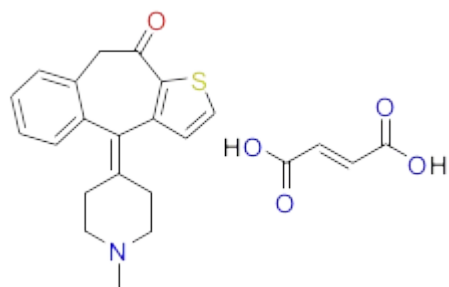
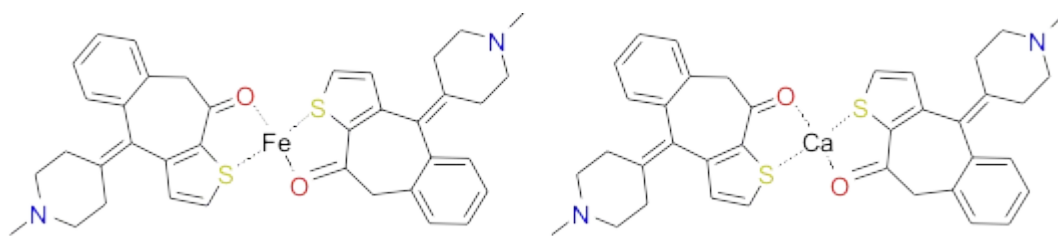


**The identification of ketotifen as a novel cardioprotective agent in patients  
undergoing anthracyclines chemotherapy**

**List of Figures, Charts, and Tables**



**Figure I:** Structural formula of ketotifen fumarate



**Figure II:** Suggested ketotifen chelates with iron, and calcium

**Table I:** Results of complexmetric titration of ketotifen and blank samples against solutions of  $\text{Fe}(\text{OH})_2$  and  $\text{Ca}(\text{OH})_2$ .

Experiment #	Endpoint of $\text{Fe}(\text{OH})_2$	Endpoint of $\text{Ca}(\text{OH})_2$
1.	5.6 mL	8.0 mL
2.	5.8 mL	8.2 mL
3.	5.7 mL	8.1 mL
Blank	0.1 mL	0.1 mL

**Table II:** Measured biomarkers and echocardiograms of patients in control and ketotifen groups at baseline and after 6 months of treatment with anthracyclines.

Biomarkers	Control group N = 55	Ketotifen group N = 56	P-value	Control group N = 55	Ketotifen group N = 56	P-value
	At baseline			After 6 months		
LDH (U/L)	259.25 $\pm$ 16.72	255.87 $\pm$ 24.12	0.363	530.00 $\pm$ 26.06	227.53 $\pm$ 25.73	0.001*
CK-MB (ng/mL)	14.37 $\pm$ 2.49	14.46 $\pm$ 1.33	0.550	32.99 $\pm$ 4.92	17.64 $\pm$ 2.81	0.006*
Troponin I (ng/mL)	0.15 $\pm$ 0.09	0.16 $\pm$ 0.07	0.134	0.51 $\pm$ 0.09	0.15 $\pm$ 0.08	0.001*
ACL IgG (U/L)	6.91 $\pm$ 0.8	6.13 $\pm$ 0.20	0.048	14.38 $\pm$ 1.66	4.74 $\pm$ 0.62	0.002*
Iron ( $\mu\text{g}/\text{dL}$ )	89.06 $\pm$ 6.5	90.9 $\pm$ 8.73	0.464	178.25 $\pm$ 10.49	46.53 $\pm$ 6.34	0.008*
TIBC ( $\mu\text{g}/\text{dL}$ )	296.00 $\pm$ 26.33	298.07 $\pm$ 28.96	0.334	238.63 $\pm$ 17.62	320.13 $\pm$ 19.66	0.001*
Ferritin ( $\mu\text{g}/\text{L}$ )	196.63 $\pm$ 12.99	194 $\pm$ 17.84	0.786	269.31 $\pm$ 23.71	64.6 $\pm$ 9.74	0.001*
EF %	67% $\pm$ 4.00	68% $\pm$ 5.00	0.401	62% $\pm$ 3.00	68% $\pm$ 4.00	0.009*

All data are representing mean  $\pm$  SD.

SD: Standard deviation; LDH: lactate Dehydrogenase enzyme; CK-MB: Creatine kinase-MB iso-enzyme; Troponin I: it is a part of the troponin protein complex in the myocardium.; ACL IgG: Anti-cardiolipin antibody (autoantibodies); TIBC: total iron-binding capacity; EF: ejection fraction.

A paired t-test is used through SPSS for statistical analysis

\*  $p$ -value considered statistically significant if equal to or less than 0.05.

**Table III:** Mean serum levels of biomarkers and echocardiograms in control versus ketotifen group at baseline and after 6 months of treatment with anthracyclines.

Biomarkers	Control group n = 55	Control group n = 55	<i>p-value</i>	ketotifen group n = 56	Ketotifen group n = 56	<i>p-value</i>
	At baseline	After 6 months		At baseline	After 6 months	
<b>LDH (U/L)</b>	259.25 ± 16.72	530.00 ± 26.06	0.007*	255.87 ± 24.12	227.53 ± 25.73	0.297
<b>CK-MB (ng/mL)</b>	14.37 ± 2.49	32.99 ± 4.92	0.009*	14.46 ± 1.33	17.64 ± 2.81	0.102
<b>Troponin I (ng/mL)</b>	0.15 ± 0.09	0.51 ± 0.09	0.001*	0.16 ± 0.07	0.15 ± 0.08	0.562
<b>ACL IgG (U/L)</b>	6.91 ± 0.8	14.38 ± 1.66	0.003*	6.13 ± 0.20	4.74 ± 0.62	0.213
<b>Iron (µg/dL)</b>	89.06 ± 6.5	178.25 ± 10.49	0.001*	90.9 ± 8.73	46.53 ± 6.34	0.004*
<b>TIBC (µg/dL)</b>	296.00 ± 26.33	238.63 ± 17.62	0.005*	298.07 ± 28.96	320.13 ± 19.66	0.303
<b>Ferritin (µg/l)</b>	196.63 ± 12.99	269.31 ± 23.71	0.0139*	194 ± 17.84	64.6 ± 9.74	0.001*
<b>EF %</b>	67% ± 4.00	62% ± 3.00	0.080	68% ± 5.00	68% ± 4.00	0.924

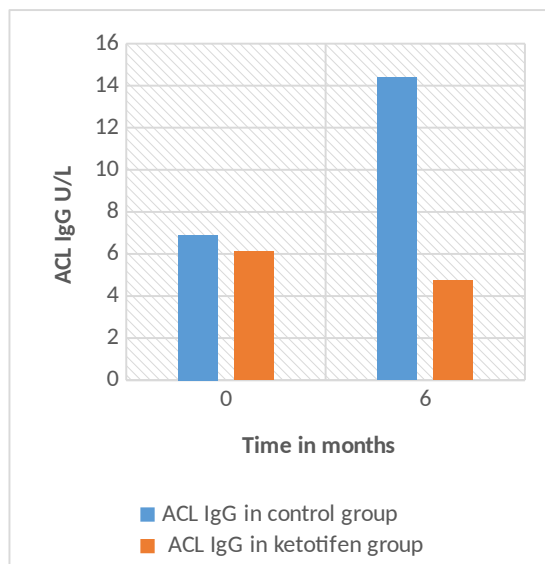
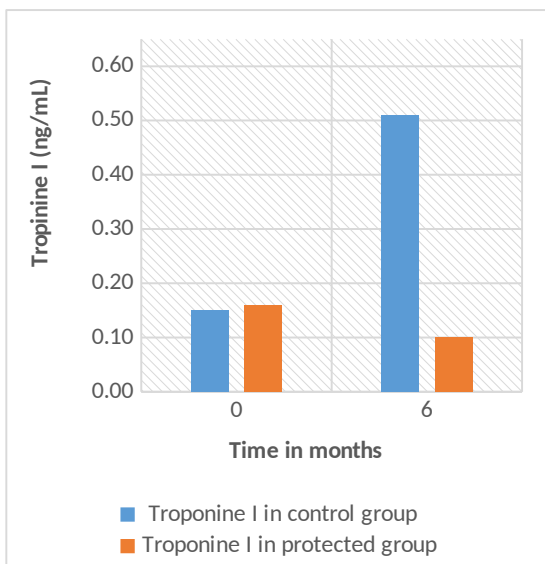
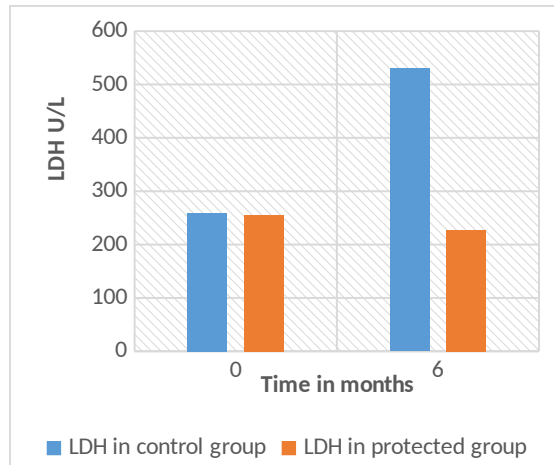
All data are representing mean ± SD.

SD: standard deviation; LDH: lactate dehydrogenase enzyme; CK-MB: creatinine kinase-MB iso-enzyme.

Troponin I: it is a part of the troponin protein complex in the myocardium.; ACL IgG: anti-cardiolipin antibody (autoantibody); TIBC: Total Iron Binding Capacity; EF: ejection fraction.

A paired t-test is used through SPSS for statistical analysis.

\* *p*-value is equal to less than 0.05 (statistically significant).



**Chart 1:** Changes in LDH U/L (upper row), Troponin I (lower left), and ACL Ig (lower right) in both groups before and after treatment with anthracyclines.

Control group: patients who received anthracyclines only without protection.

Protected group: patients who received anthracyclines plus protection by ketotifen