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Evaluation Of Effect Of Red Ginseng On Combination Effect Of Sildenafil Citrate With Isosorbide Dinitrate On Heart And Kidney Of Experimental Rats.

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ABSTRACT

Sexual dysfunction affect a significant percentage of men all over the world.Sildenafil citrate has revolutionized the treatment of male sexual dysfunction however its use has been considered dangerous in certain situations especially with nitrates treated patients. Red Ginseng is a plant of medical importance as a potent antioxidant, it has a role in improving sexual performance and also has role inimproving BP stability in certain studies (1) .

Keywords: ginseng ,sildenafil citrate ,isosorbide dinitrate, cardiotoxicity, nephrotoxicity.

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INTRODUCTION

Erectile dysfunction also known as impotence is a type of sexual dysfunction characterized by the inability to develop or maintain an erection of the penis during sexual activity.(1)The first line of treatment of erectile dysfunction consist of a trial of PDE5 inhibitor such as sildenafil.

The food and drug administration (FDA) has warned against the use of the impotence drug sildenafil(vigra) by person taking medication that contain nitrates as both cause the muscles that control the size of blood vessels to relax.so blood pressure to drop,when sildenafil and nitrate are taken together the effect are greater than when either one is used alone and marked drop of BP (2).

Gienseng is a plant of medical importance and it has been used by elderly Asian to boost physical and mental vitality ,the biological name is panax ginseng .the most importantpart of ginseng is the root and its chemical constituents are arabinose,comphermucilage,resin,starch and saponin(3).Panax ginseng is a potent antioxidant since it acts as an active free radical scavenger (4). It reduces tissue damage ,reinforces the immune system and helps to keep blood sugar under control(5). Chewing low dose Korean red ginseng render patients better resistance to acute BP reduction during hemodialysis via activation of vasoconstrictor (endothelin 1 and angiotensin II).(6)

The aim of our work : To evaluate the effect of red ginseng on combination effect of sildenafil with isosorbide di nitrate on heart and kidney of experimental rats both pathologically and laboratory .

MATERIALS AND METHODS

Healthy 60 adult male Wister albino rats weighting 200-250 mg were randomly selected for this study at animal house of faculty of medicine Cairo university.

The animals were placed at temperature (21+ or -2 C^{o}) and humidity controlled room with 12 hour light-dark cycles and fed standard pellet chow and water ad libitum. all experimental procedures were conducted in accord with the principles for the care and use of laboratory animals in research and approved by the local ethics committee. all efforts were made to minimize animal suffering and reduce the number of animals used (7).After a quarantine period of 7 days ,60 male rats wererandomly divided into 6 groups, each consisting of 10 animals.

Group A was used as control group.
Group B receive ginseng powder dissolved in water orally 200 mg/Kg as by conversion of adult human dose (7) to animal dose (8).
Group C receive sildenafil citrate at a dose of 20 mg/kg orally.(9)
Group D receive isosorbide dinitrate at a dose of 25 mg/kg. (10)
Group E receive sildenafil at dose of 20 mg/kg orally, and isosorbide di nitrate at dose of 25 mg/kg .
Group F receive sildenafil at dose of 20 mg/kg orally, isosorbide di nitrate at dose of 25 mg/kg and ginseng powder dissolved in water orally 200 mg/Kg.

All this groups was evaluated for penile size measurements , at start and at end of the study.

The rats were sacrificed 24 h following the last herbal dose , blood samples were collected and serum was separated at 3000 J for 10 minutes. serum level of creatinine ,urea, Aspartate transaminase (AST), creatinine kinase(CK) ,CKMB, Lactate dehydrogenase(LDH) and Tropnin I were collected from all groups .A longitudinal section from left kidney and from the heart was excised from all rats on all groups for histological examination. sample of renal tissue and heart were fixed in 10% buffered formalin, embedded in paraffin wax, sectioned stained with hematoxylin and eosin and examined under light microscope.

Statistical Analysis

Data were analyzed using statistical program for social science(SPSS) version 20.0.Quantitative data were expressed as mean+ or - standard deviation(SD).

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Qualitative data were expressed as frequency and percentage.\The following tests were done:

A one way analysis of variance (ANOVA) when comparing between more than two means.

Probability (P-value)

- P-value ≤0.05 was considered significant.
- P-value ≤0.001 was considered as highly significant.
- P-value >0.05 was considered insignificant.

Table (1): Comparison between groups according laboratory data.

	Group A	Group B	Group C	Group D	Group E	Group F	ANOVA	p-value
Urea Mean±SD Range	27.50±7.62 17-38	40.90±9.34 27-51	51.40±2.17 49-55	34.10±9.45 22-50	69.10±11.78 52-86	38.50±5.89 30-48	31.807	**<0.001**
Creatinine Mean±SD Range	0.59±0.08 0.48-0.68	0.50±0.06 0.42-0.58	0.46±0.07 0.32-0.55	0.46±0.07 0.32-0.55	1.79±0.21 1.5-2.1	0.48±0.05 0.43-0.55	244.040	**<0.001**
AST Mean±SD Range	54.05±8.78 38-65.3	158.80±29.86 80-192	136.40±24.20 100-163	50.90±11.20 33-65	156.00±28.36 120-190	158.80±22.12 105-186	55.265	**<0.001**
CK Mean±SD Range	119.80±33.38 88-170	675.00±352.52 200-1292	560.20±121.52 420-790	549.60±108.13 400-700	845.00±266.34 400-1110	655.60±251.30 388-993	12.470	**<0.001**
CKMB Mean±SD Range	0.27±0.12 0.1-0.4	0.16±0.12 0-0.3	0.27±0.05 0.2-0.3	0.15±0.11 0-0.3	0.57±0.14 0.4-0.8	0.06±0.08 0-0.2	27.584	**<0.001**
LDH Mean±SD Range	429.50±63.19 280-488	1537.30±843.25 800-3087	1373.10±338.47 910-1724	752.60±164.27 600-1000	1307.50±365.90 899-1800	1122.10±273.42 820-1551	9.898	**<0.001**
Troponin I Mean±SD Range	0.20±0.11 0-0.3	0.20±0.11 0-0.3	0.20±0.11 0-0.3	0.20±0.11 0-0.3	0.65±0.13 0.5-0.8	0.20±0.11 0-0.3	28.256	**<0.001**

This table shows statistically significant difference between groups according to laboratory data.

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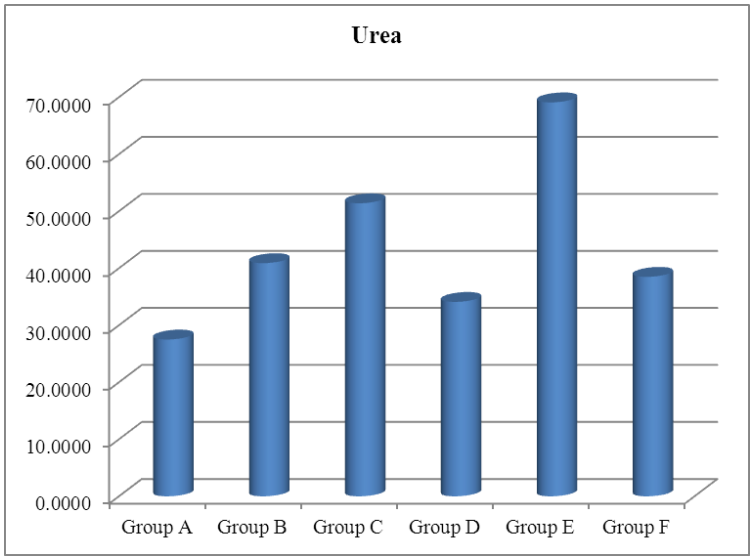

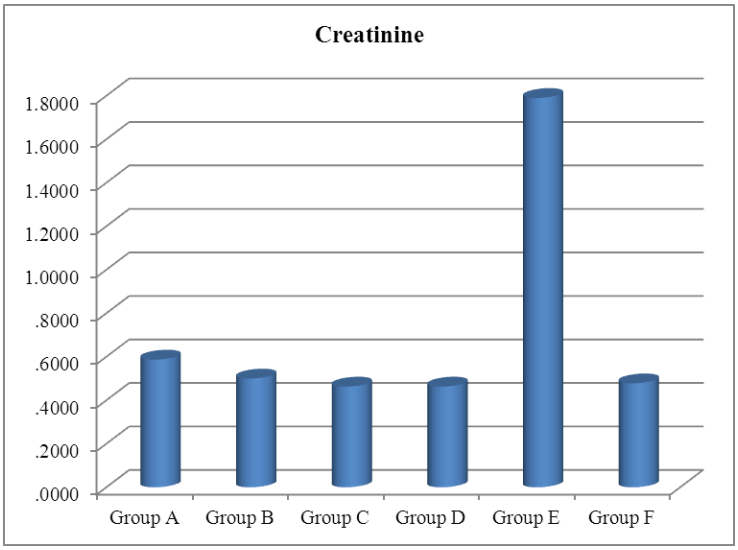

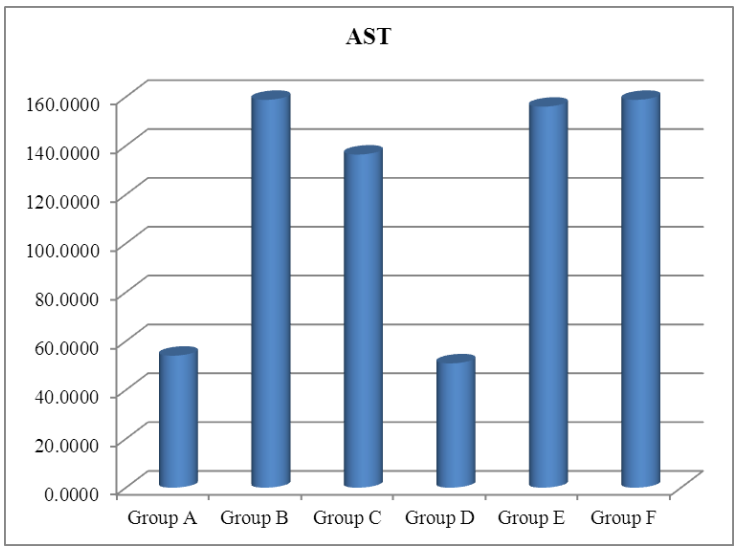

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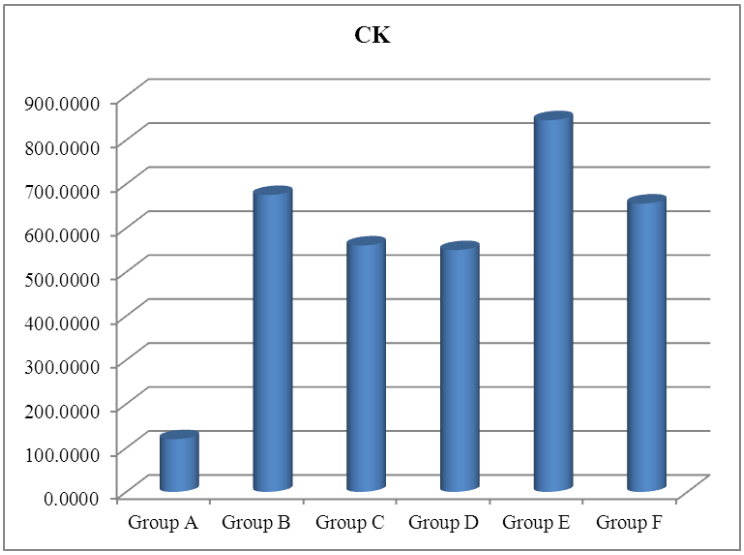

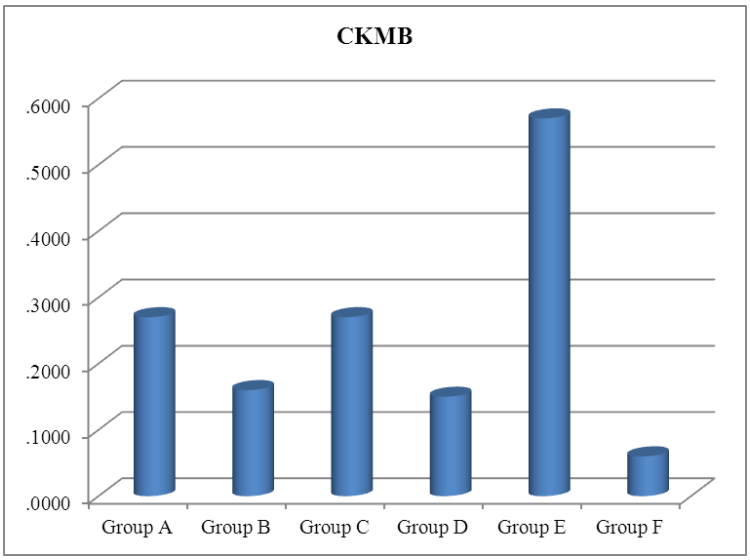

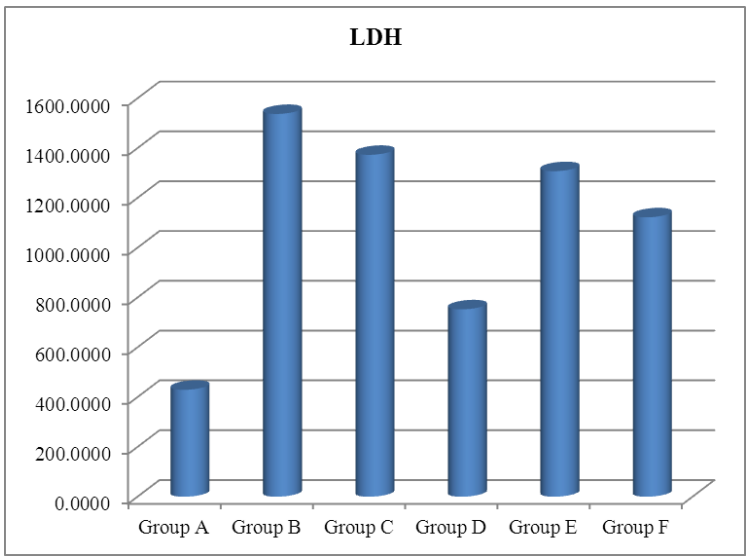

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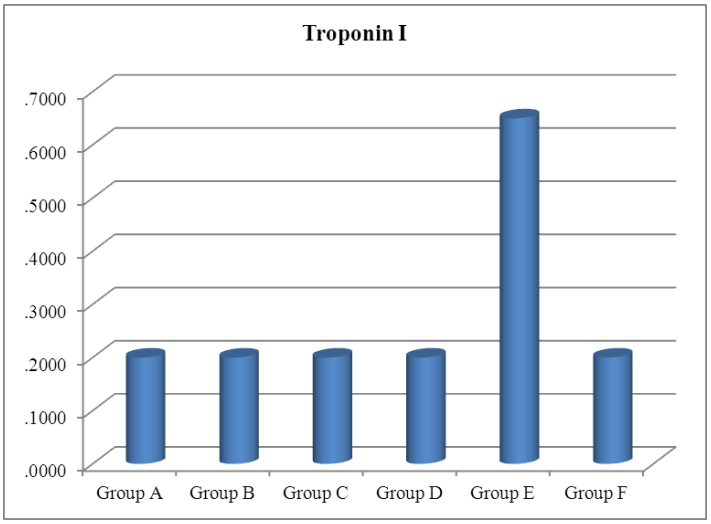

Table (2): Comparison between groups according pathology on penis.

Pathology on penis	Group A	Group B	Group C	Group D	Group E	Group F	x2	p-value
Un remarkable pathological changes	10 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	60.000	**<0.001**
Vasodilatation +congestion	0 (0%)	10 (100%)	10 (100%)	10 (100%)	10 (100%)	10 (100%)		
Total	10 (100%)	10 (100%)	10 (100%)	10 (100%)	10 (100%)	10 (100%)		

This table shows statistically significant difference between groups according pathology on penis.

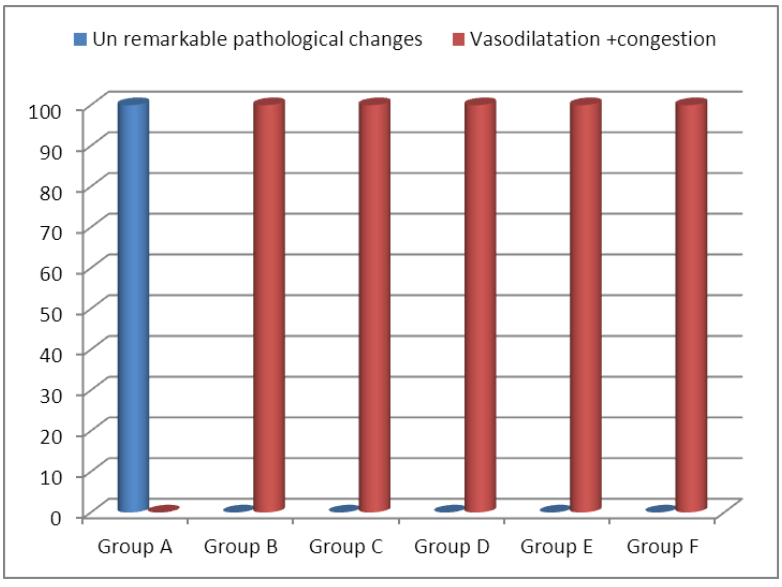

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Table (3): Comparison between groups according pathology on kidney.

Pathology on kidney	Group A	Group B	Group C	Group D	Group E	Group F	x2	p-value
Interstitial nephritis, vacular changes, increased glomerular cellularity	0 (0%)	0 (0%)	0 (0%)	0 (0%)	10 (100%)	0 (0%)	118.044	**<0.001**
Mild congestion	0 (0%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)		
Un remarkable pathological changes	10 (100%)	9 (90%)	2 (20%)	10 (100%)	0 (0%)	0 (0%)		
Vacular changes	0 (0%)	0 (0%)	4 (40%)	0 (0%)	0 (0%)	7 (70%)		
Vacular changes+ increased glomerular cellularity	0 (0%)	0 (0%)	4 (40%)	0 (0%)	0 (0%)	3 (30%)		
Total	10 (100%)	10 (100%)	10 (100%)	10 (100%)	10 (100%)	10 (100%)		

This table shows statistically significant difference between groups according pathology on kidney.

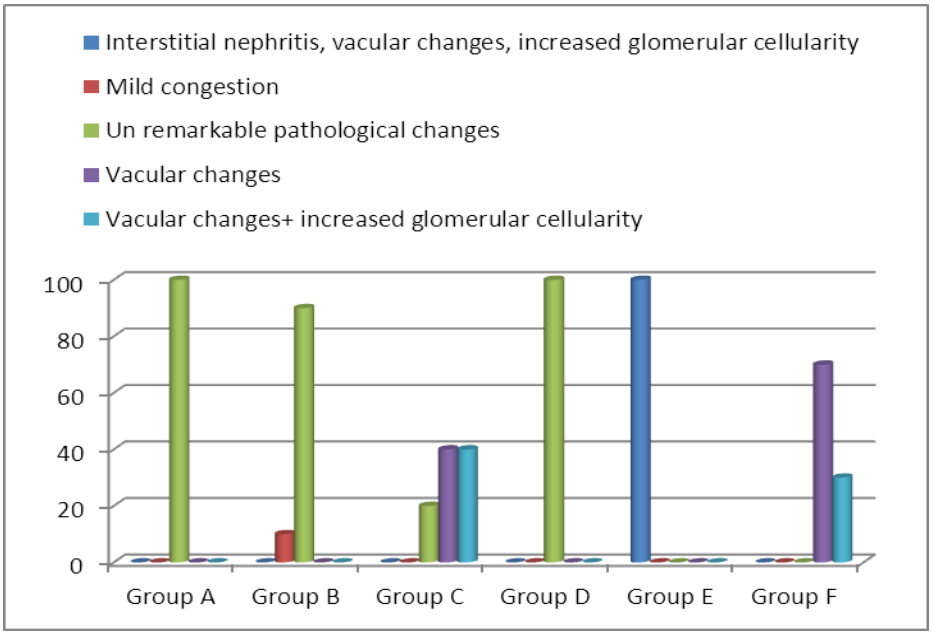

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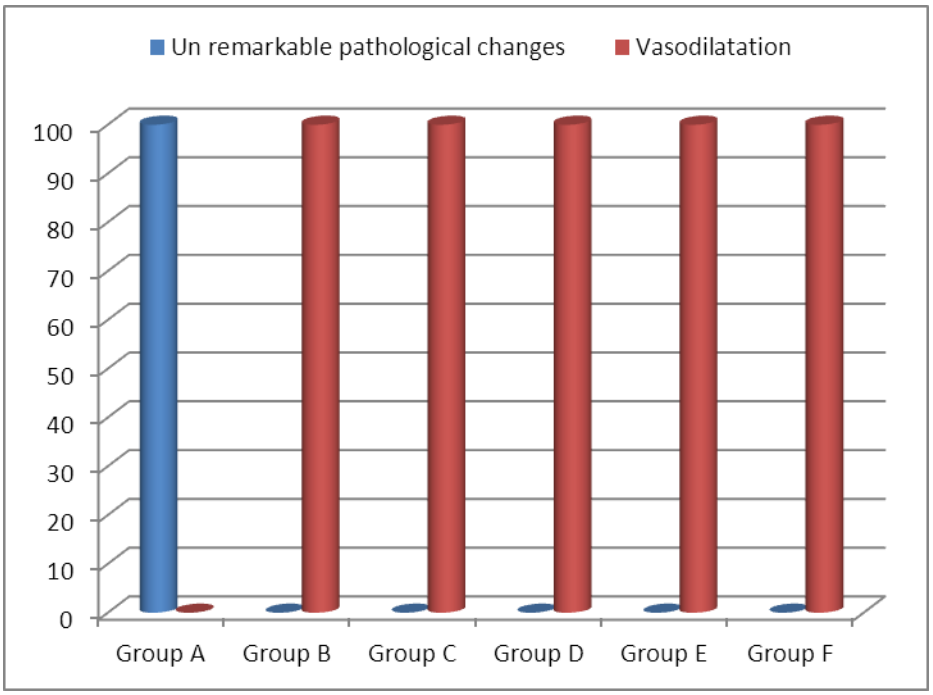
Table (4): Comparison between groups according pathology on heart.

Pathology on heart	Group A	Group B	Group C	Group D	Group E	Group F	x2	p-value
Un remarkable pathological changes	10 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	60.000	**<0.001**
Vasodilatation	0 (0%)	10 (100%)	10 (100%)	10 (100%)	10 (100%)	10 (100%)		
Total	10 (100%)	10 (100%)	10 (100%)	10 (100%)	10 (100%)	10 (100%)		

This table shows statistically significant difference between groups according pathology on heart.



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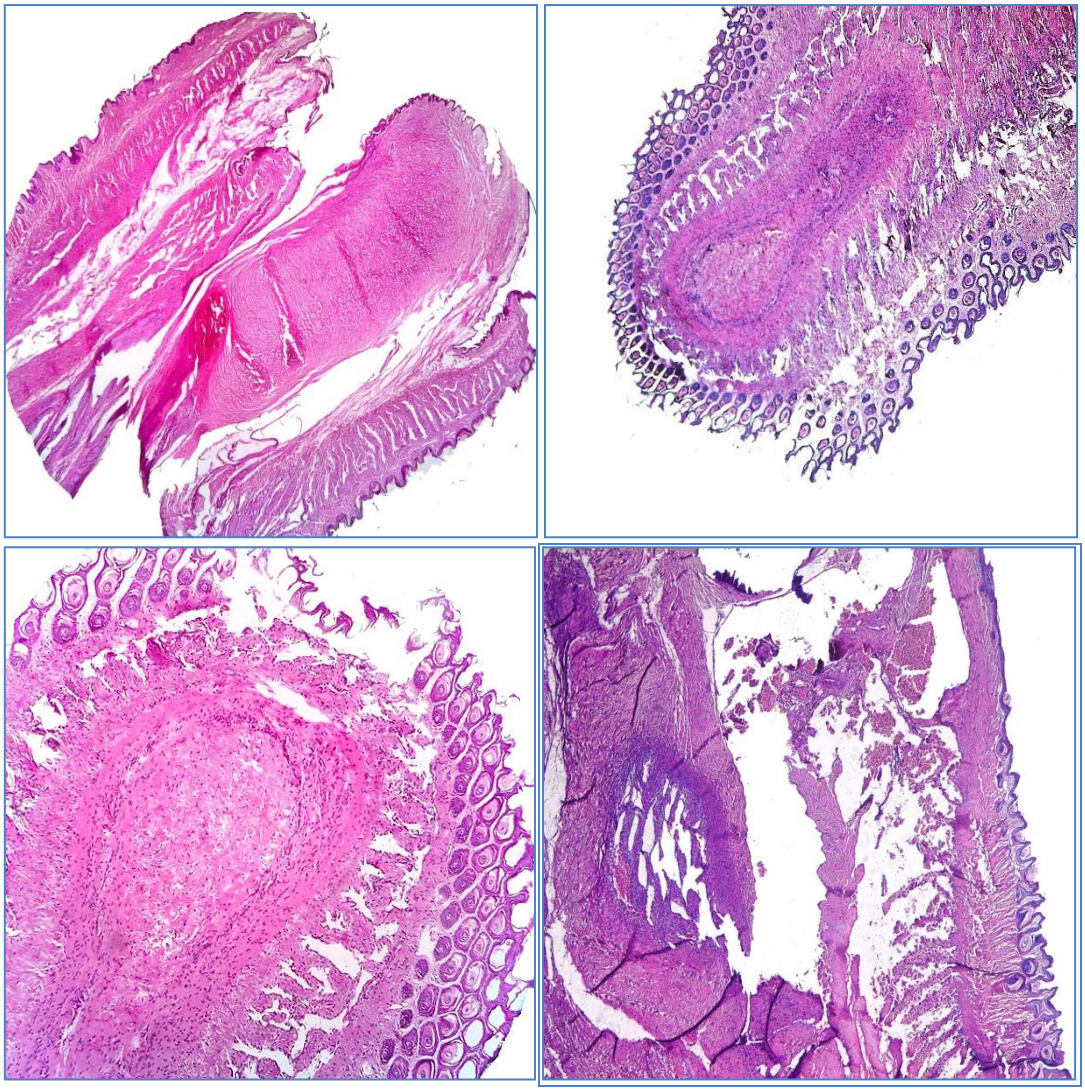

Fig. 1: Section of albino mice penis, control, showing unremarkable changes *(Haematoxylin-eosin, low power).*

Fig. 2: Section of, Sildenafil drug treated, albino mice penis showing vascular dilatation *(Haematoxylin-eosin, low power).*

Fig. 3: Section of, Sildenafil, Dinitrite, Ginseng, and Saline drug treated, albino mice penis showing vascular dilatation *(Haematoxylin-eosin, low power).*

Fig. 4: Section of, Sildenafil and Dinitrite drug treated, albino mice penis showing marked vascular dilatation *(Haematoxylin-eosin, high power).*

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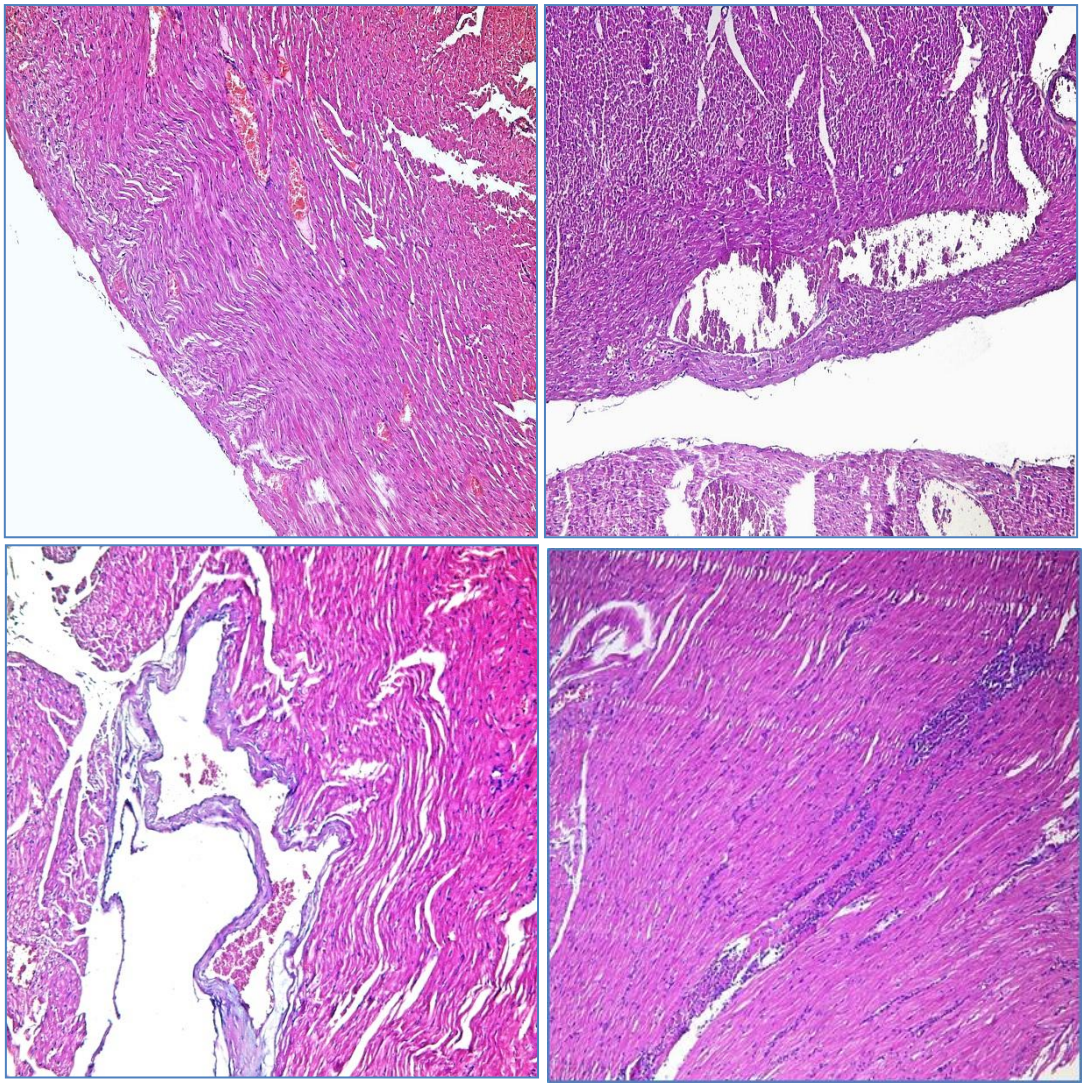

Fig. 5: Section of albino mice myocardium, control, showing unremarkable changes *(Haematoxylin-eosin, low power).*

Fig. 6: Section of, Sildenafil, Dinitrite, Ginseng, and Saline drug treated, albino mice myocardium showing vascular vasodilation *(Haematoxylin-eosin, high power).*

Fig. 7: Section of, Sildenafil and Dinitrite drug treated, albino mice myocardium showing vascular vasodilation *(Haematoxylin-eosin, high power).*

Fig. 8: Section of, Sildenafil and Dinitrite drug treated, albino mice myocardium showing focal interstitial inflammation *(Haematoxylin-eosin, high power).*

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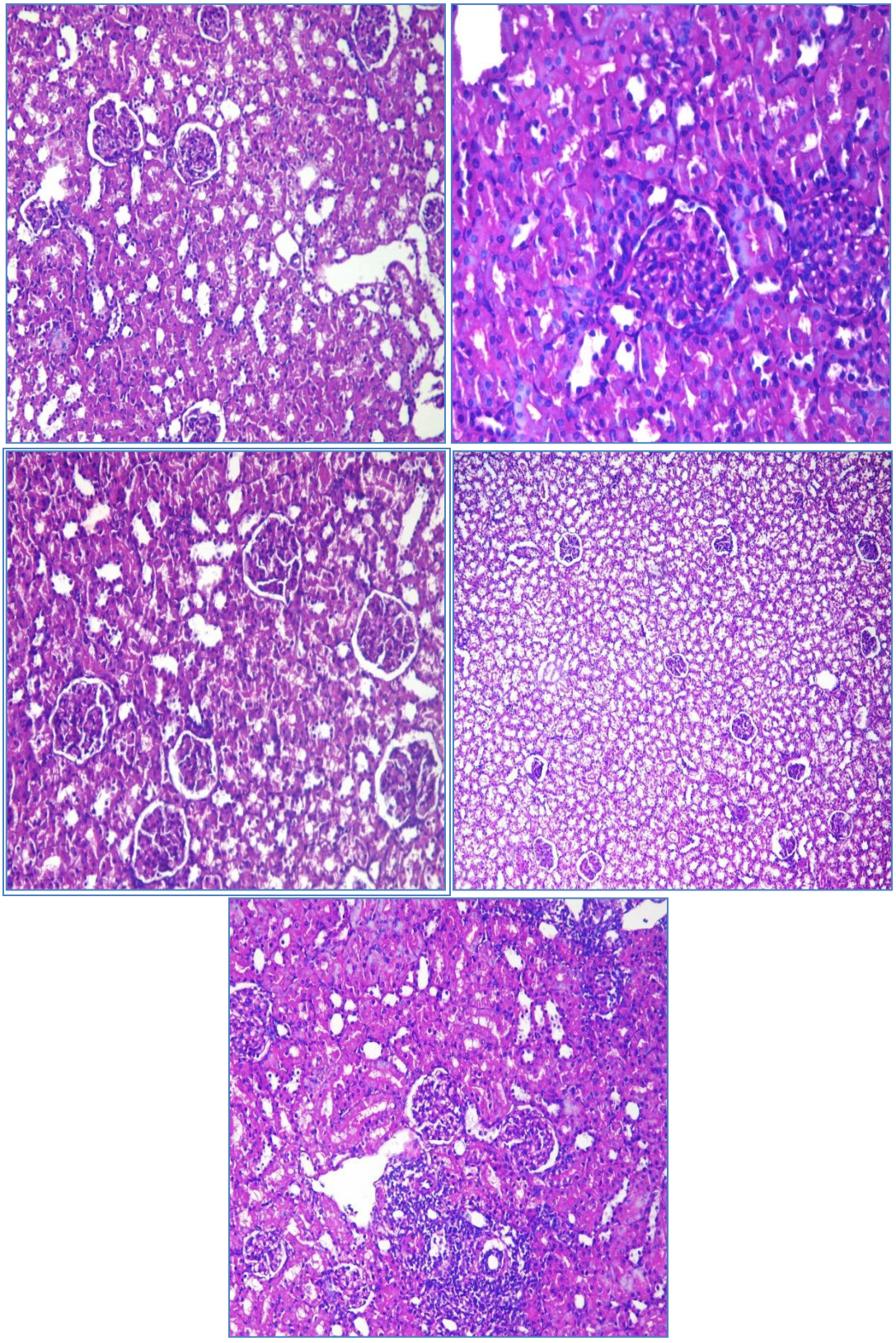

Fig. 9: Section of albino mice kidney, control, showing unremarkable changes *(Haematoxylin-eosin, high power).*

Fig. 10: Section of albino mice kidney, drug treated with Sildenafil, showing glomerular hypercellularity *(Haematoxylin-eosin, high power).*

Fig. 11: Section of albino mice kidney, drug treated with Sildenafil, Dinitrite, Ginseng, and Saline, showing glomerular collapse and hydropic change in the renal tubules *(Haematoxylin-eosin, high power).*

Fig. 12: Section of albino mice kidney, **drug treated with Sildenafil and Dinitrite,** showing vacuolar changes in the renal tubules, and glomerular shrinkage ***(Hematoxylin and eosin, low power).***
Fig. 13: Section of albino mice kidney, **drug treated with Sildenafil and Dinitrite,** showing focal interstitial nephritis ***(Haematoxylin-eosin, high power).***

DISCUSSION

Regarding kidney function tests:

- Regarding **urea** all groups are higher than control group with high significant difference between group E(sildenafil and dinitrate) and control groups.
- Regarding **creatinine** no difference between all groups and control group as all within normal range of lab exceptgroup E (sildenafil and dinitrate)which show high statistically significant difference between control group and other groups with high creatinine above normal range of creatinine in rats as result show mean +-SD 1.79+-0.21.

Regarding cardiac enzyme

- Regarding **CK,CKMB** and **troponin I** show high statistically significant difference between group E(sildenafil and dinitrate) by comparison with control group and all other groups.
- Regarding **AST,LDH** is highly significant statistically differences in all groups by comparison with control group.

Pathological result on **penis**,**kidney** and **heart** of rats show:

- **Penis** :high statistically significant difference show vasodilation and congestion in all groups by comparison with control group which show unremarkable pathological changes.
- **Kidney**: regarding pathological changes on kidney group A control group, group B,D and Fshow no pathological changes but group c (sildenafil citrate group) show vascular changes (congestion) 40% and group E(sildenafil and dinitrate) show 70% vascular changes and 30 % show vascular changes and increase glomerular cellularity.
- **Heart**: regarding pathological changes on the heart it show highly statistically significant difference between all groups and control group as all groups show 100 % vasodilation+ congestion but unremarkable pathological changes on the heart in control group.

CONCLUSION

The combination of dinitrate and sildenafil citrate has risky effect on heart and kidney of experimental rats both laboratory and pathologically.

Red ginseng has significant effect on decreasing the risk of combination of sildenafil citrate and dinitrate on heart and kidney of experimental rats both laboratory and pathologically with preserved vasodilation and congestion on penis and heart,mostly due to improve compensatory response to acute volume changes via activation of vasoconstrictor endothelin I and angiotensin II so we suggest more study on this effect.

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