocytic infiltration of portal tract, hydropic degeneration of hepatocytes with obliteration of some sinusoids, and fatty changes appearing as intracytoplasmic microvesicles .

Comparison between etodolac and meloxicam treated groups

Etodolac exerted hepatic lesions which were slightly less than those induced by meloxicam.

4-Renal Changes

4-A. Biochemical changes

Etodolac treated rats showed a significant increase ($P<0.05$) in serum BUN, but a non significant increase ($P>0.05$) in serum Cr when compared to control group. Rats treated with meloxicam showed a very highly significant increase ($P<0.001$) in serum BUN, but a non significant increase ($P>0.05$) in serum Cr when compared to control group.

Comparison between etodolac and meloxicam treated groups: Meloxicam showed a very highly significant increase ($P<0.001$) in serum BUN, but a non significant increase ($P>0.05$) in serum Cr when compared to etodolac group.

4-B. Histopathological changes:

Control Group

Histopathological examination of the kidney of control rats showed normal architecture in all rats in the form of cortex contains normal renal corpusles. The proximal convoluted tubules were formed of pyramidal cells with central rounded nuclei and acidophilic cytoplasm. The distal convoluted tubules contain cubical cells with apical rounded nuclei. The medulla contains collecting tubules lined with cubical and columnar cells.

Etodolac treated group

The microscopic findings of nephrotoxic effect of etodolac were moderate lesions. There were dilatation and congestion of intertubular vessels, inflammatory cellular infiltration mostly perivascular, interstitial hemorrhage, cloudy swelling, and mild glomerular hemorrhage. Also, there were hypercellularity of the glomeruli, and lymphocytic infiltration.

Meloxicam treated group

The microscopic findings of nephrotoxic effect of meloxicam were moderate lesions. There were dilatation and congestion of intertubular vessels, inflammatory cellular infiltration mostly perivascular, interstitial hemorrhage, hydropic changes, and mild glomerular hemorrhage. Also, there were hypercellularity of the glomeruli, and lymphocytic infiltration.

Comparison between etodolac and meloxicam treated groups: Meloxicam exerted renal lesions which were slightly more severe than those induced by etodolac.

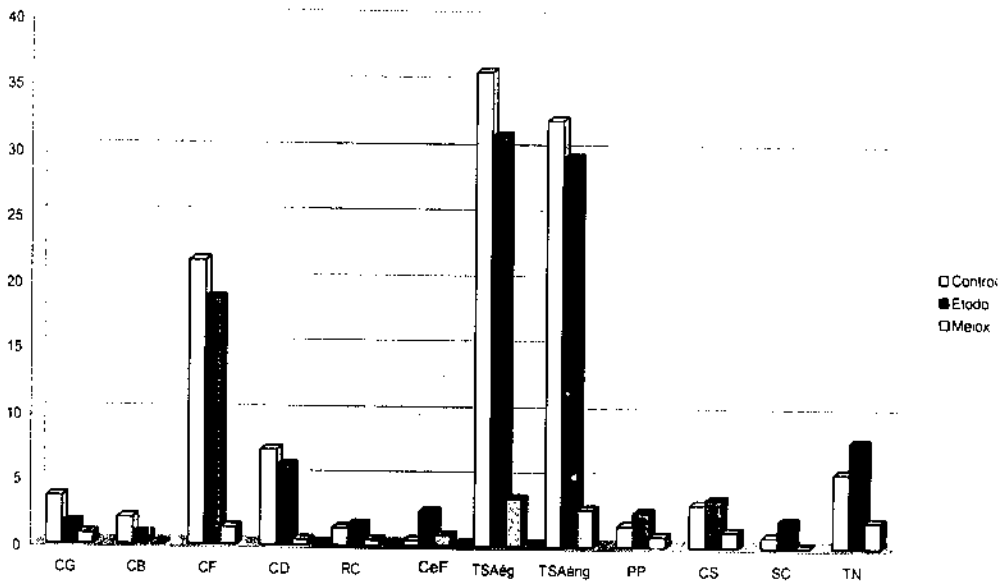
Table (1): Comparison of chromosomal aberrations in metaphases (n=250) of acute etodolac and meloxicam treated groups vs. control group.

Chromos. aberrations	Control		Acute				X^2	P
			etodolac		meloxicam			
	No	%	No	%	No	%		
A-Structural								
-Gap	2	0.8	4	1.6	9	3.6	5.31	>0.05
-Break	0	0.0	2	0.8	5	2.0	5.48	>0.05
-Frag	3	1.3	47*	18.8	54*	21.6	51.20	<0.001
-Deletion	1	0.4	15*	6.0	18*	7.2	15.22	<0.001
-Ring chrom.	1	0.4	4	1.6	3	1.3	1.77	>0.05
-Cent fusion	2	0.8	6	2.6	1	0.4	2.72	>0.05
-Total é gab	9	3.6	78*	31.2	90*	36.0	84.79	<0.001
-Total without gab	7	2.8	74*	29.6	81*	32.4	78.85	<0.001
B-Numerical								
-Polyploidy	2	0.8	6	2.6	4	1.6	2.03	>0.05
-Separation	3	1.2	9	3.6	8	3.2	3.18	>0.05
-Stick chrom	0	0.0	5	2.0	2	0.8	5.48	>0.05
-Total numer	5	2	20	8	14	5.6	9.25	<0.01

* sig. higher number than control

N.B. There is non sig. difference between etodolac and meloxicam treated groups.

Comparison of chromosomal aberration in metaphases (n=250) of acute etodolac and meloxicam treated group vs control group.



Histogram (1)

Table(2): Effects of acute etodolac toxicity on serum levels of ALT, AST, ALP, Bilirubin, BUN and creatinine in normal adult female albino rats.

Liver and kidney function tests	Control X ± SD	Acute etod X ± SD	t-test	P-value	Signif.
Liver function					
ALT(IU/L)	27.25±6.94	34.25±4.24	2.43	<0.05	*
AST (IU/L)	25.78±5.14	81.79±8.69	17.54	<0.001	* * *
Bil (mg/dl)	0.26±0.03	0.31±0.05	2.91	<0.05	*
ALP(IU/L)	103.88±14.80	280.33±5.91	31.32	<0.001	* * *
Kidney function					
BUN(mg/dl)	67.41±8.56	75.12±5.28	2.17	<0.05	*
Cr (mg/dl)	1.03±0.18	1.05±0.20	0.21	>0.05	NS

N.B

X = Represent mean values of twenty rats

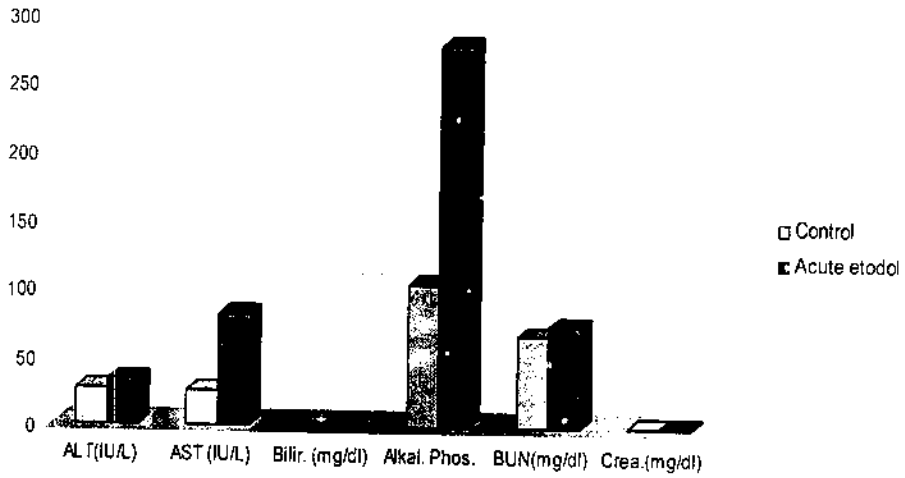
NS= Non significant

* = Significant

** = Highly significant

* * *= Very highly significant

Liver and kideny function tests of acute etodolae group and control.



Histogram (2)

Table (3): Effects of acute meloxicam toxicity on serum levels of ALT, AST, ALP, Bil, BUN and Cr in normal adult female albino rats.

Liver and kidney function tests	Control X ± SD	acute melox X ± SD	t-test	P-value	Signif.
Liver function					
ALT(IU/L)	27.25±6.94	129.92±6.63	15.22	<0.001	* * *
AST (1U/L)	25.78±5.14	86.42±3.08	45.26	<0.001	* * *
Bil(mg/dl)	0.26±0.03	0.37±0.16	3.02	<0.01	* *
ALP (IU/L)	103.88±14.80	231.82±14.6	17.41	<0.001	* * *
Kidney function					
BUN(mg/dl)	67.41±8.56	89.67±8.44	5.24	<0.001	* * *
Cr (mg/dl)	1.03±0.18	1.27±0.87	0.76	>0.05	NS

N.B

X = Represent mean values of twenty rats

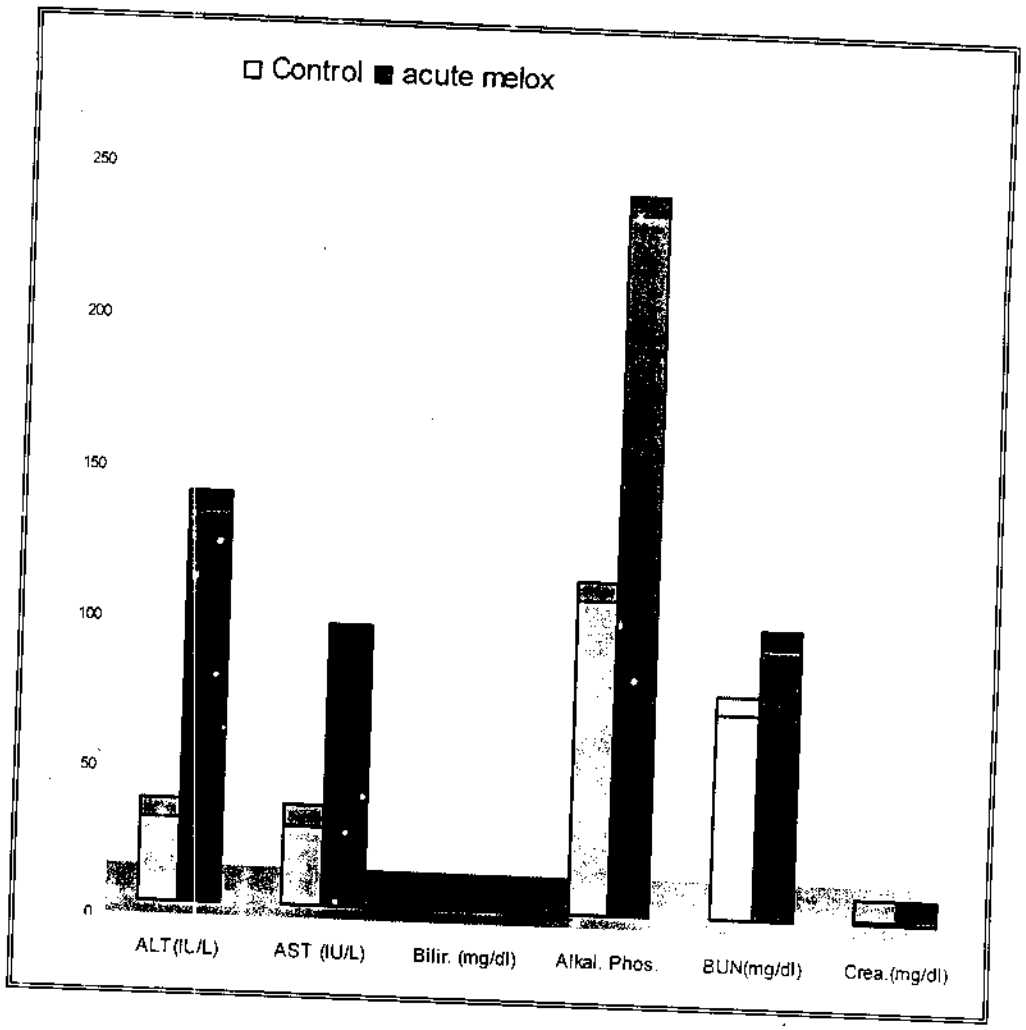
NS= Non significant

* = Significant

** = Highly significant

*** = Very highly signilicant

Liver and kidney function tests of acute meloxicam group and control.



Histogram (3)

Table(4): Comparison between the effects of acute toxicity of etodolac & meloxicam on serum levels of ALT, AST, ALP, Bil, BUN and creatinine in normal adult female albino rats.

Liver and kidney function tests	acute etodolac X ± SD	acute meloxicam X ± SD	t-test	P-value	Signif.
Liver function					
ALT(IU/L)	34.25±4.24	129.92±6.63	16.83	<0.001	* * *
AST (IU/L)	81.79±8.69	86.42±3.08	2.25	<0.05	*
Bil (mg/dl)	0.31±0.05	0.37±0.16	1.01	>0.05	NS
ALP (IU/L)	280.33±5.91	231.82±14.6	8.71	<0.001	* * *
Kidney function					
BUN(mg/dl)	75.12±5.28	89.67±8.44	4.13	<0.001	* * *
Cr (mg/dl)	1.05±0.20	1.27±0.87	0.70	>0.05	NS

N.B

X = Represent mean values of twenty rats

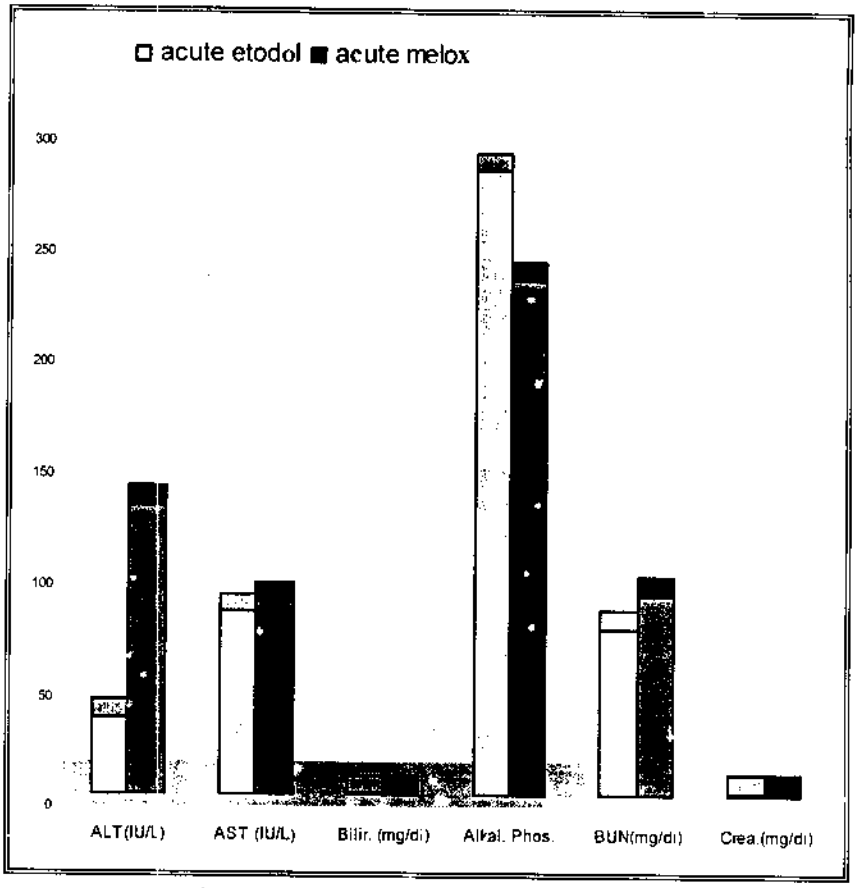
NS= Non significant

* = Significant

** = Highly significant

* * *= Very highly significant

Liver and kidney function tests of acute etodolac and acute meloxicam groups.



Histogram (4)

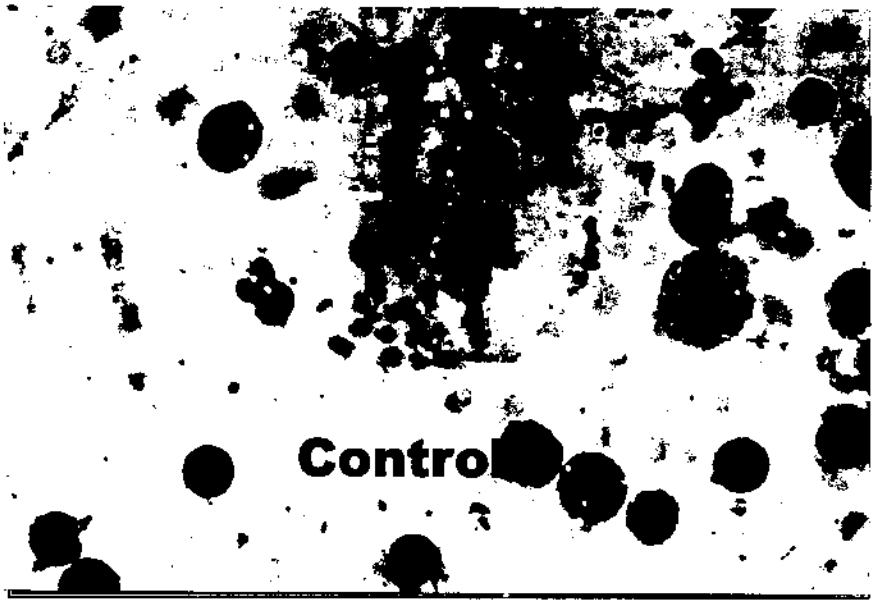


Figure (6): A photomicrograph of a normal metaphase spread prepared from the bone marrow cells of a control rat showing normal metaphase (Giemsa Stain Original Magnification {OM} x 1000).

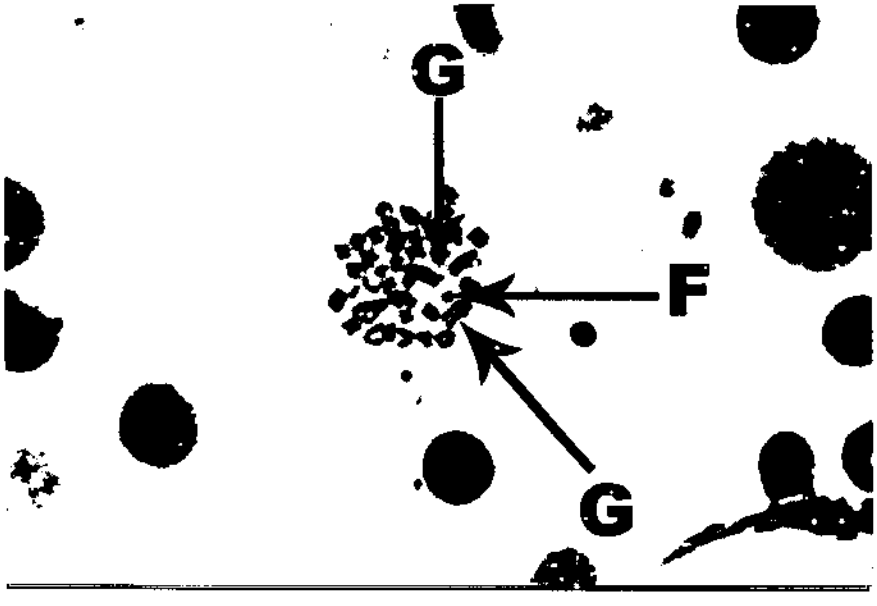
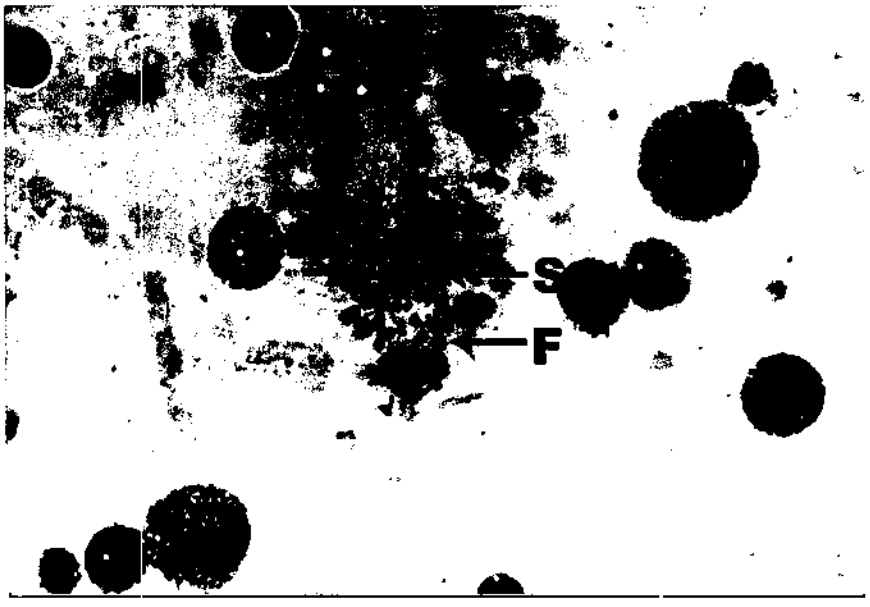


Figure (7): A photomicrograph of a metaphase spread showing chromatid gap (G) and chromatid fragment (F) in bone marrow cells of rats treated with siagle toxie dose of Etod (Giemsa Stain OM x 1000).



Figure(8): A photomicrograph of a metaphase spread showing chromatid fragment (F) and chromatid separation (S) in bone marrow cells of rats treated with single toxic dose of Melox (Giemsa Stain OM x 1000).

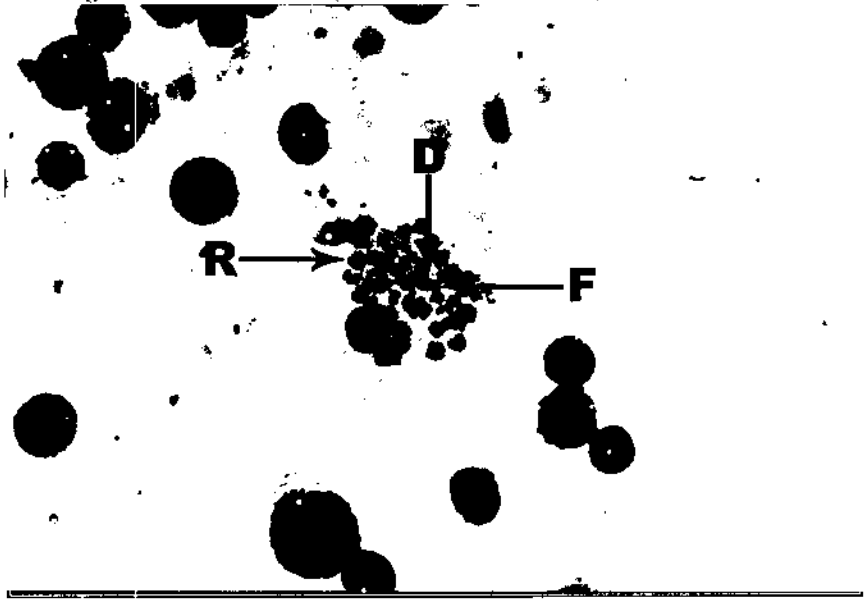
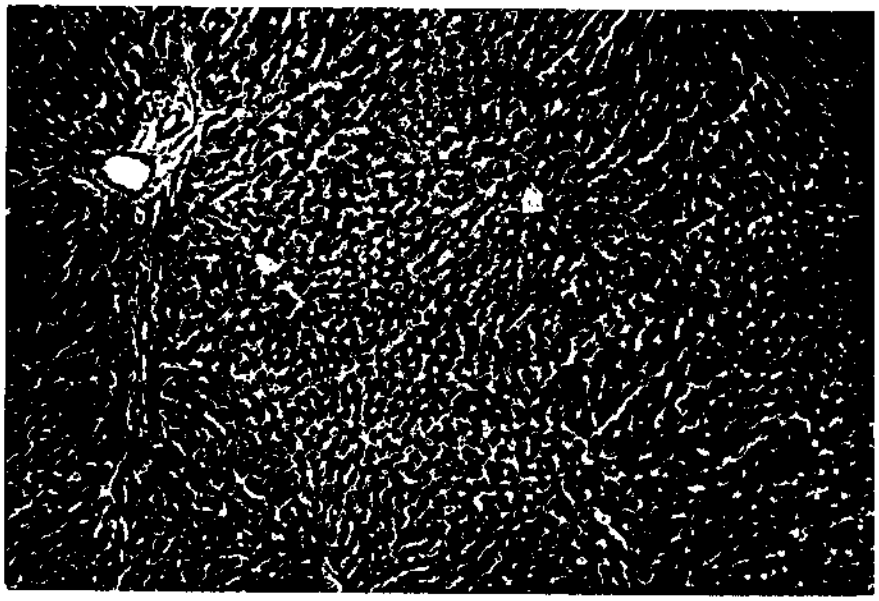


Fig. (9): A photomicrograph of a metaphase spread in bone marrow cells af rats treated once orally with 1/2 the LD_{50} of Melox showing chromatid deletion (D), ch. fragment (F) and ring chromosome (R) (Giemsa Stain OM x 1000).



Figure(10): A photomicrograph of a section in rat liver of a control group showing ordinary arranged cords of normal hepatocytes and normal portal tracts, central vein and sinusoids (H x & E x 100).

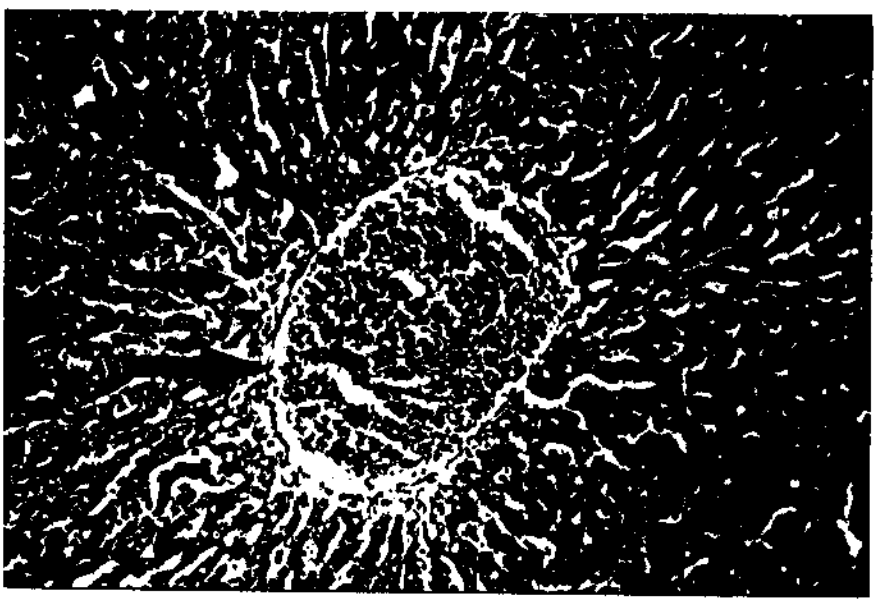


Figure (11): A photomicrograph of a section in rat liver treated once orally with 1/2 of the LD_{50} of Melox showing congested central vein (A) and sinusoids (B) (H x & E x 400).

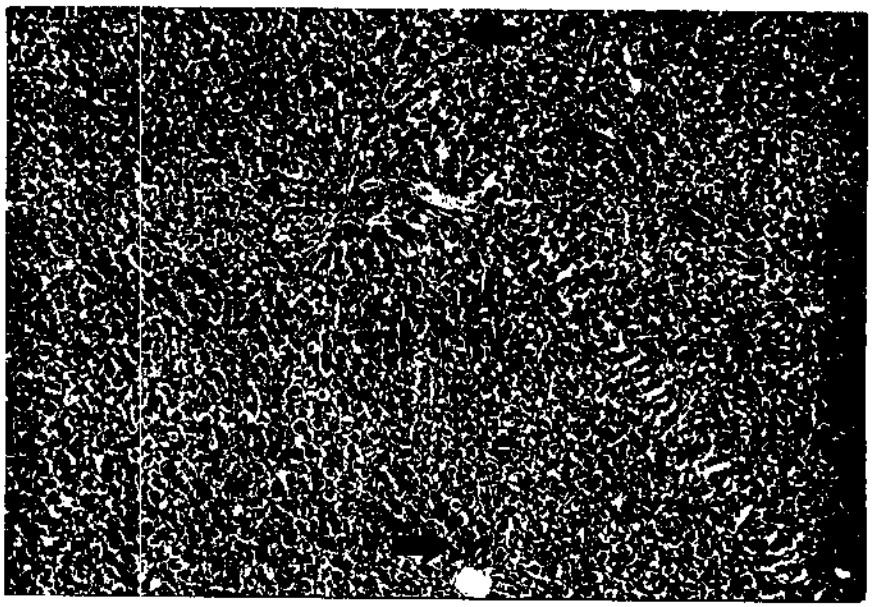


Figure (12): A photomicrograph of a section in rat liver treated once orally with 1/2 the LD_{50} of Etod showing hydropic hepatocellular degeneration (A), with obliteration of sinusoids (B) (H x & E x 100).

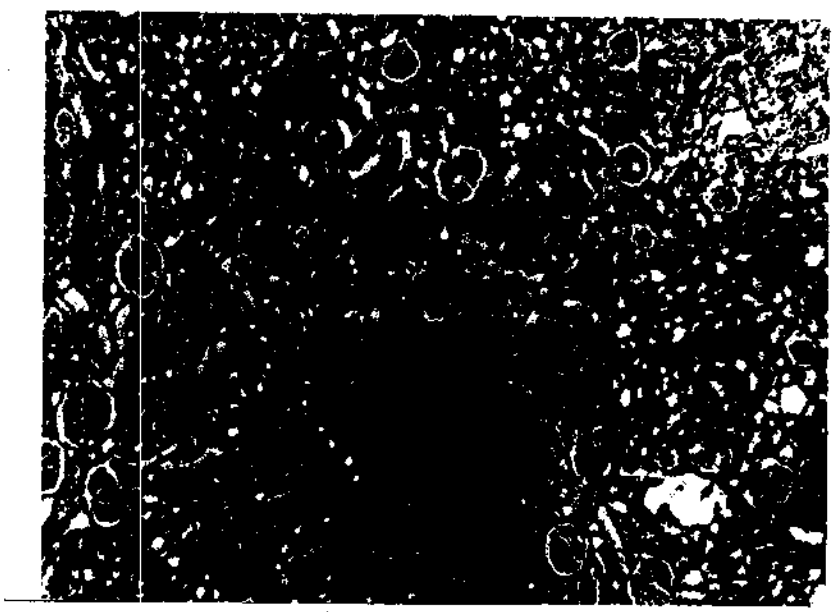


Figure (13): A photomicrograph of a section in rat kidney of a control group showing normal glomeruli and tubules (H x & E x 100).

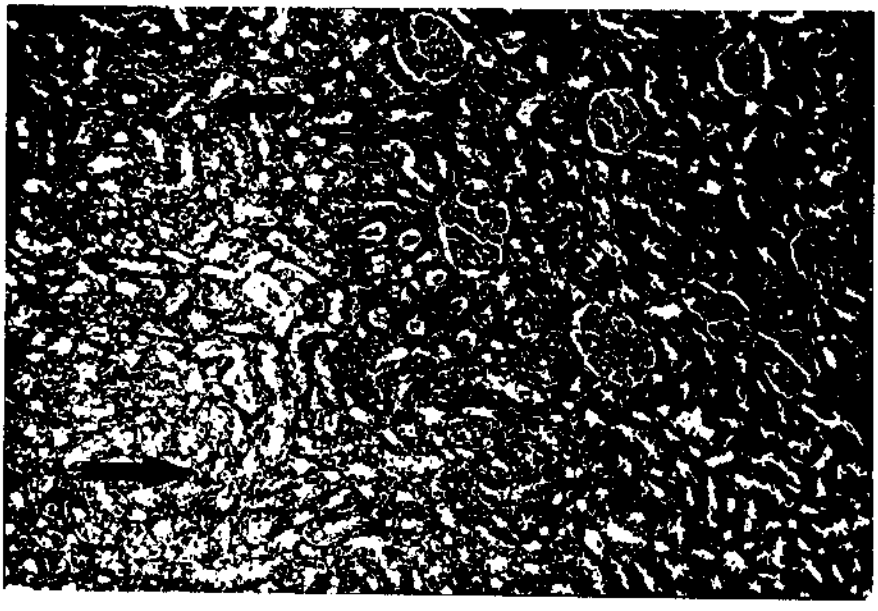


Figure (14): A photomicrograph of a section in rat kidney treated once orally with 1/2 the LD_{50} of Melox showing hydropic degeneration (A) and congested capillaries (B) (H x & E x 400).

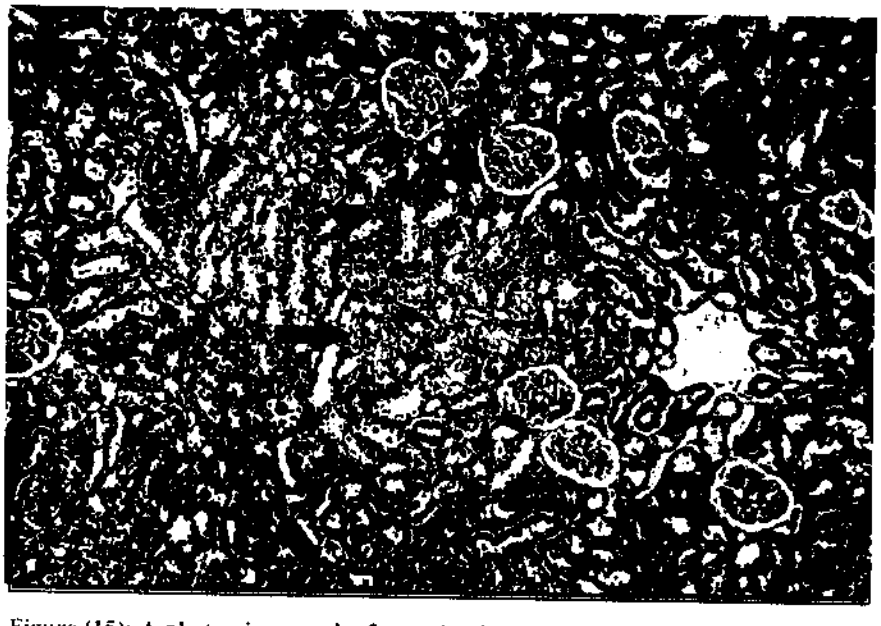


Figure (15): A photomicrograph of a section in rat kidney treated once orally with 1/2 the LD_{50} of Etod showing hydropic degeneration (A), hypercellular glomeroli (B) and congested capillaries (C) (H x & E x 400).

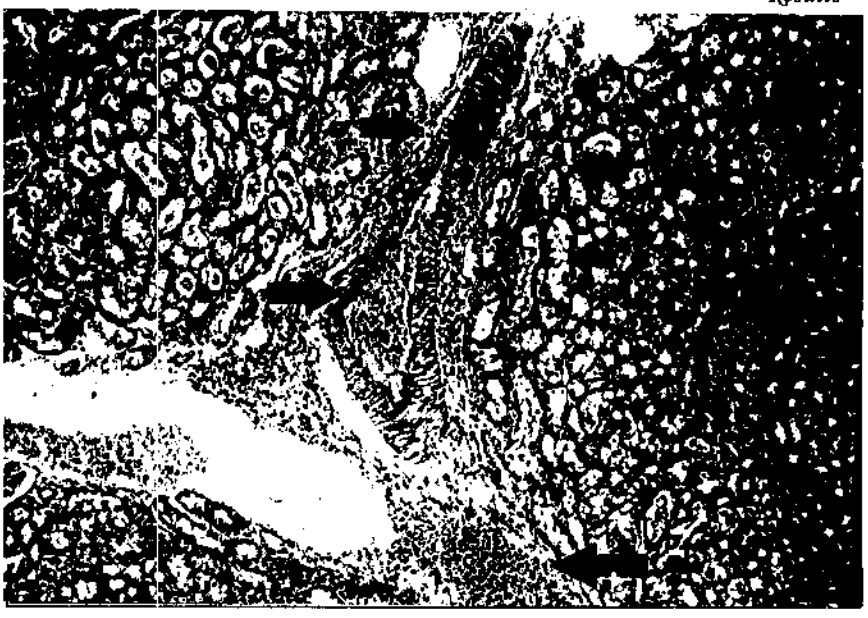


Figure (16): A phntomicrograph of a section in rat kidney treated once orally with 1/2 the LD_{50} of Melox showing dilated congested blood vessels(A), interstitial hemorrhage(B), hydropic degeneration (C), perivascular inflammatory cellular infiltration (D) (H x & E x 400).

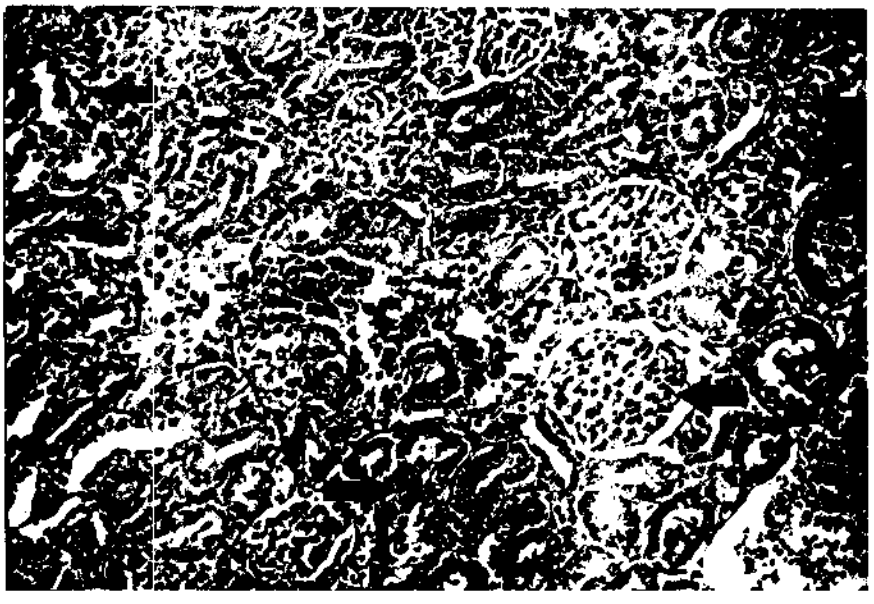


Figure (17): A phntomicrograph of a section in rat kidney treated once orally with 1/2 the LD_{50} of Melox showing congested intertubular blood vessels (A), glomerular hemorrhage (B), and hydropic degeneration (C) (H x & E x 400).

II-Short Term Chronic Toxicity Study

The results of this study were statistically analyzed and arranged in tables (5-12) and graphically illustrated in histograms (5-12) with figures (13-32) showing chromosomal and histopathological changes.

1- Weight, behavior, concentration, and number of deaths:

There were no detectable changes in weight between control and treated rats. Rats showed normal activity, normal feeding rate, and there were no morphological abnormalities. Rats were alert and showed normal movements.

The number of deaths that occurred after 2 and 4 weeks of administration of the $1/10^{th}$ of the LD_{50} of meloxicam was 2 and 3 rats respectively. While, no deaths were reported after 2 and 4 weeks of administration of the $1/10^{th}$ of the LD_{50} of etodolac (each group compromised of 20 rats).

2- Chromosomal Study

Changes in the chromosomal pattern produced by repeated dose etodolac and meloxicam for 2 weeks and 4 weeks have been statistically analyzed and outlined in tables (5 - 6), graphically illustrated in histograms (5 - 6), and photographed in figures (13-19).

I-At the end of the 2^{nd} week

Etodolac-treated rats showed a very highly significant increase ($P<0.001$) in the percentage of CF, total with gap as well as total without gap structural anomalies and a highly significant increase ($P<0.01$) in the percentage of CD as compared with those in control rats.

Etodolac treated rats showed a significant increase ($P<0.05$) in the percentage of PP, as compared with those in control rats. Etodolac induced a non significant increase ($P>0.05$) in the percentage of CG, CB, CeF, RC, CS and SC as compared with those in control rats.

Meloxicam-treated rats showed a very highly significant increase ($P<0.001$) in the percentage of CF, total with gap as well as total without

gap structural anomalies and a highly significant increase (P<0.01) in the percentage of CD as compared with those in control rats.

Meloxicam induced a non significant increase (P>0.05) in the percentage of CG, CB, RC, CeF, PP, CS, SC as compared with those in control rats.

Comparison between etodolac and meloxicam treated groups

Meloxicam induced a significant increase (P<0.05) in the percentage of CD and a non significant increase (P>0.05) in the percentage of CG, CB, CF, RC, CeF, total with gap, total without gap, PP,CS, and SC as compared with those in etodolac-treated rats.

II-At the end of the 4th week

Etodolac induced a very highly significant increase (P<0.001) in the percentage of CF, total with gap and total without gap, a significant increase (P<0.05) in the percentage of CS and CD and non significant increase (P>0.05) in the percentage of CG, CB, RC, CeF, PP, and SC as compared with those in the control rats.

Meloxicam induced a highly significant increase (P<0.001) in the percentage of CF, total with gap and total without gap, a significant increase (P<0.05) in the percentage of CD and non significant increase (P>0.05) in the percentage of CG, CB, RC, CeF, PP, CS and SC as compared with those in the control rats.

Comparison between etodolac and meloxicam treated groups: Etodolac-treated group showed a non significant increase (P>0.05) in the percentage of CG, CB, CF, CD, RC, CeF, total with gap, total without gap, PP, CS, and SC as compared with those in meloxicam treated group.

3- Hepatic changes.

3-A. Biochemical changes

At the end of the 2nd week

Etodolac treated rats showed a very highly significant increase ($P<0.001$) in serum AST, bilirubin, and ALP and a highly significant increase ($P<0.01$) in serum ALT when compared with those in control rats.

Also meloxicam treated rats showed a very highly significant increase ($P<0.001$) in serum ALT, AST, bilirubin, and ALP when compared with those in control rats.

Comparison between etodolac and meloxicam treated groups

Meloxicam showed a very highly significant increase ($P<0.001$) in serum ALP, a highly significant increase ($P<0.01$) in serum BIL, a significant increase ($P<0.05$) in serum ALT but a non significant increase ($P>0.05$) in serum AST when compared with those of etodolac treated rats.

At the end of the 4th week

Etodolac treated rats showed a very highly significant increase ($P<0.001$) in serum ALT, and ALP but a non significant increase ($P>0.05$) in AST, and bilirubin, when compared with those in control rats.

Also meloxicam treated rats showed a very highly significant increase ($P<0.001$) in serum ALT, and ALP but a non significant increase ($P>0.05$) in AST, and bilirubin, when compared with those in control rats.

Comparison between etodolac and meloxicam treated groups:

Meloxicam showed a very highly significant increase ($P<0.001$) in serum ALP, a highly significant increase ($P<0.01$) in serum AST, but a non significant increase ($P>0.05$) in serum ALT and BIL when compared with those of etodolac treated rats.

3-B. Histopathological changes

The results obtained from the effects of etodolac and meloxicam at the end of the 2nd and 4th week after daily oral administration of 1/10th of their LD_{50} on liver histopathology were photographed in figures (20-24).

I-At the end of the 2nd week

Etodolac treated group

The histopathological changes in the rats' liver showed moderate hepatic lesions due to intoxication with etodolac including, dilatation and congestion of the central vein and sinusoids, dilatation of portal venules, lymphocytic infiltration of portal tract, hydropic degeneration of hepatocytes, fatty changes (microvesicular type), and hepatic focal necrosis.

Meloxicam treated group

The histopathological changes in the rats' liver treated by meloxicam showed moderate hepatic lesions, including, dilatation and congestion of the central vein and sinusoids, dilatation of portal venules and lymphocytic infiltration of portal tract, bile ductular proliferation, diffuse vacuolar degeneration of hepatocytes with obliteration of some sinusoids, and fatty changes appearing as intracytoplasmic microvesicles.

Comparison between etodolac and meloxicam treated groups: Meloxicam exerted hepatic lesions which were slightly more severe than those induced by etodolac.

II- At the end of the 4th week

Etodolac treated group

The histopathological changes in the rats' liver showed mild to moderate hepatic lesions due to intoxication with etodolac including, dilatation and congestion of the central vein and sinusoids, dilatation of portal venules ,lymphocytic infiltration of portal tract, hydropic degeneration of hepatocytes, hemosidren pigment (indicating old hemorrhage) , hepatic focal necrosis .

Meloxicam treated group

The histopathological changes in the rats' liver treated by meloxicam showed mild to moderate hepatic lesions, including, dilatation and congestion of the central vein and sinusoids, dilatation of portal venules

and lymphocytic infiltration of portal tract, marked eosinophilia, vacuolar degeneration of hepatocytes, hepatic focal necrosis.

Comparison between etcdolac and meloxicam treated groups: Meloxicam exerted hepatic lesions which were slightly more severe than those induced by etodolac.

4-Kidney function changes

I-At the end of the 2nd week

Etodolac treated rats showed a very highly significant increase ($P<0.001$) in serum BUN and serum Cr when compared with those in control rats. While meloxicam treated rats showed a very highly significant increase ($P<0.001$) in serum Cr but a non significant increase ($P>0.05$) in serum BUN when compared with those in control rats.

Comparison between etodolac and meloxicam treated groups:

Etodolac showed a significant increase ($P<0.05$) in serum BUN and a non significant increase ($P>0.05$) in serum Cr when compared with those of meloxicam treated rats.

II-At the end of the 4th week

Etodolac treated rats showed a significant increase ($P<0.05$) in serum BUN hut a non significant increase ($P>0.05$) in serum Cr when compared with those in control rats. Also meloxicam treated rats showed a significant increase ($P<0.05$) in serum BUN and and a non significant increase ($P>0.05$) in serum Cr when compared with those in control rats.

Comparison between etodolac and meloxicam treated groups: Etodolac showed a non significant increase ($P>0.05$) in serum Cr and BUN when compared with those of meloxicam treated rats.

4-B. Histopathological changes

The results obtained from the effects of etodolac and melnxicam at the end of the 2nd and 4th week after daily oral administration of 1/10th of their LD_{50} on kidney histopathology were photographed in figures (25-30).

I-At the end of the 2nd week

Control Group

Histcpathological examination of the kidney of control rats showed normal architecture in all rats in the form of cortex contains normal renal corpusles. The proximal convoluted tubules are formed of pyramidal cells with central rounded nuclei and acidophilic cytoplasm. The distal convoluted tubules contain cubical cells with epical rounded nuclei. The medulla contains collecting tubules lined with cubical and columnar cells.

Etodolac treated group

The microscopic findings of nephrotoxic effects of etodolac were moderate lesions. There were dilatation and congestion of intertubular vessels, inflammatory infiltrate, interstitial hemorrhage, cloudy swelling, focal hydropic changes, focal hyaline cast formation, and mild cellular oedema.

Meloxicam treated group

The microscopic findings of nephrotoxic effects of meloxicam were moderate lesions. There were dilatation and congestion of intertubular vessels, chronic lymphoplasma infiltration, perivascular focal inflammatory cellular infiltration, interstitial hemorrhage, cloudy swelling, hydropic changes, glomerular hemorrhage.

Comparison between etodolac and meloxicam treated groups: Meloxicam exerted renal lesions which were similar to those induced by etodolac.

II-At the end of the 4th week

Etodolac treated group

The microscopic findings of nephrotoxic effects of etodolac were mild to moderate lesions. There were dilatation and congestion of intertubular vessels, inflammatory cellular infiltration mostly perivascular, interstitial hemorrhage, cloudy swelling, severe stromal inflammation, and mild glomerular hemorrhage.

Meloxicam treated group

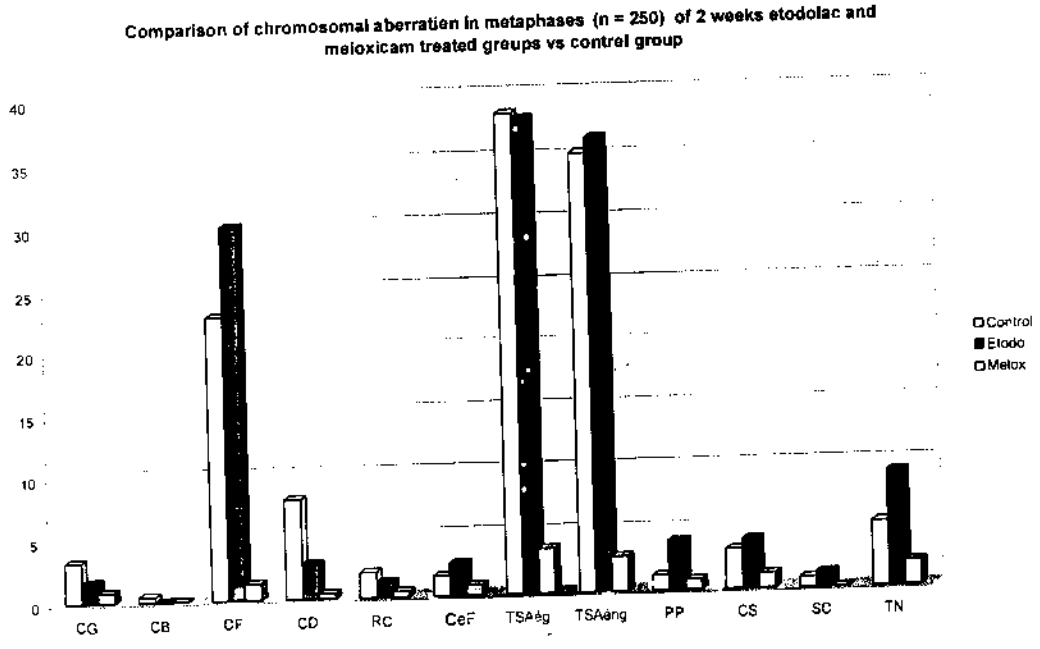
The microscopic findings of nephrotoxic effects of meloxicam were mild to moderate lesions. There were dilatation and congestion of intertubular vessels, inflammatory cellular infiltration mostly perivascular, interstitial hemorrhage, cloudy swelling, and mild glomerular hemorrhage.

Comparison between etodolac and meloxicam treated groups: Meloxicam exerted renal lesions which were similar to those induced by etodolac.

Table (5): Comparison of chromosomal aberrations in metaphases (n=250) of 2 weeks etodolac and meloxicam treated groups vs. control group.

Chromos. aberrations	Cntrol		2 weeks treated				X^2	P
			etodolac		meloxicam			
	No	%	No	%	No	%		
A-Structural								
-Gap	2	0.8	4	1.6	8	3.2	4.08	>0.05
-Break	0	0.0	0	0.0	1	0.4	2.0	>0.05
-Frag	3	1.3	75*	30.0	57*	22.8	76.10	<0.001
-Deletion	1	0.4	7*	2.8	12*	8.0	9.35	<0.01
-Ring chrom.	1	0.4	3	1.2	5	2.0	2.7	>0.05
-Cent fusion	2	0.8	6	2.6	4	1.6	2.03	>0.05
-Total ć gab	9	3.6	95*	38.0	96*	38.4	102.04	<0.001
-Total without gab	7	2.8	91*	36.4	88*	35.2	97.42	<0.001
B-Numerical								
-Polyploidy	2	0.8	10*	4.0	3	1.2	7.76	<0.05
-Separation	3	1.2	10	4.0	8	3.2	3.82	>0.05
-Stick chrom.	0	0.0	3	1.2	2	0.8	2.82	>0.05
-Total numer.	5	2	23*	9.2	13	5.2	12.59	<0.01

* sig. higher number than control.


Comparison of chromosomal aberration in metaphases (n = 250) of 2 weeks etodolac and meloxicam treated groups vs control group
40
35
30
25
20
15
10
5
0
CG
CB
CF
CD
RC
CeF
TSAég
TSAáng
PP
CS
SC
TN
Control
Etodo
Melox

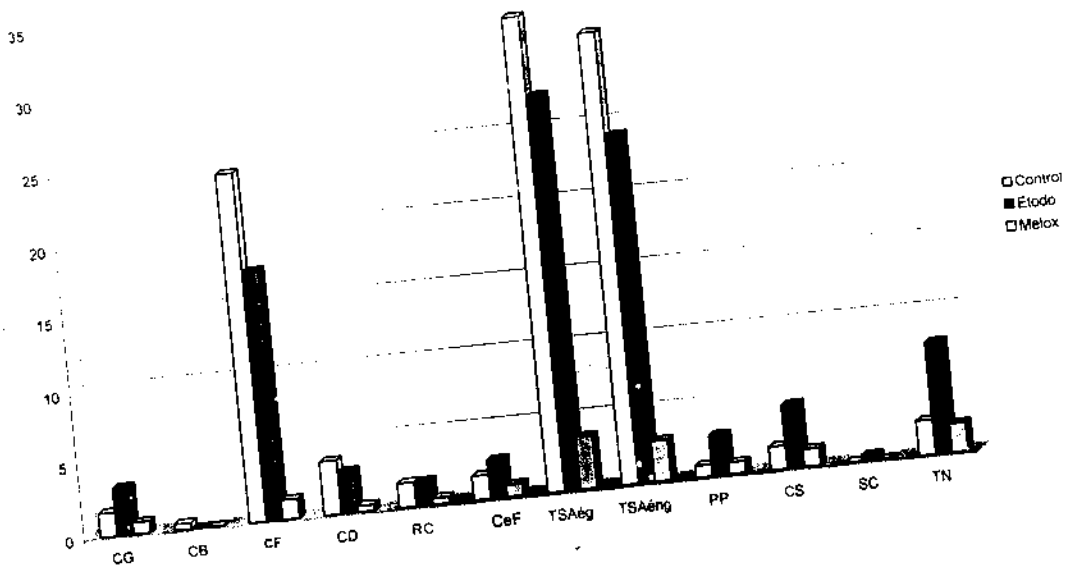
Histogram (5)

Table (6): Comparison of chromosomal aberration in metaphases (n=250) of 4 weeks etodolac and meloxicam treated groups vs. control group.

Chromos. aberrations	Control		4 weeks treated				X^2	P
			etodolac		meloxicam			
	No	%	No	%	No	%		
A-Structural								
-Gap	2	0.8	8	3.2	4	1.6	4.08	>0.05
-Break	0	0.0	0	0.0	1	0.4	2.0	>0.05
-Frag	3	1.3	43*	17.2	60*	24.0	56.45	<0.001
-Deletion	1	0.4	7*	2.8	9*	3.6	6.26	<0.05
-Ring chrom.	1	0.4	4	1.6	4	1.6	2.02	>0.05
-Cent fusion	2	0.8	6	2.6	4	1.6	3.51	>0.05
-Total é gab	9	3.6	68*	27.2	82*	32.8	71.88	<0.001
-Total without gab	7	2.8	60*	24.0	78*	31.2	69.88	<0.001
B-Numerical								
-Polyploidy	2	0.8	7	2.8	2	0.8	4.61	>0.05
-Separation	3	1.2	11*	4.4	4	1.6	6.49	<0.05
-Stick chrom.	0	0.0	1	0.4	0	0.0	2.0	>0.05
-Total numer.	5	2	19	7.6	6	2.4	12.71	<0.01

* sig. higher number than control.

Comparison of chromosomal aberration in metaphases (n=250) of 4 weeks etodolac and melexicam treated greups vs contrel group.



Histogram (6)

Table(7): Effects of 2 weeks etodolac toxicity on serum levels of ALT, AST, ALP, Bil, BUN and creatinine in normal adult female albino rats.

Liver and kidney function tests	Control X ± SD	2week etodolac X ± SD	t-test	P-value	Signif.
Liver function					
ALT(IU/L)	27.25±6.94	132.36±35.65	3.74	<0.01	* *
AST (IU/L)	25.78±5.14	76.81±15.49	13.98	<0.001	* * *
Bil (mg/dl)	0.26±0.03	0.36±0.06	4.64	<0.001	* * *
ALP (IU/L)	103.88±14.80	489.62±11.99	57.28	<0.001	* * *
Kidney function					
BUN(mg/dl)	67.41±8.56	87.41±5.01	5.70	<0.001	* * *
Cr (mg/dl)	1.03±0.18	2.17±0.09	16.02	<0.001	* * *

N.B

X = Represent mean values of ten rats

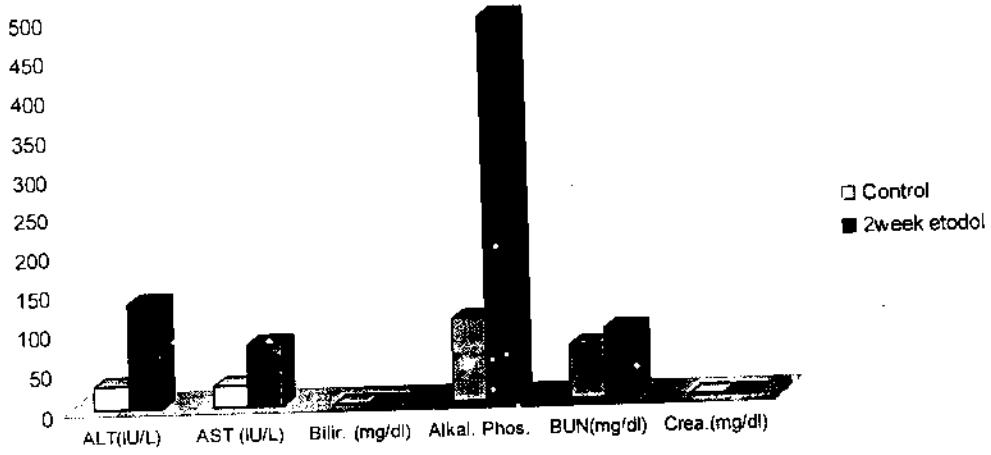
NS= Non significant

* = Significant

** = Highly significant

*** = Very highly significant

Liver and kidney function tests of two weeks etodolac treated group and control.



Histogram (7)

Table(8): Effects of 2 weeks meloxicam toxicity on serum levels of ALT, AST, ALP, Bil, BUN and creatinine in normal adult female albino rats.

Liver and kidney function tests	Control X ± SD	2week meloxicam X ± SD	t-test	P-value	Signif.
Liver function					
ALT(IU/L)	27.25±6.94	170.56±28.75	8.31	<0.001	* * *
AST (IU/L)	25.78±5.14	96.17±26.13	11.82	<0.001	* * *
Bilir. (mg/dl)	0.26±0.03	0.45±0.14	3.95	<0.001	* * *
ALP (IU/L)	103.88±14.80	513.22±45.29	24.30	<0.001	* * *
Kidney function					
BUN(mg/dl)	67.41±8.56	75.57±24.62	0.89	>0.05	NS
Cra (mg/dl)	1.03±0.18	2.01±0.35	7.04	<0.001	* * *

X = Represent mean values of ten rats

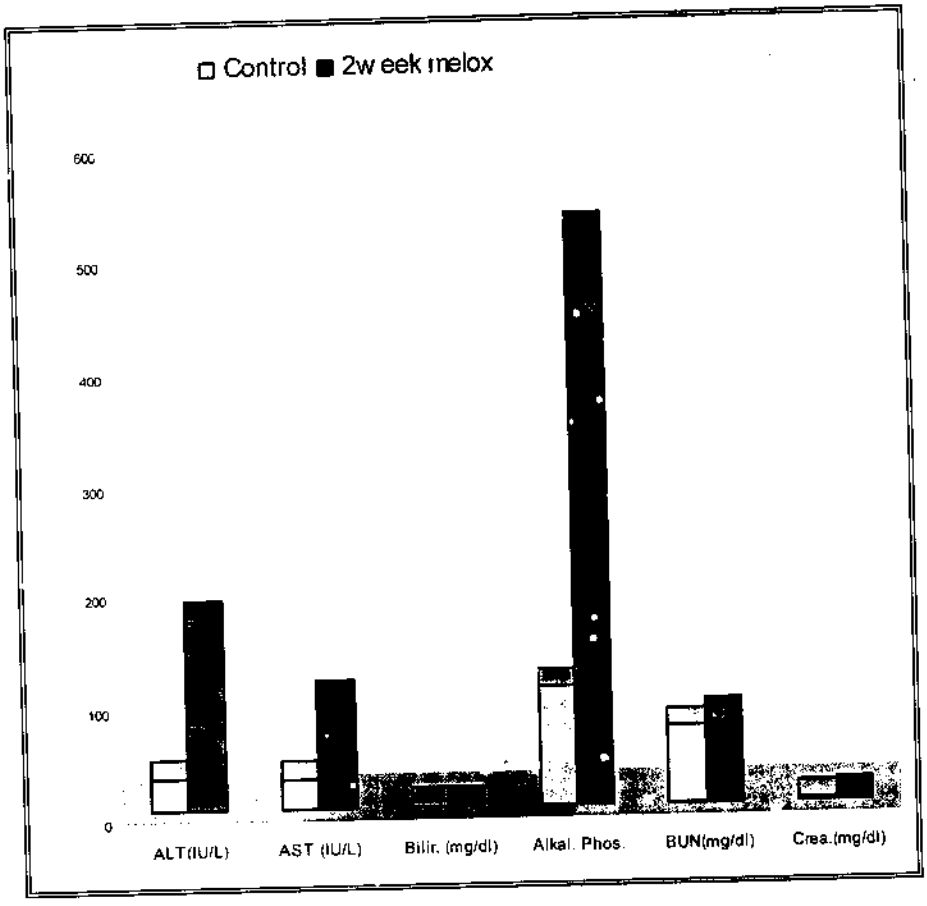
NS = Non significant

* = Significant

** = Highly significant

***= Very highly significant

Liver and kidney function tests of two weeks meloxicam treated group and control.



Histogram (8)

Table (9): Comparison between the effects of 2 weeks etodolac & meloxicam toxicity on serum levels of ALT, AST, ALP, Bil, BUN and creatinine in normal adult female albino rats.

Liver and kidney function tests	2week etodolac X ± SD	2week meloxicam X ± SD	t-test	P-value	Signif.
Liver function					
ALT(IU/L)	132.36±35.65	170.56±28.75	2.36	<0.05	*
AST (IU/L)	86.81±15.49	96.17±26.13	1.38	>0.05	NS
Bil (mg/dl)	0.36±0.06	0.45±0.14	2.64	<0.01	**
ALP (IU/L)	489.62±11.99	513.22±45.29	7.46	<0.001	***
Kidney function					
BUN(mg/dl)	87.41±5.01	75.57±24.62	2.11	<0.05	*
Cr (mg/dl)	2.17±0.09	2.01±0.35	0.47	>0.05	NS

X = Represent mean values of ten rats

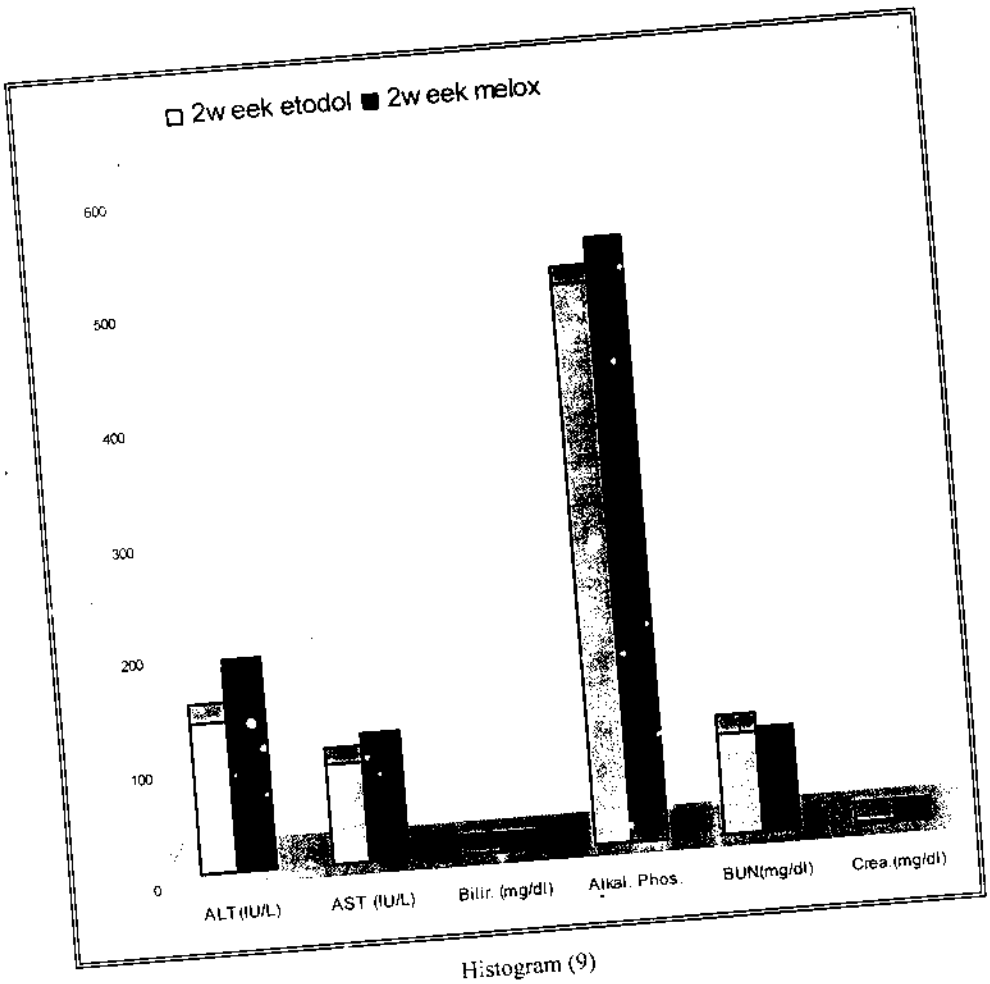
NS = Non significant

* = Significant

** = Highly significant

*** = Very highly significant

Liver and kidney function tests of two weeks treated etodolac and meloxicam groups.



Histogram (9)

Table (10): Effects of 4 weeks etodolac toxicity on serum levels of ALT, AST, ALP, Bil, BUN and creatinine in normal adult female albino rats.

Liver and kidney function tests	Control X ± SD	4week etodolac X ± SD	t-test	P-value	Signif.
Liver function					
ALT (IU/L)	27.25±6.94	136.28±22.87	6.21	<0.001	* * *
AST (IU/L)	25.78±5.14	22.36±3.39	1.67	>0.05	NS
Bil (mg/dl)	0.26±0.03	0.23±0.14	0.40	>0.05	NS
ALP (IU/L)	103.88±14.80	163.45±19.93	6.79	<0.001	* * *
Kidney function					
BUN(mg/dl)	67.41±8.56	74.45 ±12.52	2.08	<0.05	*
Cr (mg/dl)	1.03±0.18	1.26±0.33	1.73	>0.05	NS

X = Represent mean values of ten rats

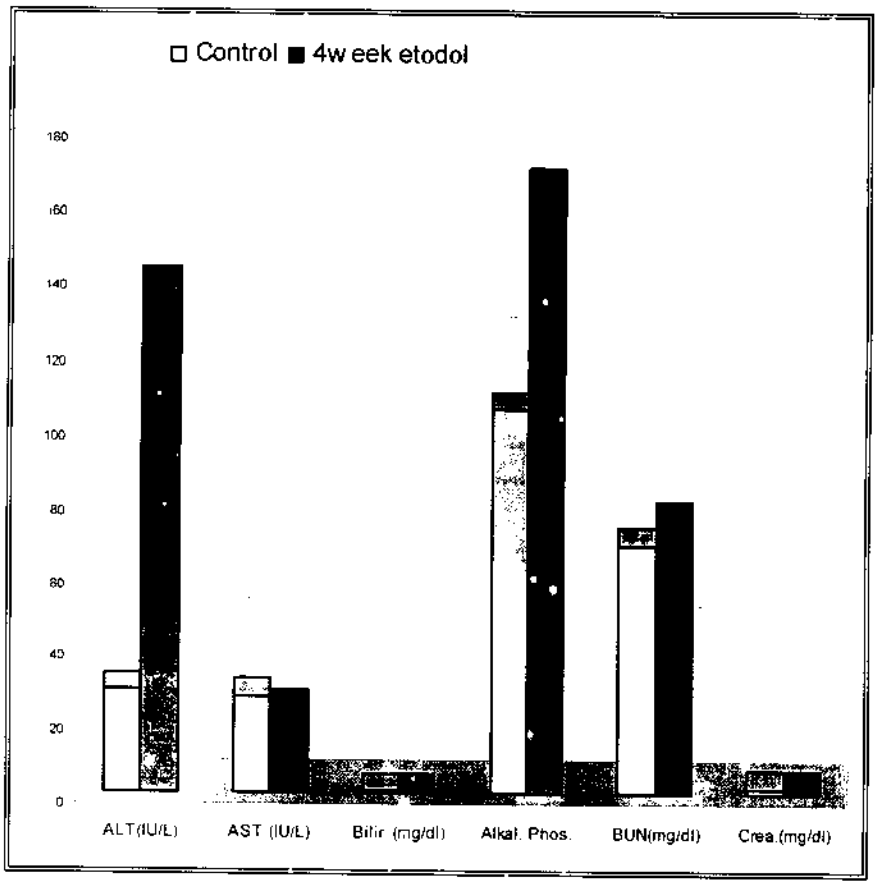
NS = Non significant

* = Significant

** = Highly significant

* * *= Very highly significant

Liver and kidney function tests of four weeks treated etodolac group and control



Histogram (10)

Table (11): Effects of 4 weeks meloxicam toxicity on serum levels nf ALT, AST, ALP, Bil, BUN and crea'inine in normal adult female albino rats.

Liver and kidney function tests	Control X ± SD	4week meloxicam X ± SD	t-test	P-value	Signif.
Liver function					
ALT (IU/L)	27.25±6.94	147.37±39.50	28.75	<0.001	* * *
AST (IU/L)	25.78±5.14	27.91±2.76	1.63	>0.05	NS
Bil (mg/dl)	0.26±0.03	0.26 ±0.40	0.07	>0.05	NS
ALP (IU/L)	103.88±14.80	237.14±47.56	7.57	<0.001	* * *
Kidney function					
BUN(mg/dl)	67.41±8.56	74.93 ±13.15	2.14	<0.05	*
Cr (mg/dl)	1.03±0.18	1.02±0.17	0.11	>0.05	NS

X = Represent mean values of ten rats

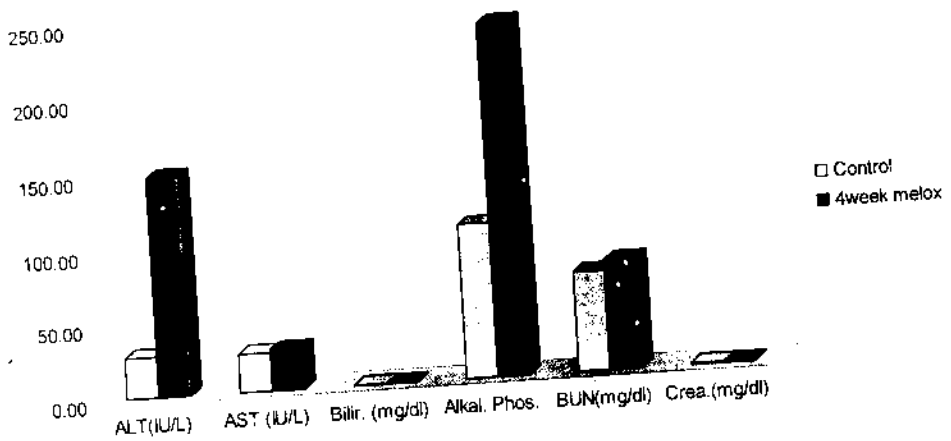
NS = Non significant

* = Significant

** = Highly significant

* * *= Very highly significant

Liver and kidney function tests of four weeks treated meloxicam group and control



Histogram (11)

Table (12): Comparison between the effects of 4 weeks etodolac & meloxicam toxicity on serum levels of ALT, AST, ALP, Bilirubin, BUN and creatinine in normal adult female albino rats.

Liver and kidney function tests	4week etodolac X ± SD	4week meloxicam X ± SD	t-test	P-value	Signif.
Liver function					
ALT (IU/L)	136.28±22.87	147.37±39.50	0.69	>0.05	NS
AST (IU/L)	22.36±3.39	27.91±2.76	3.59	<0.01	* *
Bil (mg/dl)	0.23±0.14	0.26 ±0.40	0.20	>0.05	NS
ALP (IU/L)	163.45±19.93	237.14±47.56	4.04	<0.001	* * *
Kidney function					
BUN(mg/dl)	74.45 ±12.52	74.93 ±13.15	0.12	>0.05	NS
Cr (mg/dl)	1.26±0.33	1.02±0.17	1.83	>0.05	NS

X = Represent mean values of ten rats

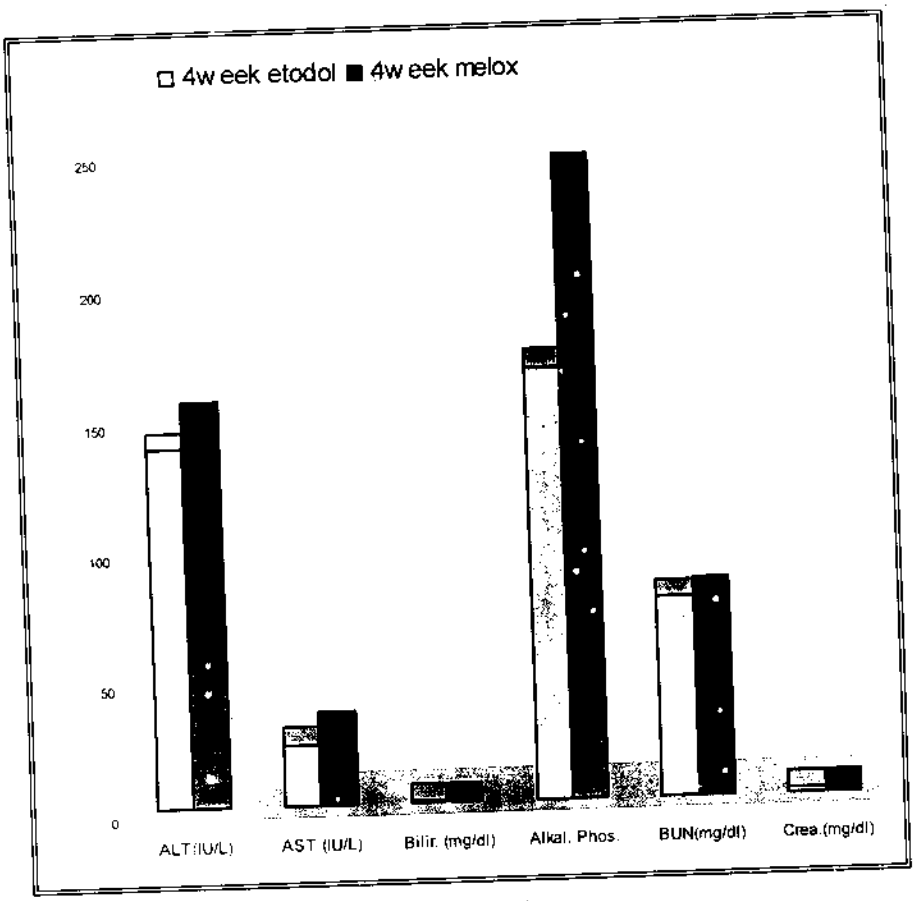
NS = Non significant

* = Significant

** = Highly significant

* * *= Very highly significant

Liver and kidney function tests of four weeks treated etodolac and meloxicam groups



Histogram (12)

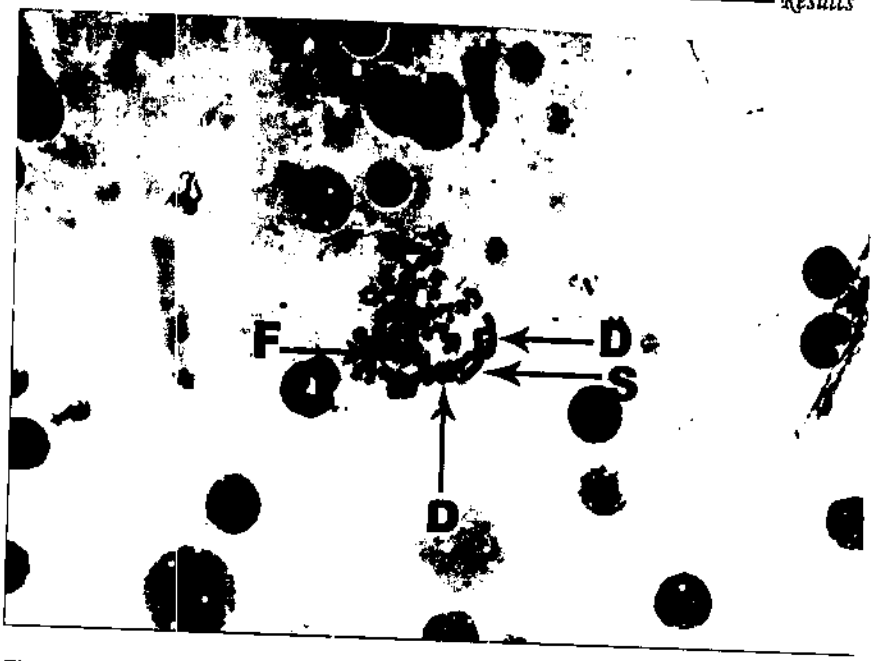


Fig. (18): A photomicrograph of a metaphase spread in bone marrow cells of rats treated with 1/10 the LD_{50} of Melox orally daily for 2 weeks showing chromatid frag.(F), seperartion (S) and deletion (D) (Giemsa Stain OM x 1000).

Figure (19): A photomierograph of a metaphase spread in bone marrow cells of rats treated with 1/10 the LD_{50} of Etod orally daily for 2 weeks showing multiple fragments (F) (Giemsa Stain OM x 1000).

Figure (20): A photomicrograph of a metaphase spread in bone marrow cells of rats treated with 1/10 the LD_{50} of Mclox orally daily for 2 weeks showing ring chromosome (R) and chromatid deletion (D).(Giemsa Stain OM x 1000).

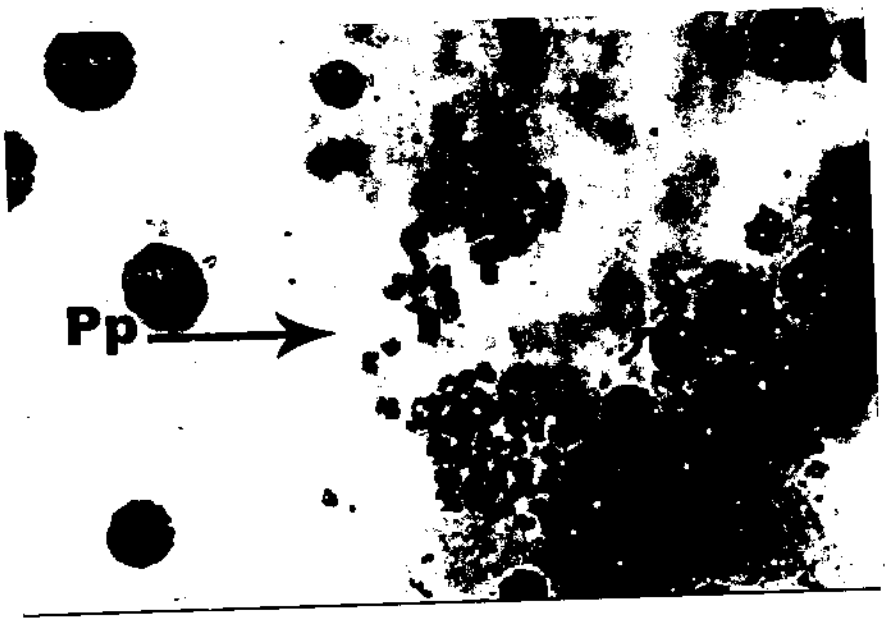


Figure (21) A photomicrograph of a metaphase spread in bone marrow cells of rats treated with 1/10 the LD_{50} of Etod orally daily for 2 weeks showing polyploidy (Pp) (Giemsa Stain OM x 1000).

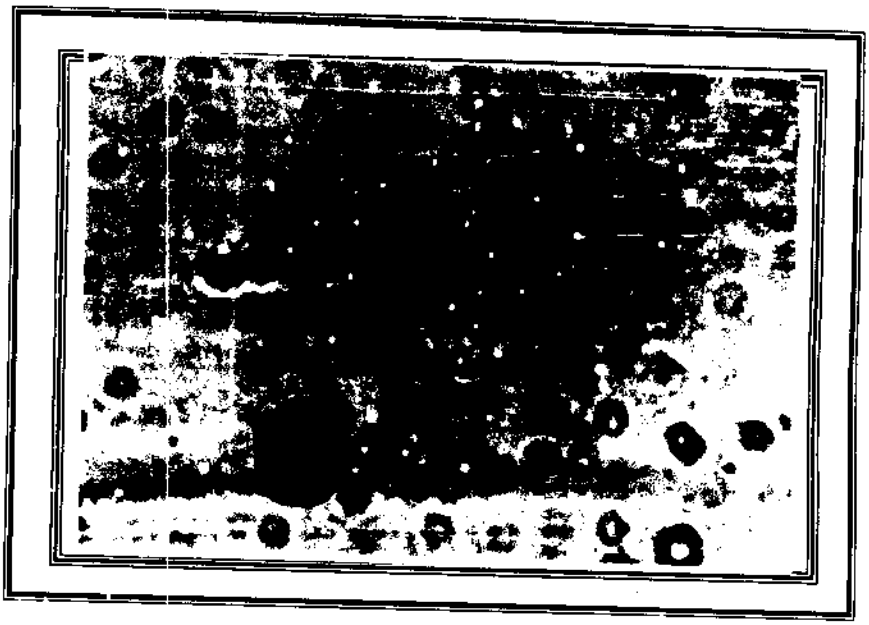


Figure (22): A photomicrograph of a metaphase spread in bone marrow cells of rats treated with 1/10 the LD_{50} of Melox orally daily for 4 weeks showing chromatid break (B) (Giemsa Stain OM x 1000).

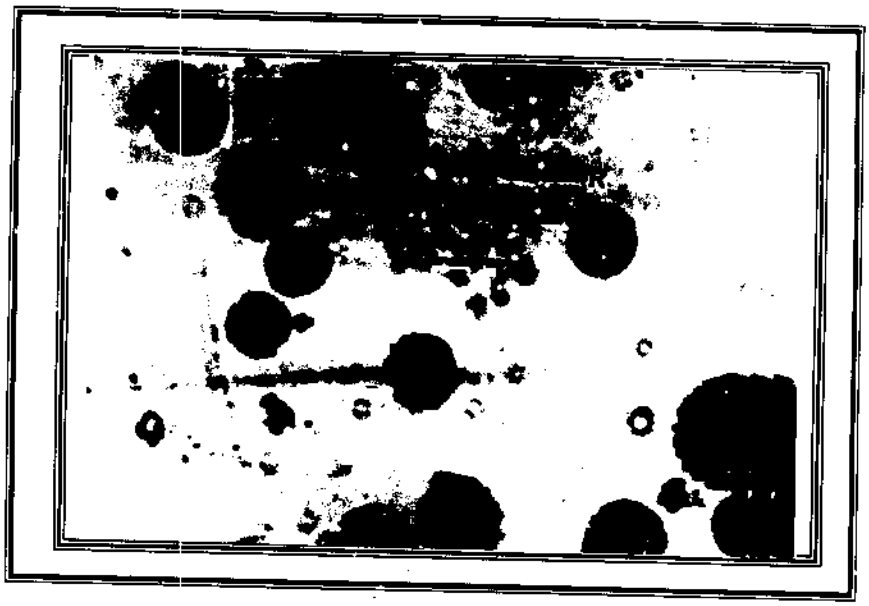


Fig. (23): A photomicrograph of a metaphase spread in bone marrow cells of rats treated with 1/10 the LD_{50} of Melox orally daily for 4 weeks showing centric fusion(CF) chromxtid deletion(D), ond ring chromosome(R) (Giemsa Stain OM x 1000).

Figure (24): A photomicrograph of a metaphase spread in bone marrow cells of rats treated with 1/10 the LD_{50} of Etod orally daily for 4 weeks showing stieky chrom. (St.) and chromatid deletion (D) (Giemsa Stain OM x 1000).

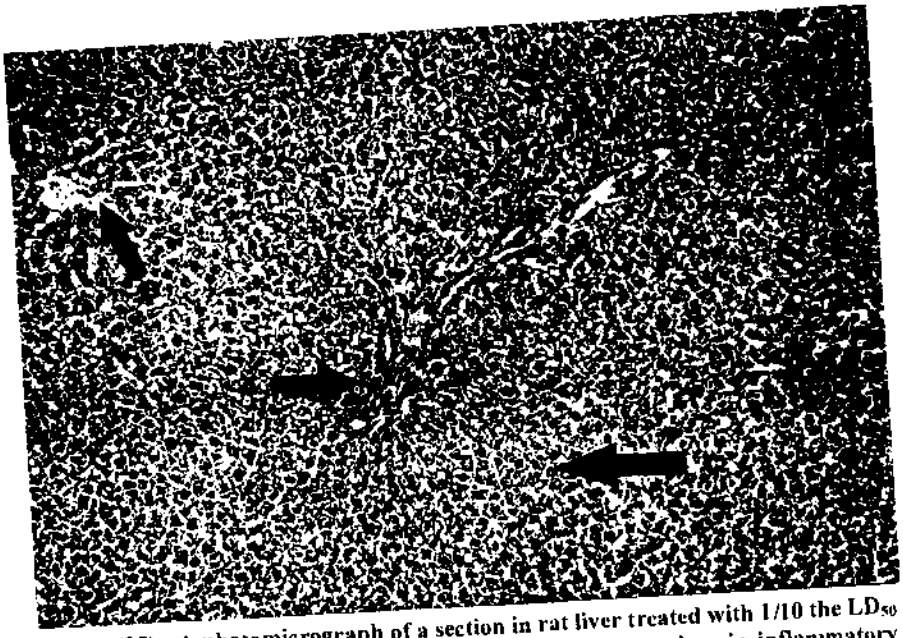


Figure (25): A photomicrograph of a section in rat liver treated with 1/10 the LD_{50} of Melox orally daily for 2 weeks shuwing portal tract chronic inflammatory cellular infiltration (A), congested sinusoids (B), and hepatocellular degeneration (C) (H x & E x 100).

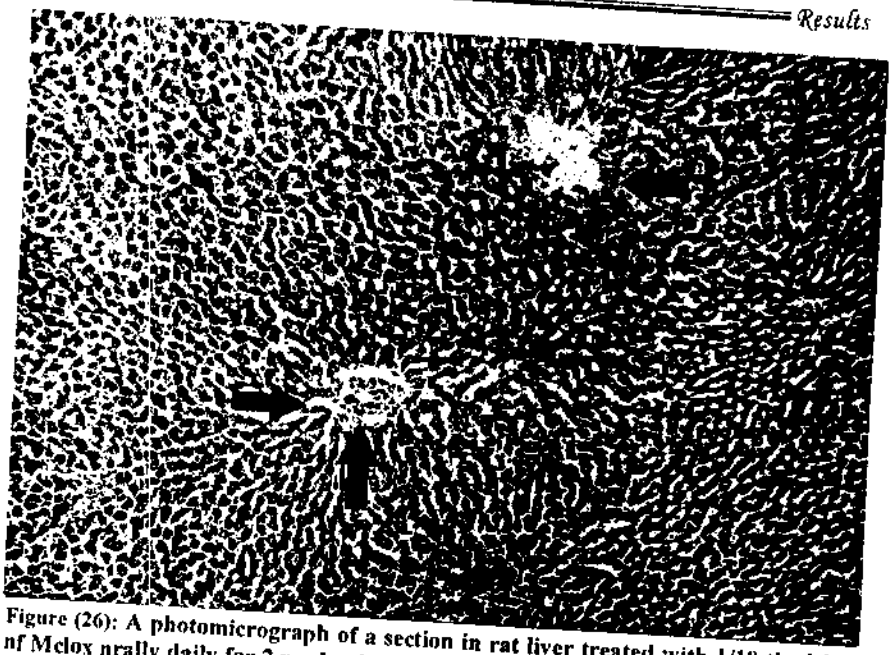


Figure (26): A photomicrograph of a section in rat liver treated with 1/10 the LD_{50} nf Mclox nrally daily for 2 weeks showing congested central vein and sinusnids (A) & focal necrnsis around central vein (B) (H x & E x 100).

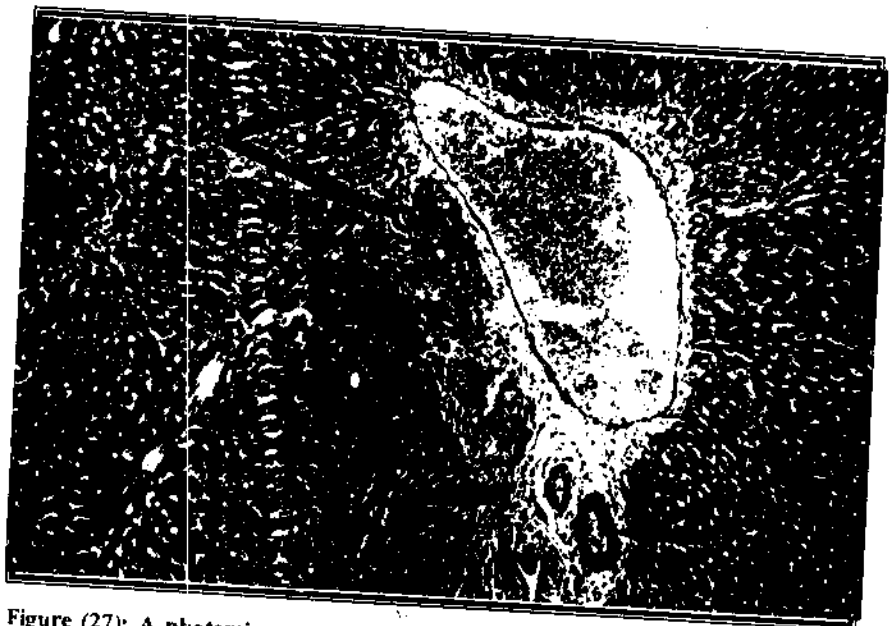


Figure (27): A photomierograph uf a seetion in rat liver treated with 1/10th the LD_{50} of Etnd orally daily for 2 wceks showing portal tract with bilc duetular proliferatinn (A), congested blood vessels (B), and chronic inflammatory cellular infiltration (C) (H x & E x 100).

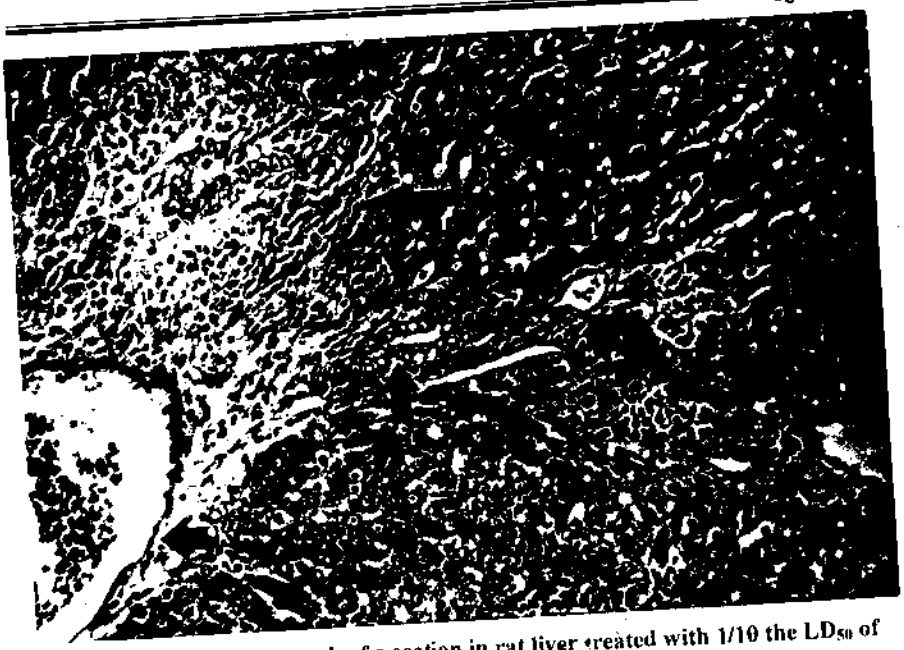


Fig.(28): A photomicrograph of a section in rat liver treated with 1/10 the LD_{50} of Melox orally daily for 4 weeks shawing portal tract lymphocytic infiltration (A), bile ductular proliferation (B), congested blood vessels (C) (H x & E x 400).

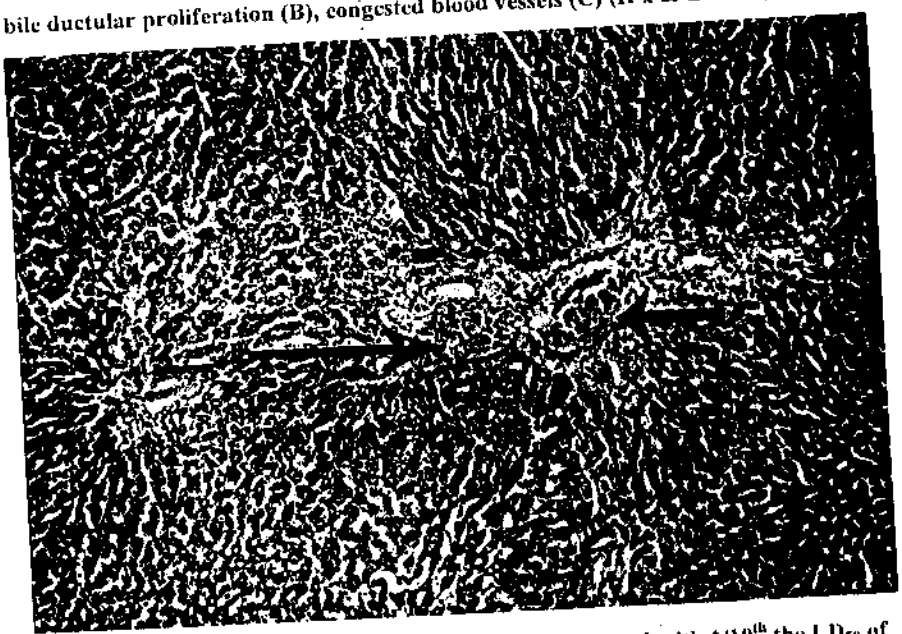


Fig.(29): A photomicrograph of a section in rat liver treated with $t/10^{th}$ the LD_{50} of Etod orally daily for 4 weeks showing dilated congested portal tract blood vessels (A), portal tract chronic inflammatory cellular infiltration (B) (H x & E x 100).

Figure (30): A photomicrograph of a section in rat kidney treated with 1/10th the LD_{50} of Etod orally daily for 2 weeks showing dilated congested blood vessels (A), perivascular chronic inflammatory cellular infiltration (B), and congested glomeruli (C) (H x & E x 400).

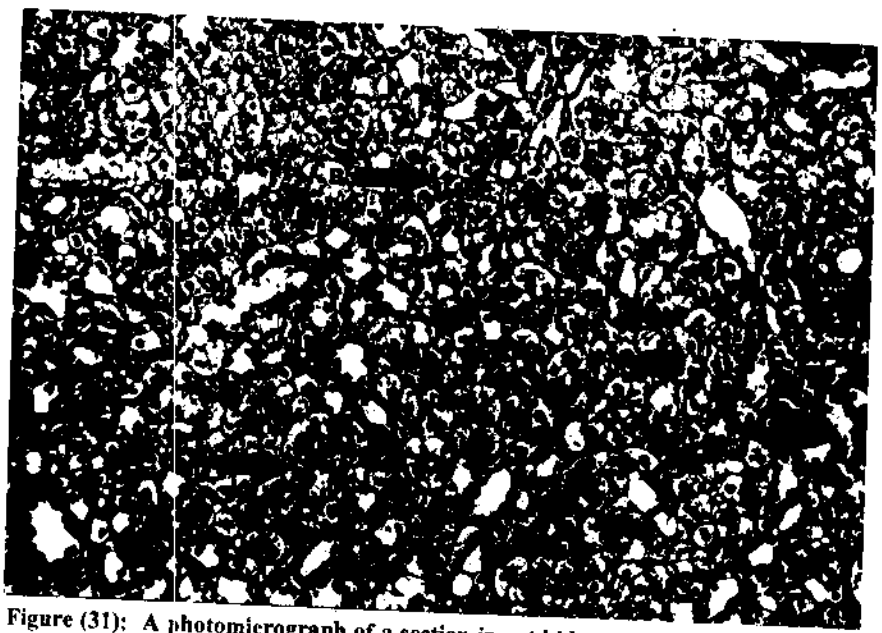


Figure (31): A photomicrograph of a section in rat kidney treated with 1/10th the LD_{50} of Melox orally daily for 2 weeks showing hydropic degeneration of tubules (A) and congested capillary blood vessels (B) (H x & E x 400).

Fig. (32): A photomicrograph of a section in rat kidney treated with 1/10th the LD_{50} of Melox rally daily for 2 weeks showing congested intertubular capillaries (A), interstitial lymphocytic infiltration (B) and intratubular hyaline cast (thyroidization of the tubules) (C) (H x & Ex 400).

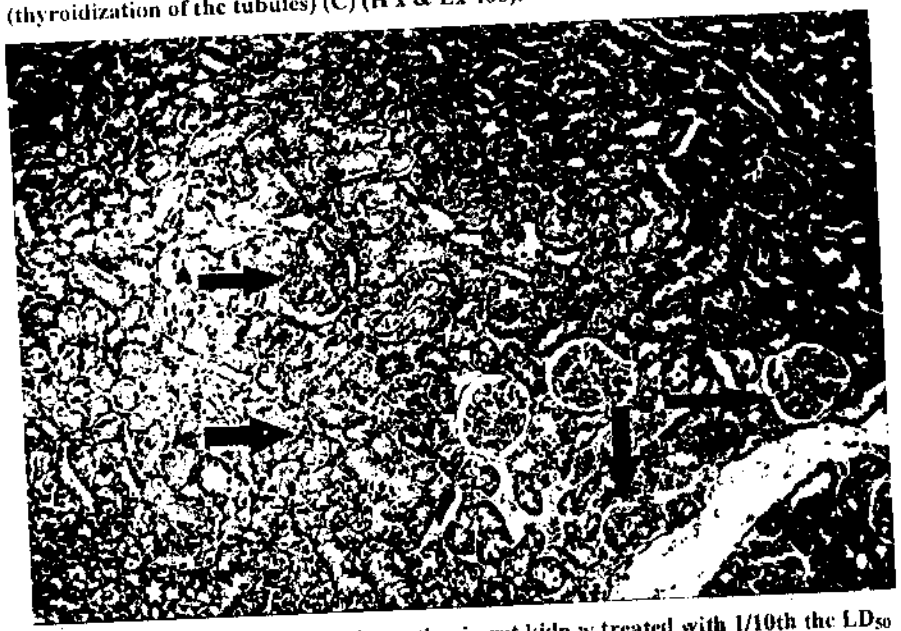


Fig. (33): A photomicrograph of o section in rat kidney treated with 1/10th the LD_{50} of Etod orally daily for 4 weeks showing interstitial mild chrooic inflammatory cellular infiltration (A), congested blood vessels and glomeruli (B), and cloudy swelling of the tubules (C) (H x & Ex 400).

Fig. (34): A photnmierngraph nf a seetinn in rat kidney treated with 1/10th the LD_{50} of Melox orally daily for 4 weeks shnwing perivascular chronie inflammatory eellular infiltratinn (A), atrophie glomeruli (B) and congested hlond vessels (C) (H x & E x 400).

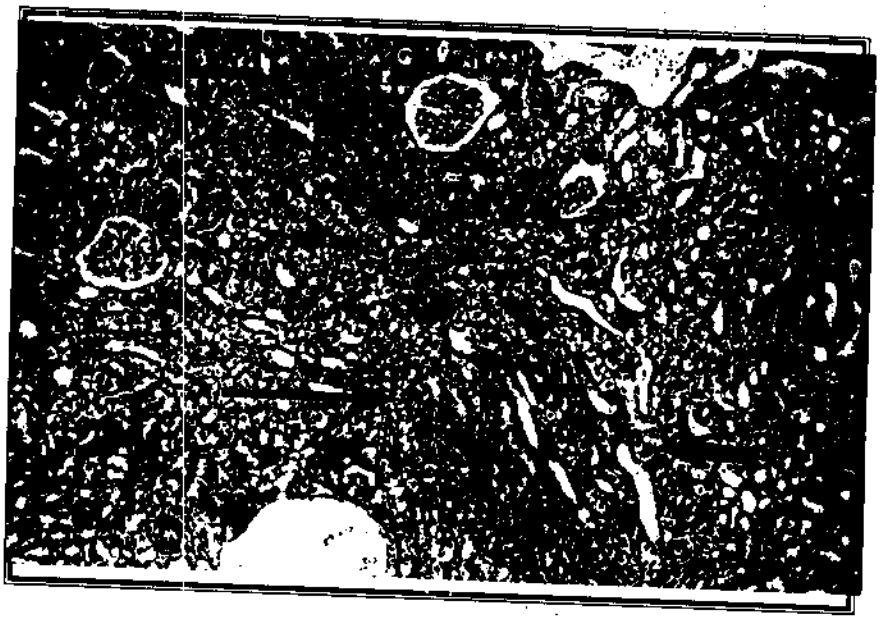


Figure (35): A phntomierograph nf a section in rat kidney treated with 1/10th the LD_{50} of Meinx orally daily for 4 weeks showing hydropie degeoeratioo (A), atraphic glomeruli (B) and congested capillaries (C) (H x & E x 400).

III-At the end of the follow up period

1- Chromosomal Study

Changes in the chromosomal pattern produced by repeated dose etodolac and meloxicam after 4 weeks of drug cessation have been statistically analyzed and outlined in tables (13-16), graphically illustrated in histogram (13-16).

Etodolac induced a highly significant increase ($P<0.01$) in the total with gap and total without gap, and a non significant increase ($P>0.05$) in the percentage of CG, CB, CD, CF, RC, CeF, PP, CS and SC as compared with those in the control rats.

Meloxicam induced a highly significant increase ($P<0.01$), in the percentage of total with gap, and total without gap, and a significant increase ($P<0.05$) in CS but a non significant increase ($P>0.05$) in the percentage of CG, CB, CD, CF, RC, CeF, PP and SC as compared with those in control rats.

Comparison between etodolac and meloxicam treated groups

Meloxicam induced a non significant increase ($P>0.05$) in the percentage of CG, CB, CF, CD, RC, CeF, total with gap, and total without gap, PP, CS and SC as compared with those in etodolac treated rats.

2- Hepatic changes

2-A. Biochemical changes:

After the 4th week of the follow up period etodolac treated rats showed a very highly significant increase ($P<0.001$) in serum ALT and a non significant increase ($P>0.05$) in serum AST, BIL, and ALP when when compared with those in control rats.

Also meloxicam treated rats showed a very highly significant increase ($P<0.001$) in serum ALT and a non significant inerease ($P>0.05$) in serum AST, BIL, and ALP when when compared with those in control rats.

Comparison between etodolac and meloxicam treated groups

Meloxicam showed a non significant increase (P>0.05) in serum ALT, AST, BIL, and ALP when compared with those of etodolac treated rats.

2-B. Histopathological changes:

The results obtained from the effects of etodolac and meloxicam at the end of the follow up period on kidney histopathology were photographed in figure (31).

The previously mentioned histopathological changes which produced by the 2 drugs in the rats' livers at the end of the follow up period were readily reversible.

3- Renal changes

3-A. Biochemical changes:

After the 4th week of the follow up period both etodolac and meloxicam treated rats showed a non significant increase (P>0.05) in serum Cr and BUN when compared with those in control rats.

Comparison between etodolac and meloxicam treated groups

After the end of the follow up period meloxicam showed a non significant increase (P>0.05) in serum Cr and BUN when compared with those of etodolac treated rats.

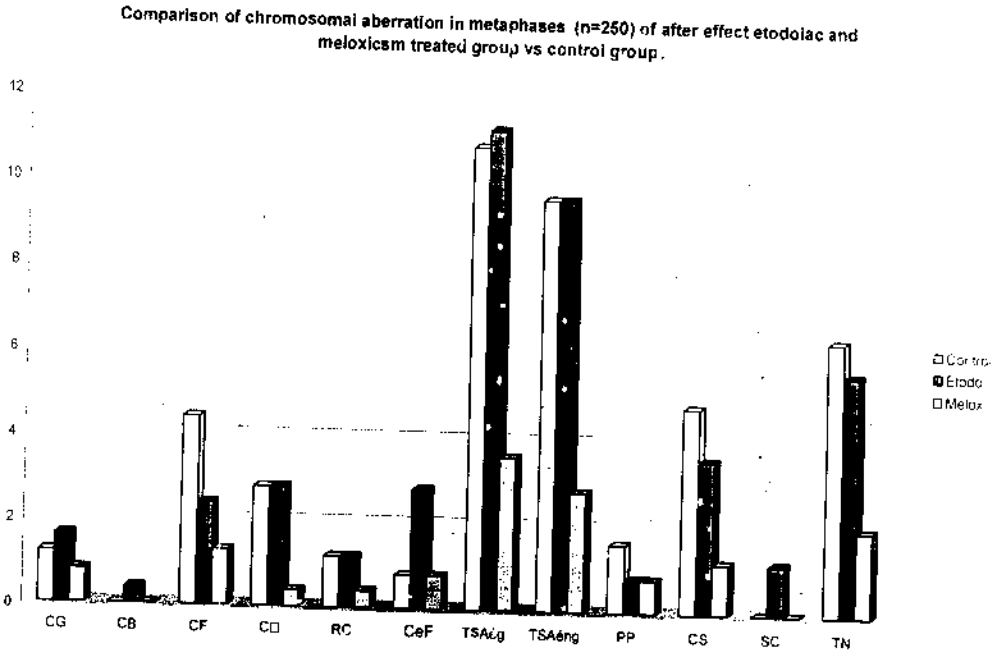
3-B. Histopathological changes:

The results obtained from the effects of etodolac and meloxicam at the end of the follow up period on kidney histopathology were photographed in figure (32).

The previously mentioned histopathological changes which produced by the 2 drugs in the rats' kidneys at the end of the follow up period were readily reversible.

Table (13): Comparison of chromosomal aberrations in metaphases (n=250) of after effect etodolac and meloxicam treated groups vs. control group.

Chromos. abcrrations	Control		After effect				X^2	P
			etodolac		meloxicam			
	No	%	No	%	No	%		
A-Structural								
-Gap	2	0.8	4	1.6	3	1.2	0.67	>0.05
-Break	0	0.0	1	0.4	0	0.0	2.0	>0.05
-Frag	3	1.3	6	2.4	11	4.4	5.03	>0.05
-Deletion	1	0.4	7	2.8	7	2.8	4.90	>0.05
-Ring chrom.	1	0.4	3	1.2	3	1.2	1.15	>0.05
-Cent fusion	2	0.8	7	2.8	2	0.8	4.61	>0.05
-Total é gab	9	3.6	28*	11.2	27*	10.8	11.72	<0. 01
-Total without gab	7	2.8	24*	9.6	24*	9.6	11.34	<0.01
B-Numerical								
-Polyploidy	2	0.8	2	0.8	4	1.6	1.01	>0.05
-Separation	3	1.2	9	3.6	12*	4.8	5.42	<0.05
-Stick chrom.	0	0.0	3	1.2	0	0.0	6.02	>0.05
- Total number	5	2	14	5.6	16	6.4	6.17	>0.05



Histogram (13)

Table (14): Effects of after effect etodolac on serum levels of ALT, AST, ALP, Bil, BUN and creatinine in normal adult female albino rats.

Liver and kidney function tests	Control X ± SD	After effect etodolac X ± SD	t-test	P-value	Signif.
Liver function					
ALT(IU/L)	27.25±6.94	90.63±6.60	20.9	<0.001	***
AST (IU/L)	25.78±5.14	28.08±7.44	1.14	>0.05	NS
Bil (mg/dl)	0.26±0.03	0.26±0.41	0.07	>0.05	NS
ALP (IU/L)	103.88±14.80	116.14±31.23	1.59	>0.05	NS
Kidney function					
BUN(mg/dl)	67.41±8.56	67.57 ±18.17	0.04	>0.05	NS
Cr mg/dl)	1.03±0.18	1.01±0.40	0.13	>0.05	NS

X = Represent mean values of ten rats

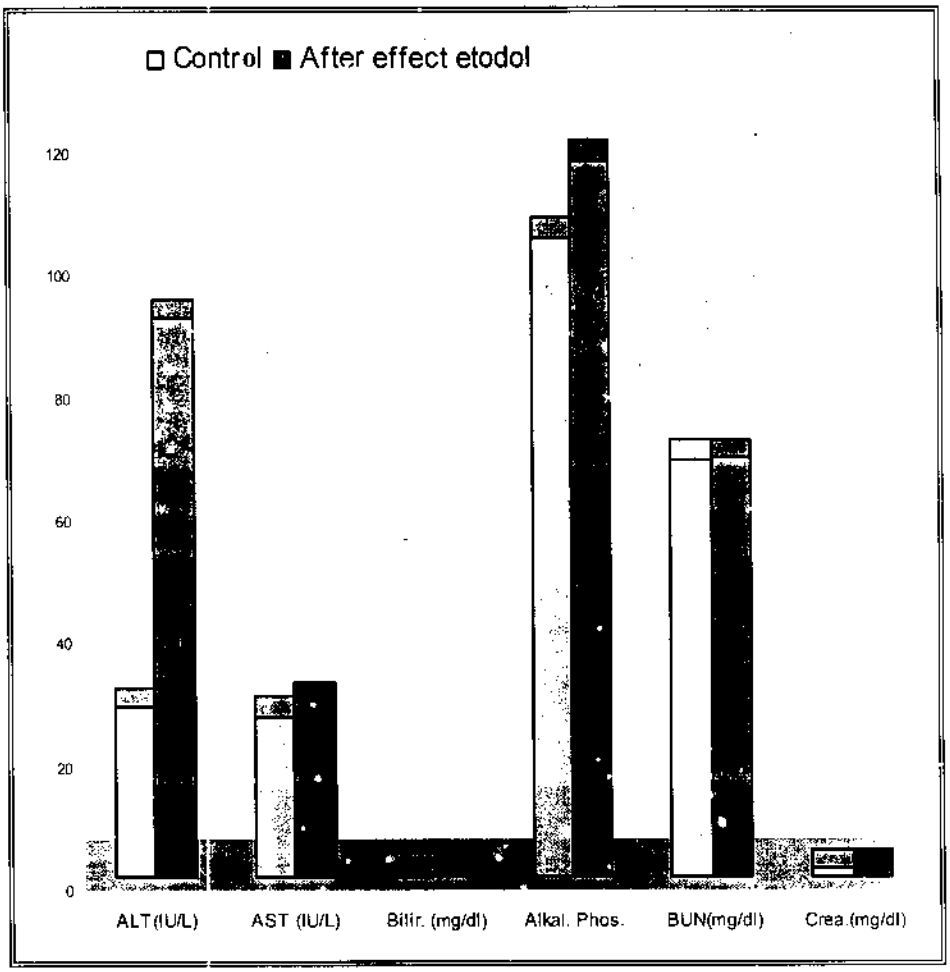
NS = Non significant

* = Significant

** = Highly significant

*** = Very highly significant

Liver and kidney function tests of after effect etodolac group and control



Histogram (14)

Table (15): Effects of after effect meloxicam on serum levels of ALT, AST, ALP, Bil, BUN and creatinine in normal adult female albino rats.

Liver and kidney function tests	Control X ± SD	After effect meloxicam X ± SD	t-test	P-value	Signif.
Liver function					
ALT(IU/L)	27.25±6.94	100.27±26.28	1.64	<0.001	***
AST (IU/L)	25.78±5.14	22.08±7.44	1.83	>0.05	NS
Bil (mg/dl)	0.26±0.03	0.26±0.05	0.49	>0.05	NS
ALP (IU/L)	103.88±14.80	112.63±11.81	1.31	>0.05	NS
Kidney function					
BUN(mg/dl)	67.41±8.56	69.82±6.13	1.02	>0.05	NS
Cr (mg/dl)	1.03±0.18	1.13±0.04	1.53	>0.05	NS

X = Represent mean values of ten rats

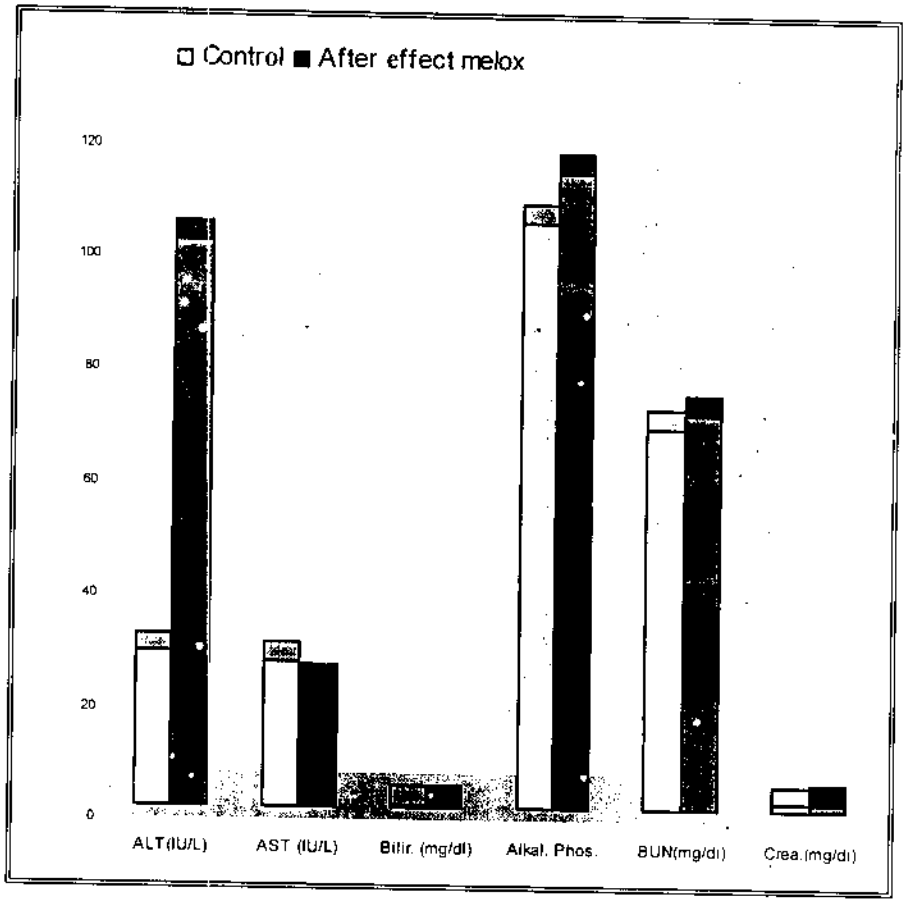
NS = Non significant

* = Significant

** = Highly significant

*** = Very highly significant

Liver and kidney function tests of after effect meloxicam group and control



Histogram (15)

Table (16): Comparison between after effect etodolac and meloxicam on serum levels of ALT, AST, ALP, Bil, BUN and creatinine in normal adult female albino rats.

Liver and Kidney function tests	After effect etodolac X ± SD	After effect meloxicam X ± SD	t-test	P-value	Signif.
Liver function					
ALT(IU/L)	90.63±6.60	100.27±26.28	1.01	>0.05	NS
AST (IU/L)	28.08±7.44	22.08±7.44	1.80	>0.05	NS
Bilir. (mg/dl)	0.26±0.41	0.26±0.05	0.01	>0.05	NS
ALP(IU/L)	126.14±31.23	112.63±11.81	1.14	>0.05	NS
Kidney function					
BUN(mg/dl)	67.57 ±18.17	69.82±6.13	0.52	>0.05	NS
Cr (mg/dl)	1.01±0.40	1.13±0.04	0.84	>0.05	NS

X = Represent mean values of ten rats

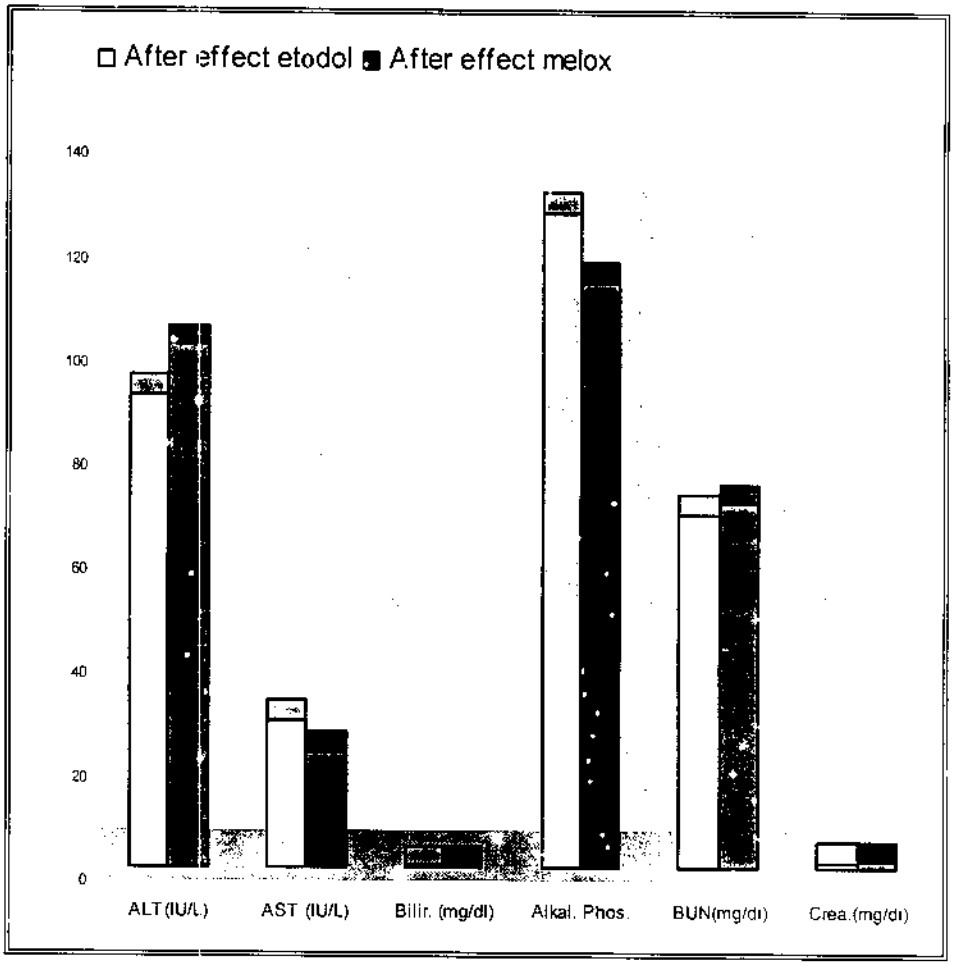
NS = Non significant

* = Significant

** = Highly significant

*** = Very highly significant

Liver and kidney function tests of after effect etodolac and meloxicam treated groups



Histogram (16)

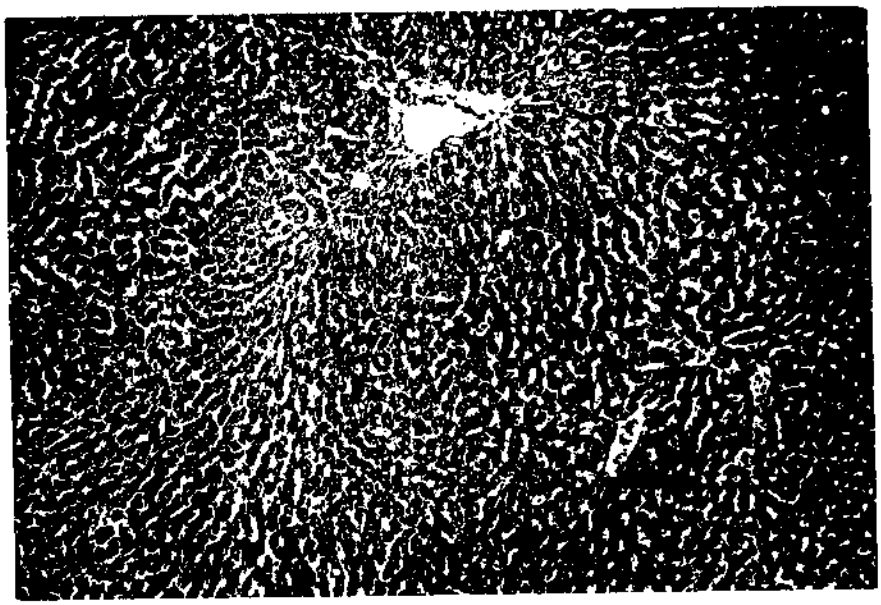


Figure (36): A photomierograph of a section in rat liver of the after effect Etod (treated with 1/10th the LD_{50} of Etod orally daily for 4 weeks followed by discontinuation for 4 weeks) showing minimal changes (H x & E x 100).

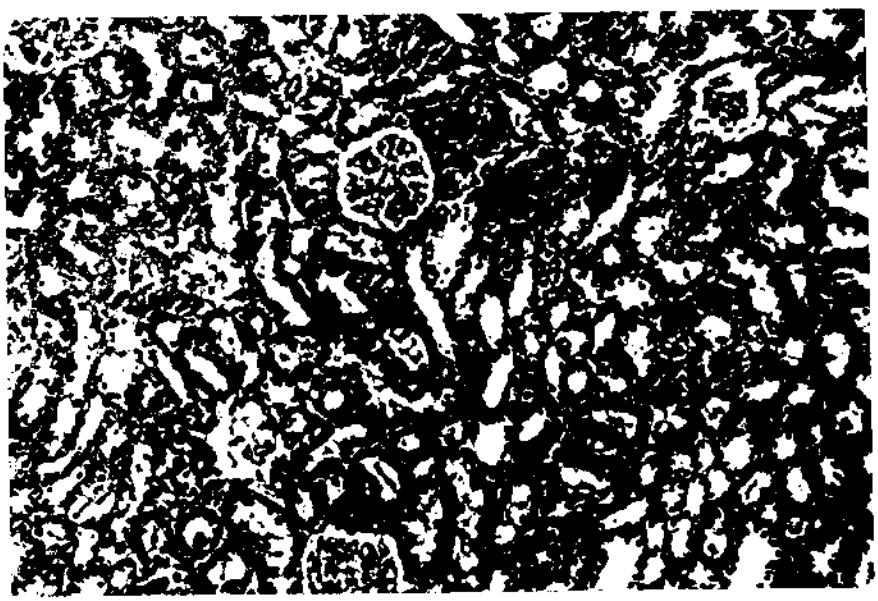


Figure (37): A photomierograph of a section in rat kidney of the after effect Melox (treated with 1/10th the LD_{50} of Melox orally daily for 4 weeks followed by discontinuation for 4 weeks)showing minimal changes (H x & Ex 100). (H x & E x 400).

IV-Results of apoptosis (DNA fragmentation)

Acute toxicity study:

Acute liver toxicity (Figure 33):

Comparison between etodolac treated group and controls

There was a significant higher mean value of maximal optical density of acute etodolac toxicity group than controls at 600 base pair [1.26±0.09 versus 1.09±0.09; respectively,$p<0.05$, table (17)].

Comparison between meloxicam treated group and controls

There was a significant lower mean value of maximal optical density of acute meloxicam toxicity group than controls at intact DNA [91.4±4.38 versus 112.4±3.2 ;respectively, $p<0.05$,table (17)] while there is a significant higher mean value of maximal optical density of acute meloxicam toxicity group than controls at 600, 400 and 200 base pair [1.72±0.62, 1.68±0.64 and 1.57±0.54 versus 1.09±0.09, 0.88±0.20 and 0.67±0.21 respectively, $p<0.05$,table (17)]

Comparison between etodolac and meloxicam treated groups

There was a significant higher mean value of maximal optical density of acute meloxicam toxicity group than acute etodolac toxicity group at 400, 200 base pair [1.68±0.64 and 1.57±0.54 versus 0.93±0.3, and 0.70±0.01 respectively, $p<0.05$, table (17)].

Acute renal toxicity (Figure 33):

Comparison between etodolac treated group and controls

There was a significant lower mean value of maximal optical density of acute etodolac toxicity group than controls at intact DNA, [133.97±12.54 versus 167.85±15.73 respectively, $p<0.05$, table (18)].

While there was a significant higher mean value of maximal optical density of acute etodolac toxicity group than controls at 600, 400, 200 base pair [84.62±10.08, 73.85±3.88 and, 51.08±4.39 versus 47.40±1.20, 38.20±3.47 and, 17.70±6.4 respectively, $p<0.05$, table (18)].

Comparison between meloxicam treated group and controls

There was a significant lower mean value of maximal optical density of acute meloxicam toxicity group than controls at intact DNA [133.68±14.53 versus 167.85±15.73 respectively, $p<0.05$, table (18)].

While there was a significant higher mean value of maximal optical density of acute meloxicam toxicity group than controls at 600, 400, 200 base pair [74.63±2.51, 56.98±2.23 and, 37.50±18.10 versus 47.40±1.20, 38.20±3.47 and, 17.70±6.4 respectively, $p<0.05$, table (18)].

Comparison between etodolac and meloxicam treated groups

There was a significant lower mean value of maximal optical density of acute meloxicam toxicity group than acute etodolac toxicity group at 400 base pair [56.98±2.23 versus 73.85±3.88 respectively, $p<0.05$, table (18)].

2- Short term chronic toxicity study

The apoptotic changes obtained from the effects of etodolac and meloxicam at the end of the 2nd and 4th week after single daily oral administration of 1/10th of their LD_{50} as well as at the end of the follow up period were photographed in figures (34-36).

At the end of the 2nd week

Liver toxicity (Figure 34):

Comparison between etodolac treated group and controls

There was a significant higher mean value of maximal optical density of 2 weeks etodolac toxicity group than controls at intact DNA, 400, 200. base pair [172.45±5.93, 57.90±3.11, and 27.05±4.95, versus 1.91±0.81, 34.10±8.92,and 16.15±6.45 ;respectively,$p<0.05$, table (19)].

Comparison between meloxicam treated group and controls

There was a significant higher mean value of maximal optical density of 2 weeks meloxicam toxicity group than controls at intact DNA,

400 , 200 base pair [187.38±2.09, 51.65±2.48, and 23.20±1.70, versus 1.91±0.81, 34.10±8.92,and 16.15±6.24 ;respectively,p<0.05, table (19)].

Cnmparison between etodolac and meloxicam treated groups

There was a significant higher mean value of maximal optical density of 2 weeks meloxicam toxicity group than 2 weeks etodolac toxicity group at intact DNA [187.38±2.09 versus 172.45±5.93 respectively, p<0.05, table (19)].

While there was a significant lower mean value of maximal optical density of 2 weeks meloxicam toxicity group than 2 weeks etodolac toxicity group at 400 base pair [51.65±2.48 versus 57.90±3.11 respectively, p<0.05, table (19)].

Kidney toxicity (Figure 36):

Comparison between etodolac treated group and contrnls

There was a significant lower mean value of maximal optical density of 2 weeks etodolac toxicity group than controls at intact DNA [55.50±21.92 versus 113.00±2.3 ; respectively, p<0.05, table (20)]. While there was a significant higher mean value of maximal optical density of 2 weeks etodolac toxicity group than controls at 600, 400, 200 base pair [54.50±33.23, 45.15±23.83 and 35.60±13.29 versus3.10±0.90, 2.10±0.3 and 1.30±0.02 respectively , p<0.05, table (20)].

Comparison between meloxicam treated group and controls

There was a significant lower mean value of maximal optical density of 2 weeks meloxicam toxicity group than controls at intact DNA [63.33±25.66 versus 113.00±2.3 ; respectively, p<0.05, table (20)]. While there was a significant higher mean value of maximal optical density of 2 weeks meloxicam toxicity group than controls at 600, 400, 200 base pair [71.01±2.64, 69.00±13.27 and 39.73±19.83 versus 3.10±0.90, 2.10±0.3 and 1.30±0.02 respectively , p<0.05, table (20)].

Comparison between etodolac and meloxicam treated groups

There was a significant higher mean value of maximal optical density of 2 weeks meloxicam toxicity group than 2 weeks etodolac toxicity group at 600, 400, 200 base pair [71.01±2.64, 69.00±13.27 and 39.73±19.83 versus 54.50±33.23, 45.15±23.83 and 35.60±13.29respectively, $p<0.05$, table (20)].

At the end of the 4th week

Liver toxicity (Figure 37):

Comparison between etodolac treated group and controls

There was a significant lower mean value of maximal optical density of 4 weeks etodolac toxicity group than controls at intact DNA [142.40±2.55 versus 151.09±4.23; respectively, $p<0.05$, table (21)]. While there was a significant higher mean value of maximal optical density of 4weeks etodolac toxicity group than controls at intact 400, 200 base pair [20.30±1.48, and 13.10±1.34, versus 16.11±5.62, and 10.10±2.37; respectively, $p<0.05$, table (21)].

Comparison between meloxicam treated group and controls

There was a significant lower mean value of maximal optical density of 4weeks meloxicam toxicity group than controls at intact DNA [130.95±9.26 versus 151.09±4.23; respectively, $p<0.05$, table (21)]. While there was a significant higher mean value of maximal optical density of 4 weeks meloxicam toxicity group than controls at 600, 400, 200 base pair [62.23±20.05, 41.65±14.28, and 21.85±6.58 versus 25.10±9.88, 16.11±5.62, and 10.10±2.37 ;respectively, $p<0.05$, table (21)].

Comparison between etodolac and meloxicam treated groups

There was a significant lower mean value of maximal optical density of 4weeks meloxicam toxicity group than etodolac at intact DNA [130.95±9.26 versus 142.40±2.55; respectively, $p<0.05$, table (21)].

There was a significant higher mean value of maximal optical density of 4 weeks meloxicam toxicity group than 4 weeks etodolac toxicity group at 600, 400, 200 base pair [62.23±20.05, 41.65±14.28, and 21.85±6.58 55 versus 30.80±3.25, 20.30±1.48, and 13.10±1.34, respectively, $p<0.05$, table (21)].

Renal toxicity (Figure 37):

Comparison between etodolac treated group and controls

There was a significant lower mean value of maximal optical density of 4 weeks etodolac toxicity group than controls at intact DNA [113.80±4.20 versus 142.7±5.46 ; respectively, $p<0.05$. table (22)]. While there was a significant higher mean value of maximal optical density of 4 weeks etodolac toxicity group than controls at 600, 400. 200 base pair [79.01±6.41, 60.20±10.20, and 38.90±7.62 versus45.90±3.75. 33.10±1.74 and 18.35±2.78 respectively, $p<0.05$, table (22)].

Comparison between meloxicam treated group and controls

There was a significant lower mean value of maximal optical density of 4 weeks meloxicam toxicity group than controls at intact DNA [129.10±7.73 versus 142.7±5.56 ; respectively, $p<0.05$, table (22)]. While there was a significant higher mean value of maximal optical density of 4 weeks meloxicam toxicity group than controls at 600, 400, 200 base pair [65.20±9.42, 46.95±2.54 and 32.55±8.73 versus 45.90±3.75, 33.10±1.74 and 18.35±2.78 respectively , $p<0.05$, table (22)].

Comparison between etodolac and meloxicam treated groups

There was a significant higher mean value of maximal optical density of 4 weeks meloxicam toxicity group than 4 weeks etodolac toxicity group at intact DNA [129.10±7.73 versus 113.80±4.20 respectively, $p<0.05$. table (22)]. While there was a significant lower mean value of maximal optical density of 4 weeks meloxicam toxicity group than 4 weeks etodolac toxicity group at 600, 400, 200 base pair [65.20±9.42,

46.95±2.54 and 32.55±8.73 versus 79.01±6.41, 60.20±10.20, and 38.90±7.62 respectively , $p<0.05$, table (22)].

At the end of the follow up period

Liver toxicity (Figure 36):

Comparison between etodolac treated group and controls

There was a non significant mean value of maximal optical density of after effect etodolac toxicity group than controls at intact DNA, 600, 400, 200 base pair [116.00±1.13, 41.35±1.48, 34.50±1.56, and 25.00±0.99 versus 113.50±22.34, 52.35±11.51, 40.25±13.70 and 28.95±4.51 respectively, $p>0.05$, table (23)].

Comparison between meloxicam treated group and controls

There was a non significant mean value of maximal optical density of after effect meloxicam toxicity group than controls at intact DNA, 600, 400, 200 base pair [115.70±2.12, 39.20±2.97, 33.55±1.34 and 24.75±1.13 versus 113.50±22.34, 52.35±11.51, 40.25±13.70 and 28.95±4.51; respectively, $p>0.05$, table (23)].

Comparison between etodolac and meloxicam treated groups

There was a non significant mean value of maximal optical density of after effect meloxicam toxicity group than after effect etodolac toxicity group at intact DNA, 600, 400, 200 base pair [115.70±2.12, 39.20±2.97, 33.55±1.34 and 24.75±1.13 versus 116.00±1.13, 41.35±1.48, 34.50±1.56, and 25.00±0.99 respectively, $p>0.05$, table (23)].

Renal toxicity (Figure 36):

Comparisoo between etodolac treated group and controls

There was a significant lower mean value of maximal optical density of after effect etodolac toxicity group than controls at intact DNA , 600, 400, 200 base pair [121.50±0.71, 43.70±2.55, 36.95±1.20 and 26.21±1.69 versus 126.00±1.43, 48.30±2.27, 48.30±3.51 and 30.30±4.72 ; respectively, $p<0.05$, table (24)].

Comparison between meloxicam treated group and controls

There was a significant lower mean value of maximal optical density of after effect meloxicam toxicity group than controls at intact DNA, 400 base pair [120.50±0.71 and 41.98±1.45 versus 126.00±1.43, 48.30±3.51; respectively, $p<0.05$, table (24)].

Comparison between etodolac and meloxicam treated groups

There was a significant higher mean value of maximal optical density of after effect meloxicam toxicity group than after effect etodolac toxicity group at 600, 400, 200 base pair [47.63±0.11, 41.98±1.45, and 30.98±2.72 versus 43.70±2.55, 36.95±1.20 and 26.21±1.69 respectively, $p<0.05$, table (24)].

Table (17): Comparison of maximal optical density of acute effect on the liver in etodolac and meloxicam treated groups vs. control group.

	Etod group (n=20) X ± SD	Melox group (n=20) X ± SD	Cont group (n=20) X ± SD	F test	P
Intact DNA	101.63±14.3	91.4±4.38•	112.40±3.2	1.37	>0.05
At 600 bp	1.26 ±0.09*	1.72±0.62*	1.09±0.09	0.88	>0.05
At 400 bp	0.93±0.3	1.68±0.64*↕	0.88±0.20	1.72	>0.05
At 200 bp	0.70±0.01	1.57±0.54*↕	0.67±0.21	3.21	>0.05

• Sign. lower than control. * Sign. higher than control.

↕ Sign. higher than Etodolac.

Table (18): Comparison of maximal optical density of acute effect on the kidney in etodolac and meloxicam treated groups vs. control group.

	Etod group (n=20) X ± SD	Melox group (n=20) X ± SD	Cont group (n=20) X ± SD	F test	P
Intact DNA	133.97±12.54●	133.68±14.53●	167.85±15.73	2.75	>0.05
At 600 bp	84.62±10.08*	74.63±2.51*	47.40±1.20	7.44	>0.05
At 400 bp	73.85±3.88*	56.98±2.23*▼	38.20±3.47	44.48	<0.01
At 200 hp	51.08±4.39*	37.50±18.10*	17.70±6.4	3.57	>0.05

● Sign. lower than control. * Sign. higher than cnntrol.

▼ Sign. lower than Etodolac.

Table (19): Comparison of maximal optical density of 2 weeks on the liver in etodolac and meloxicam treated groups vs. control group.

	Etod group (n=10) X ± SD	Melox group (n=10) X ± SD	Cont group (n=10) X ± SD	F test	P
Intact DNA	172.45±5.93*	187.368±2.09*↕	1.91±0.81	645.22	<0.01
At 600 bp	77.65±8.27	68.85±13.58	59.25±12.51	0.93	>0.05
At 400 bp	57.90±3.11*	51.65±2.48*▼	34.10±8.92	24.11	<0.05
At 200 bp	27.05±4.95*	23.20±1.70*	16.15±6.45	2.89	>0.05

↕ Sign. higher than Etodolac. * Sign. higher than control.

▼ Sign. lower than Etodolac.

Table (20): Comparison of maximal optical density of 2 weeks on the kidney in etodolac and meloxicam treated groups vs. control group.

	Etod group (n=10) X ± SD	Melox group (n=10) X ± SD	Cont group (n=10) X ± SD	F test	P
Intact DNA	55.5±21.92●	63.33±25.66●	113.0±2.3	2.01	>0.05
At 600 bp	54.50±33.23*	71.01±2.64*↕	3.1± 0.90	4.64	>0.05
At 400 bp	45.15±23.83*	69.0±13.27*↕	2.10±0.3	5.58	>0.05
At 200 bp	35.60±13.29*	39.73±19.83*↕	1.30±0.02	1.79	>0.05

↕ Sign. higher than Etodolac. * Sign. higher than control.

● Sign. lower than control

Table (21): Comparison of maximal optical density of 4 weeks on the liver in etodolac and meloxicam treated groups vs. control group.

	Etod group (n=10) X ± SD	Melox group (n=10) X ± SD	Cont group (n=10) X ± SD	F test	P
Intact DNA	142.40±2.55*	130.95±9.26▼●	t51.09±4.23	3.22	>0.05
At 600 bp	30.80± 3.25	62.23±20.05*↕	25.10±9.88	3.28	>0.05
At 400 bp	20.30±1.48*	41.65±14.28*↕	16.11±5.62	3.07	>0.05
At 200 bp	13.10±1.34*	21.85±6.58*↕	10.10±2.37	2.67	>0.05

↕ Sign. higher than Etodolac. ● Sign. lower than control.

* Sign. higher than control. ▼Sign lower than Etodolac.

Table (22): Comparison of maximal optical density of 4 weeks on the kidney in etodolac and meloxicam treated groups vs. control group.

	Etod group (n=10) X ± SD	Melox group (n=10) X ± SD	Cont group (n=10) X ± SD	F test	P
Intact DNA	113.80±4.2●	129.10±7.73↕●	142.7±5.46	10.3	<0.05
At 600 bp	79.01±6.41*	65.20±9.42*▼	45.90±3.75	28.7	<0.05
At 400 bp	60.20±10.2*	46.95±2.54*▼	33.10±1.74	32.4	<0.01
At 200 bp	38.90±7.62*	32.55±8.73*▼	18.35±2.78	21.3	<0.05

↕ Sign. higher than Etodolac.

▼ Sign. lower than Etodolac.

* Sign. higher than control.

● Sign. lower than control

Table (23): Comparison of maximal optical density of after effect on the liver in etodolac and meloxicam treated groups vs. control group.

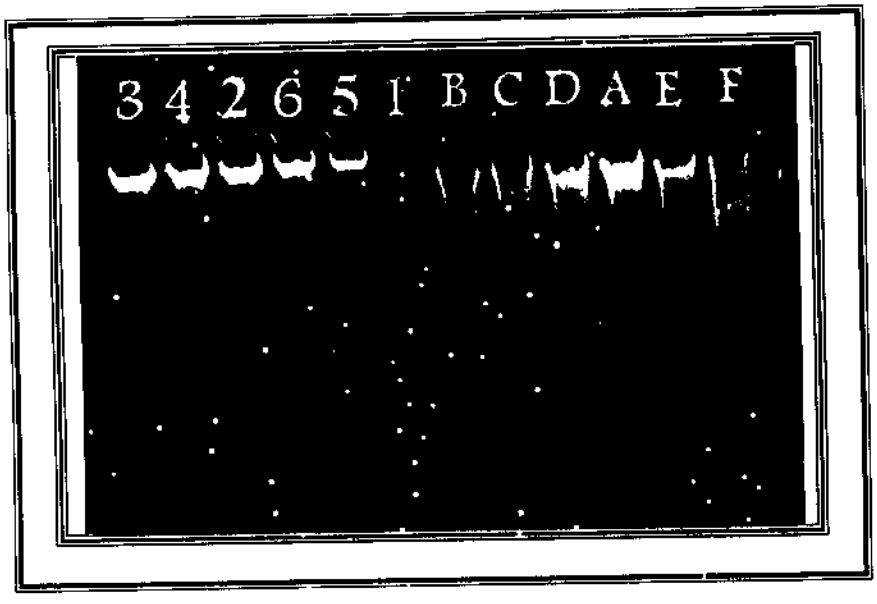
	Etod group (n=10) X ± SD	Melox group (n=10) X ± SD	Cont group (n=10) X ± SD	F test	P
Intact DNA	116.0±1.13	115.70±2.12	113.5±22.34	0.78	>0.05
At 600 bp	41.35± 1.48	39.20±2.97	52.35±11.51	10.99	>0.05
At 400 bp	34.50±1.56	33.55±1.34	40.25±13.70	7.55	>0.05
At 200 bp	25.00±0.99	24.75±1.13	28.95±4.51	5.91	>0.05

Table (24): Comparison of maximal optical density of after effect on the kidney in etodolac and meloxicam treated groups vs. control group.

	Etod group (n=10) X ± SD	Melox group (n=10) X ± SD	Cont group (n=10) X ± SD	F test	P
Intact DNA	121.50±0.71●	120.50±0.71●	126.0±1.43	21.0	<0.05
At 600 bp	43.7±2.55●	47.63±0.11↕	48.30±2.27	3.23	>0.05
At 400 bp	36.95±1.2●	41.98±1.45↕●	48.30±3.51	8.69	>0.05
At 200 bp	26.21±1.69●	30.98±2.72↕	30.30±4.72	2.44	>0.05

↕ Sign. higher than Etodolac. ● Sign. lower than control.

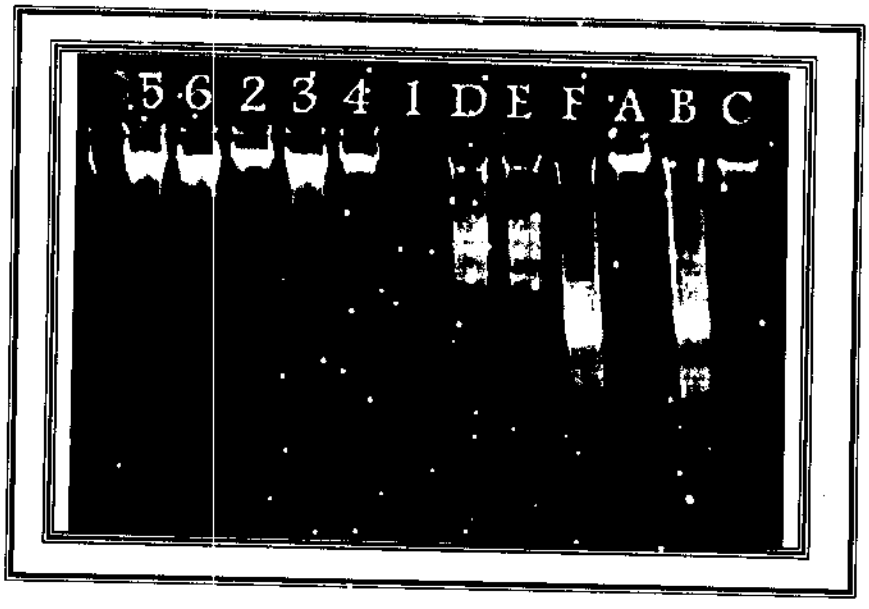
Figure (38): Gel electrophoresis of extracted DNA of rat liver (left) and kidney (right) of the studied 24 hours (acute toxicity) groups and control.



Lane 1- Ladder
Lane 2- Control
Lane 3- Etodolac
Lane 4- Etodolac
Lane 5- Meloxicam
Lane 6- Meloxicam

Lane A- Control
Lane B- Etodolac
Lane C- Etodolac
Lane D- Etodolac
Lane E- Meloxicam
Lane F- Melnxicam

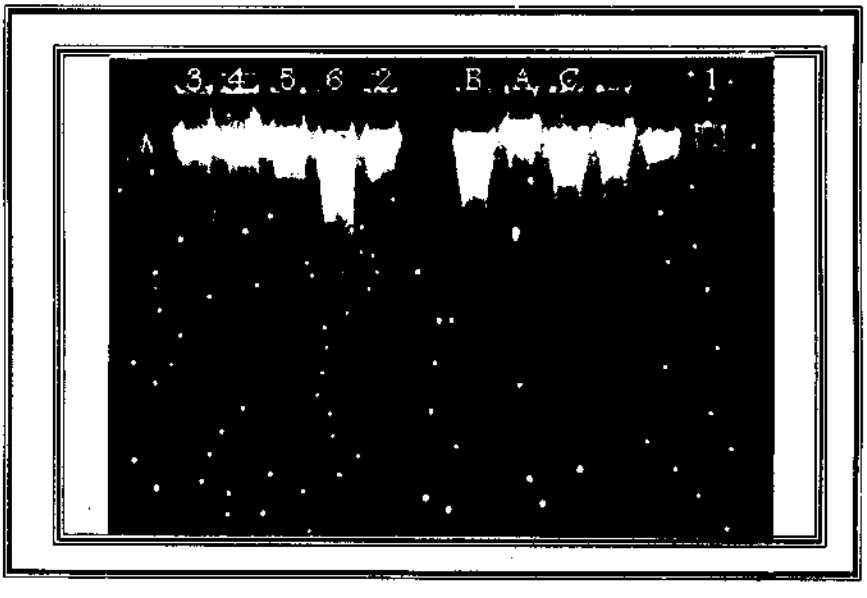
Figure (39): Gel electrophoresis of extracted DNA of rat liver (left) and kidney (right) of the studied 2 weeks (short term chronic toxicity) groups and control.



Lane 1- Ladder
Lane 2- Control
Lane 3- Etodolac
Lane 4- Etodolac
Lane 5- Meloxicam
Lane 6- Meloxicam

Lane A- Control
Lane B- Etodolac
Lane C- Etodolac
Lane D- Meloxicam
Lane E- Meloxicam
Lane F- Meloxicam

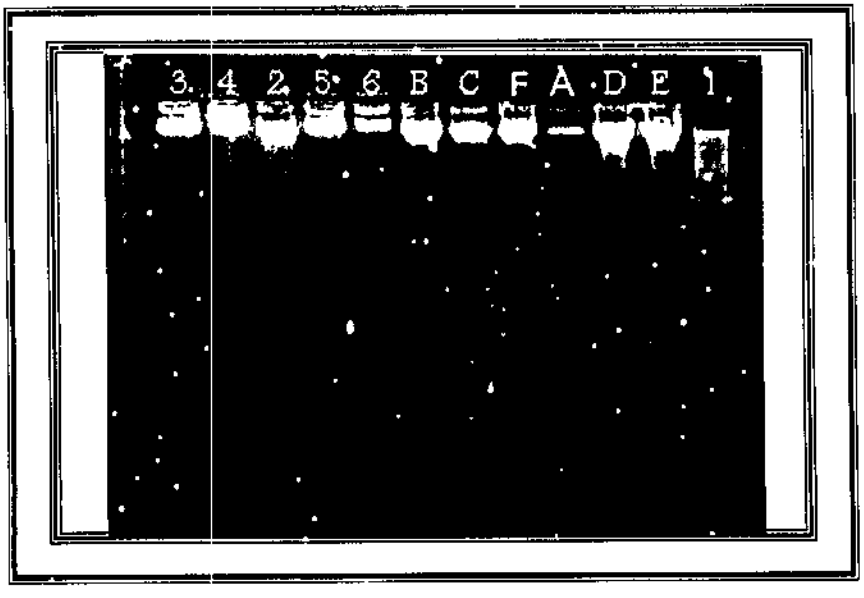
Figure (40): Gel electrophoresis of extracted DNA of rat liver (left) and kidney (right) of the studied 4 weeks (short term chronic toxicity) groups and control.



Lane 1- Ladder
Lane 2- Control
Lane 3- Etodolac
Lane 4- Etodolac
Lane 5- Meloxicam
Lane 6- Meloxicam

Lane A- Control
Lane B- Etodolac
Lane C- Meloxicam

Figure (41): Gel electrophoresis of extracted DNA of rat liver (left) and kidney (right) of the studied after effect (short term chronic toxicity) groups and control.



Lane 1- Ladder
Lane 2- Control
Lane 3- Etndnlae
Lane 4- Etodolae
Lane 5- Melnxicam
Lane 6- Mcloxicam

Lane B- Control
Lane C- Etodolac
Lane F- Etodolac
Lane D- Meloxicam
Lane E- Mcloxieam