Free Radicals and Antioxidants., 2024; 14(1):27-31.
https://www.antiox.org

Original Article

Comparative Hypertestosteronemic Effects of the Erythropoietin and the U-74389G

Constantinos Tsompos[1,*], Constantinos Panoulis[2], Aggeliki Triantafyllou[3], Constantinos Zografos[4], George C. Zografos[5], Apostolos Papalois[6]

[1]Department of Gynecology, General Hospital of Athens "G. Gennimatas", Athens, HELLAS (GREECE).
[2]Department of Obstetrics and Gynecology, Aretaieion Hospital, Athens University, Athens, Attiki, HELLAS (GREECE).
[3]Department of Biological Chemistry, Athens University, Athens, Attiki, HELLAS (GREECE).
[4]Department of Surgery, Laikon General Hospital, Athens University, Athens, Attiki, HELLAS (GREECE).
[5]Department of Surgery, Ippokrateion General Hospital, Athens University, Athens, Attiki, HELLAS (GREECE).
[6]Experimental, Educational and Research Center, ELPEN Pharmaceuticals Co Inc SA HELLAS, Cyprus European University, School of Medicine, CYPRUS.

ABSTRACT

Background: This study is to find out in which direction two antioxidant promising molecules, the erythropoietin and the U-74389G, affect serum Testosterone (T) levels and what the magnitude of this alteration is. The posttreatment effects on serum Testosterone (T) levels were calculated, separately by each drug and afterwards a comparative calculation was following. **Objectives:** The estimation was extracted by the results of the 2 previous studies, each of which had estimated a certain influence, after the respective drug administration in an induced Ischemia-Reperfusion (IR) rat experiment. **Materials and Methods:** The 2 temporal experimental endpoints at which the serum T levels were measured were the 60th reperfusion min (for the 3 groups A, C and E) as well the 120th reperfusion min (for the other 3 groups B, D and F). Especially, the groups A and B were the placebo ones, the groups C and D were the post Epo; whereas the groups E and F were the post L administration. **Results:** The first previous study of Epo presented a non-significant hypertestosteronemic effect by 0.276%±0.272% (*p*-value=0.3006). Similarly, the second previous study of U-74389G presented also a non-significant hypertestosteronemic effect by 0.111%±0.179% (*p*-value=0.5245). The results of these 2 studies co-calculated as belonging to the same experimental setting, provided the outcome of L being just by 0.4046004 [0.4035126 - 0.4056911] less hypertestoteronemic than Epo (*p*-value=0.0000). **Conclusion:** The intrinsic antioxidant capacity of U-74389G ascribes just 0.4046004 [0.4035126 - 0.4056911] less hypertestoteronemic influence than Epo (*p*-value=0.0000).

Keywords: Ischemia, Erythropoietin, U-74389G, Serum testosteronelevels, Reperfusion, Comparative hypertestosteronemia.

Correspondence:
Dr. Tsompos N. Constantinos
Department of Gynecology, General Hospital of Athens "G. Gennimatas" 154 Leof. Mesogeion, Athens 115 27, HELLAS (GREECE).
Email: constantinos1tsompos@gmail.com

Received: 17-06-2024;
Revised: 06-07-2024;
Accepted: 21-07-2024.

INTRODUCTION

The lazaroid molecule U-74389G (L) 21-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-pregna-1,4,9(11)-triene-3,20-dione maleate salt, may be not known for its hypertestosteronemic capacity (*p*-value=0.5245).[1] U-74389G as a relatively novel antioxidant agent, met exactly only in 265 published studies. The Ischemic-Reperfusive (I-R) type of settings was met in 19.62% of these studies. The tissue protective capacity of the L was appeared in these I-R studies. U-74389G is an antioxidant agent, which prevents all the lipid hyperoxidations, both iron-dependent and arachidonic acid-induced.

DOI: 10.5530/fra.2024.1.4

Erythropoietin (Epo) unknown yet for its hypertestosteronemic action (*p*-value=0.3006), is appropriate as a reference drug comparable with U-74389G.[2] Although Epo is met in a growing number of 34,467 published biomedical experiments, only 3.87% of them concern the classic I-R experiments. The objective of this study is to find out in which direction these two molecules affect serum Testosterone (T) levels and what the magnitude of this alteration is.

MATERIALS AND METHODS

Animal preparation

The research protocol, from which these results were obtained, was approved by the corresponding Ethics Committee expressed by the Veterinary licenses 3693/12-11- 2010 & 14/10-1-2012. The grant company as its locus experiment is referred in previous references.[1,2] The humanistic care of Albino

female Wistar rats, their 7 days pre-setting *ad libitum* diet, the perioperational anesthesiologic techniques, the oxygen supply, the electrocardiographic and acidometric monitoring and the post-operational euthanasia are also included in those references. The Albino female Wistar rats, aged 16-18 weeks, were randomly placed to six (6) groups of N=10 animals each. Ischemia was provoked by laparotomic clamping of the inferior aorta over renal arteries with forceps for 45 min, since preceded for all 6 groups. Thus, reperfusion of 60 min was followed in group A; of 120 min in group B; along with Epo Intravenous (IV) administration of 60 min in group C; along with Epo IV administration of 120 min in group D; along with L IV administration of 60 min in group E; and along with L IV administration of 120 min in group F. The dose was assessed for both drugs at 10 mg/Kg body mass as explained at the above references. Also, regression analysis outputs no relation between T values with animals' mass (*p*-value=0.2897).

Statistical analysis

Table 1 depicts the (%) hypertestosteronemic effect of Epo versus the reperfusion time, of L versus reperfusion time and of their ratios generated the (%) results per endpoint, as well their results of chi-square tests.

RESULTS

U-74389G caused less hypertestosteronemia by 0.8574561-fold [0.5383892 - 1.365712] after 1 hr (*p*-value=0.5185), just by 0.7325777-fold [0.7313943 - 0.733763] after 1.5 hr (*p*-value=0.0000), just by 0.6709677-fold [0.3827019 - 1.176604] after 2 hr (*p*-value=0.1646), more hypertestosteronemia by 1.313492-fold [1.311506 - 1.31548] at placebo (*p*-value=0.0000). The summary outcome was less hypertestosteronemia by 0.4046004-fold [0.4035126 - 0.4056911], than Epo when all variables (times, drugs and their interactions) were included (*p*-value=0.0000).

DISCUSSION

The first referred study is the unique one investigating the hypertestosteronemic effect of L.[1] Although the established properties of neuroprotection and membrane-stabilization one, L is settled on cell membranes, protecting the vascular endothelium from hyperoxidative damage, but hardly escapes into the blood-brain barrier. L appears to have a useful effect in ototoxicity and in Duchenne muscular dystrophy. L increases γgt enzyme, Superoxide Dismutase (SOD) enzyme and Glutathione (GSH) enzyme levels in oxygen-treated cells. It ameliorates septic states and is appropriate as an immunosuppressant agent in

Table 1: The (%) hypertestosteronemic influence of erythropoietin, of U-74389G and of their ratio in connection with reperfusion time.

Erythropoietin			
Hypertestosteronemia	±SD	Reperfusion time	*p*-value
0.470%	±4.70%	1 hr	0.4120
0.712%	±19.09%	1.5 hr	0.1080
0.953%	±13.62%	2 hr	0.0470
-0.651%	±11.50%	reperfusion	0.0792
0.276%	±2.72%	Interaction	0.3006

U-74389G			
Hypertestosteronemia	±SD	Reperfusion time	*p*-value
0.403%	±7.03%	1 hr	0.1261
0.521%	±9.37%	1.5 hr	0.0451
0.64%	±12.39%	2 hr	0.1380
-0.856%	±10.76%	reperfusion	0.0019
0.111%	±1.79%	Interaction	0.5245

U-74389G / erythropoietin ratio			
Odds ratio	[95% Conf. Interval]	*p*-values	Endpoint
.8574561	.5383892 1.365712	0.5185	1 hr
.7325777	.7313943 .733763	0.0000	1.5 hr
.6709677	.3827019 1.176604	0.1646	2 hr
1.313492	1.311506 1.31548	0.0000	reperfusion
.4046004	.4035126 .4056911	0.0000	Interaction

flap survival. L prevents learning impairments, delays the early synaptic gap transmission decay during hypoxia, benefiting the energetic state of neurons. L shows antiproliferative properties on brain tumor cells and is expected as a new promising anti-inflammatory agent for the management of reperfusion syndrome in I-R injuries.

Also, a short-term hypertestosteronemic effect of Epo administration was confirmed in non-iron deficient individuals.[2] Moslemi *et al.* found altered urine flow, tissue MDA and nitrite levels and kidney weight, but not kidney function after pretreatment with Zinc (Zn), Testosterone (T) supplementations or, combined after renal I-R injury in orchiectomized rats.[3] Ghimire *et al.* found a gender difference in young groups. Females noted a better Ventricular function (LVDP) and smaller infarcts than males, reflecting the high T levels in young males versus the low ones in females and old males.[4] Indeed, hearts from GDX males presented much better recovery of LVDP by 2.95-fold and smaller infarcts, during reperfusion than from intact males (both $p<0.05$). So, it seems that low T levels may be protective against I-R injury in cardioplegic arrest of older males. Fu *et al.* pronounced the effects of T supplementation such as heart function amelioration, increased p-Akt/Akt ratio and bcl-2 expression, whereas decreased the release of lactate dehydrogenase, in ovariectomized female I-R Sprague Dawley rats subjected to I-R injury.[5] Seara *et al.* correlated the anabolic steroids treatment excess with cardiovascular detrimental impacts, including hypertension, cardiac arrhythmias, hypertrophy and particularly acute myocardial infarction, subsequent to proved increased susceptibility to cardiac I-R injury.[6] Gholampour *et al.* found attenuated increase in serum creatinine, urea nitrogen, FSH, LH and decrease in histological damage and serum T concentration, 24 hr after berberine administration in renal I-R injury ($p<0.001$).[7] Seara *et al.* found increased infarct size, up-regulation of αMHC mRNA expression levels, myocardial stunning and heart weight, decreased βMHC mRNA expression and p-Akt levels ($p<0.05$), after T Supplementation Therapy (TST) in aged rats, but no in adult rat hearts.[8] Noroozzadeh *et al.* underestimated the history of PCOS in reproductive ages as a risk factor for reduction of heart contractile function or less tolerance to I-R injury in postmenopausal period ($p>0.05$).[9] Hu *et al.* restored normal hepatic Reperfusion Injury Salvage Kinase (RISK) versus Survivor Activating Factor Enhancement (SAFE) pathway responses in Kcne4-/- mice, canceled the Kcne4 deletion-dependent serum alanine aminotransferase elevation

Table 2: A U-74389G / erythropoietin efficacies ratios meta-analysis on 34 hematologic variables.[16]

Endpoint Variable	1 hr	*p*-value	1.5 hr	*p*-value	2 hr	*p*-value	Reper fusion time	*p*-value	interaction	*p*-value
WBC	0.957451	0.3782	1.396122	0.0000	1.918237	0.0000	1.71622	0.0000	1.601887	0.0000
RBC count	0.961059	0.0000	1.733395	0.0000	6.519657	0.0000	1.039524	0.0000	1.309673	0.0000
Hematocrit	38.424	0.0000	9.076658	0.0000	6.222898	0.0000	1.001356	0.2184	12.66419	0.0000
Hemoglobin	1.268689	0.0000	1.839035	0.0000	13.1658	0.0000	1.252422	0.0000	1.94889	0.0000
MCH	151.125	0.0000	4.246814	0.0000	2.709729	0.0000	1.177347	0.0000	4.362893	0.0000
MCV	150.8518	0.0000	4.236722	0.0000	2.704247	0.0000	1.180156	0.0000	4.352528	0.0000
MCHC	3.6046103	0.0000	1.8166222	0.0000	1.1733738	0.0000	3.044774	0.0000	1.2831629	0.0000
RbcDW	3.306773	0.0000	3.023389	0.0000	2.655885	0.0000	0.2259914	0.0000	2.370353	0.0000
Platelet count	2.42839	0.0000	6.00238	0.0000	6.1333429	0.0000	3.939027	0.0000	37.62979	0.0000
MPV	145.8532	0.0000	4.053619	0.0000	2.603947	0.0000	1.2334644	0.0000	4.164431	0.0000
Platelet DW	0.6940233	0.0000	1.319118	0.0000	2.206972	0.0000	2.2484006	0.0000	2.458888	0.0000
Plateletcrit	4.3251772	0.0000	1.4882359	0.0000	0.75145256	0.0886	5.620077	0.0000	1.0233828	0.0000
Glucose	156.4991	0.0000	4.53659	0.0000	2.81397	0.0000	0.9073196	0.0000	4.660603	0.0000
Urea	158.4209	0.0000	4.50889	0.0000	2.850291	0.0000	0.9017775	0.0000	4.632148	0.0000
Creatinine	168.9034	0.0000	4.872332	0.0000	3.039572	0.0000	1.0262016	0.0000	5.005523	0.0000
Uric acid	0.6212533	0.0000	1.106911	0.0000	1.3349	0.0027	0.44218009	0.0000	1.33234	0.0000
Total proteins	155.9562	0.0000	4.421079	0.0000	2.803573	0.0000	0.8842162	0.0000	4.541934	0.0000
Albumins	0.2457507	0.0073	0.5303472	0.0000	0.6243052	0.0465	1.237477	0.0000	0.5000416	0.0000
ALT	0.5955473	0.0000	0.86405406	0.0000	7.967324	0.0000	0.4734427	0.0000	1.6107645	0.0000
AST	1.149264	0.0391	0.9347365	0.0000	0.6695775	0.0000	0.7631082	0.0000	0.8224656	0.0000
γGT	1	1.0000	0.5367033	0.0000	1.0606061	0.8982	2.146813	0.0000	3.7264586	0.0000
ALP	134.0033	0.0000	3.602703	0.0000	2.349961	0.0000	0.7205412	0.0000	3.701187	0.0000
ACP	2.774031	0.0000	5.450674	0.0000	7.86942	0.0000	0.121724	0.0000	8.011334	0.0000

Endpoint Variable	1 hr	*p*-value	1.5 hr	*p*-value	2 hr	*p*-value	Reper fusion time	*p*-value	interaction	*p*-value
CPK	144.0769	0.0000	3.987264	0.0000	2.567192	0.0000	0.7974539	0.0000	4.09626	0.0000
CK-MB	141.313	0.0000	3.883186	0.0000	2.509108	0.0000	1.2876033	0.0000	3.989339	0.0000
LDH	142.9228	0.0000	3.944068	0.0000	2.543149	0.0000	1.2677226	0.0000	4.051881	0.0000
Sodium	1.695709	0.0000	0.8085706	0.0000	3.008772	0.0455	1.631842	0.0000	2.74914	0.0000
Potassium	1.640618	0.0000	0.968488	0.0000	3.346145	0.0000	2.414214	0.0000	11.4937	0.0000
Chloride	0.5544784	0.0007	0.8643683	0.0000	1.07745	0.5428	1.358293	0.0000	1.012762	0.0000
Calcium	0.00000334	0.0000	0.2490068	0.0000	0.1988753	0.0000	2.063208	0.0000	2.3623042	0.0000
Phosphorus	0.861859	0.1111	0.409606	0.0000	0.167592	0.0000	5.120084	0.0000	0.445513	0.0000
Magnesium	1.331108	0.0000	0.2605466	0.0000	0.5961915	0.0000	1.013227	0.0000	1.823808	0.0000
Amylase	156.4494	0.0000	4.440002	0.0000	2.813682	0.0000	0.8879931	0.0000	4.561391	0.0000
Testosterone	0.8574561	0.5185	0.7325777	0.0000	0.6709677	0.1646	1.313492	0.0000	0.4046004	0.0000
Mean	5.039084428	0.0604	1.8615942851	0.0000	2.0212783258	0.0526	1.1844183302	0.0006	2.1977197335	0.0000

and independently on genotype, augmented the hepatic post-IR GSK-3β phosphorylation response in castrated male mice.[10] Thus, KCNE4 uncovers gender-specific, hormonally influenced KCNE4-dependent or no RISK/SAFE pathway induction in cardiac IR injury. Noroozzadeh *et al.* found non statistically significant increased baseline hemodynamic parameters in hearts of adult males after prenatal androgen exposure; although being less tolerant to I-R, but non observed in female ones.[11] Gholami *et al.* detected significantly higher serum T levels but decreased apoptotic cells and cells of TUNEL (+) staining in spermatocytes and spermatid of BH and HIR groups after pretreatment with Persian honey.[12] Thus, it protects testis against side effects of chemotherapy and subsequent testicular I-R injury, increases T, FSH and LH and decrease the cellular apoptosis and damage and prevents sterility ($p<0.001$). Maldonado *et al.* showed that T administration resulted in non-significant decreased MMP-3 and 13 expressions, inflammatory infiltrates and myocardial damaged area.[13] Interestingly, 5α reductase (finasteride) administration resulted in a greater non significantly decrease in inflammatory infiltrates, scar tissue, but significant decrease of MMP-3 and 13 expressions. However, inhibition of Aromatase administrations (4-hydroxyandrostenedione), non-significantly increased all relevant parameters in gonadectomized rats. Sekerci *et al.* corrected the alterations in MDA, MPO activities, caspase-3 and SOD levels, but increased serum T levels after Platelet-Rich Plasma (PRP) treatment.[14] However, the mean caspase-3 protein, TGF-β, MPO activity, and MDA levels were not totally restored than control ones. PRP exerts beneficial effect on testicular tissues against I-R by inhibiting oxidative stress and neutrophil infiltration and increasing the antioxidant defense 1 month after detorsion in regenerative therapy. Abdel-Gaber *et al.* ameliorated the testicular weight, T and cholesterol serum levels, histopathological changes and IL-1 b immunostaining, after Diacerein (DIA)-an Interleukin-1b (IL-1b) blocker-administration in a testis I-R induced injury of rats.[15] The oxidative stress parameters attenuation was mediated by the anti-inflammatory and antioxidant activities of DIA in a torsion model of spermatic cord.

According to the above, Table 2 depicts that L causes just less hypertestosteronemia by 0.4046004-fold [0.4035126-0.4056911] than Epo after inclusion of all variables (p-value=0.0000); an attenuating trend versus time, in Epo non-deficient rats. A meta-analysis of these ratios from the same setting, for 33 other seric variables, provides comparable results (Table 2).[16]

CONCLUSION

The antioxidant L agent causes less hypertestosteronemia by 0.4046004-fold [0.4035126 - 0.4056911] than Epo after inclusion of all variables (p-value=0.0000); an attenuating trend versus short-term time frame of the rats setting. Further biochemical investigation is required about how L mediates these actions.

ACKNOWLEDGEMENT

This study was funded by a fellowship from the Experimental & Research Center of ELPEN Pharmaceuticals (E.R.C.E.), Athens, Greece.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL APPROVAL

"All applicable international, national, and/or institutional guidelines for the care and use of animals were followed."

Approving opinion of the Ethics Committee by the Veterinary licenses 3693/12-11-2010 & 14/10-1-2012.

ABBREVIATIONS

AAS: Anabolic androgenic steroids; **AT1:** Type 1 angiotensin II; **bcl:** B-cell lymphoma; **BH:** Bombyx hemolymph; **DHT:** Dihydrotestosterone; **DIA:** Diacerein; **DPP:** Dipeptidyl peptidase; **Epo:** Erythropoietin; **FSH:** Follicle-stimulating hormone; **GAP:** Growth" or "plasticity" protein; **GDX:** Ubiquitin-like protein 4A; **GPx:** Glutathione peroxidase; **GSH:** Glutathione; **GSK-3β:** Signaling effector; **HA-AKI:** Hospital-acquired acute kidney injury; **HIF:** Hypoxia-inducible factors; **HIR:** Hemolymph IR; **IL:** Interleukin; **IR:** Ischemia reperfusion; **KATP:** ATP-sensitive potassium channel; **KCNE:** Voltage-dependent potassium channel; **L:** Lazaroid; **LVDP:** Left ventricular end-diastolic pressure; **LH:** *Luteinizing hormone*; **MC:** Matricaria chamomile; **MCAO:** Middle cerebral artery occlusion; **MDA:** Malondialdehyde MHC major histocompatibility complex; **MMP:** Matrix metalloproteinases; **MPO:** Myeloperoxidase; **i/e/nNOS:** Inducible/endothelial/neuronal nitric oxide synthase; **NOx:** Nitric oxide1or2; **p-Akt:** phospho protein kinase; **PCOS:** Polycystic ovary syndrome; **PP:** Proxeed Plus; **PPARα:** Peroxisome proliferator activated receptor alpha; **PRP:** Platelet-rich plasma; **RISK:** Reperfusion injury salvage kinase; **SAFE:** Survivor activating factor enhancement; **SCD:** Sudden cardiac death; **SOD:** Superoxide dismutase; **T:** Testosterone; **TAC:** Total antioxidant capacity; **TGF:** Transforming growth factor; **(T)NF:** (Tumor) Necrosis factor; **TST:** Testosterone supplementation therapy; **TUNEL:** Terminal deoxynucleotidyl transferase (TdT) dUTP Nick-End Labeling; **Zn:** Zinc.

REFERENCES

1. Tsompos C, Panoulis C, Toutouzas K, Triantafyllou A, ZografosG, Papalois A. The effect of the antioxidant drug "U-74389G" on testosterone levels during ischemia reperfusion injury in rats. RJPT. 2016;2(1):1-3. DOI: asdpub.com/index.php/rjpt
2. Tsompos C, Panoulis C, Toutouzas K, Triantafyllou A, Zografos G, Papalois A. The Effect of Erythropoietin on Testosterone Levels During Ischemia Reperfusion Injury in Rats. ARS MedicaTomitana. 2016;4(22):264-9.
3. Moslemi F, Piudeh F, Hajian MR, Khodarahmi A, Nematbakhsh M. Testosterone and Zinc Supplementations on Renal Ischemia-Reperfusion Injury in Orchiectomized Rats. Int J Prev Med. 2019;19;10:125. DOI:10.4103/ijpvm.IJPVM_101_18
4. Ghimire A, Bisset ES, Howlett SE. Ischemia and reperfusion injury following cardioplegic arrest is attenuated by age and testosterone deficiency in male but not female mice. Biol Sex Differ. 2019; 23;10(1): 42. DOI:10.1186/s13293-019-0256-4
5. Fu L, Liu Y, Wang J, Sun Y, Zhang L, Wu T, *et al.* Cardio protection by Low-dose of Estrogen and Testosterone at the Physiological Ratio on Ovariectomized Rats During Ischemia/Reperfusion Injury. J Cardiovasc Pharmacol. 2017;70(2):87-93. DOI:10.1097/FJC.0000000000000497
6. Seara FAC, Olivares EL, Nascimento JHM. Anabolic steroid excess and myocardial infarction: From ischemia to reperfusion injury. Steroids 2020;161:108660. DOI:10.1016/j.steroids.2020.108660
7. Gholampour F, Mansourkhani MS, Owji SM. Amelioration of testicular damages in renal ischemia/reperfusion by berberine: An experimental study. Int J Reprod Biomed. 2019; 26;17(11): 799-806. DOI:10.18502/ijrm.v17i10.5488
8. Seara FAC, Barbosa RAQ, Santos MVN, Domingos AE, Monnerat G, Carvalho AB, *et al.* Paradoxical effect of testosterone supplementation therapy on cardiac ischemia/reperfusion injury in aged rats. J Steroid Biochem Mol Biol. 2019;191:105335. DOI:10.1016/j.jsbmb.2019.03.012
9. Noroozzadeh M, Raoufy MR, Yarandi RB, Shahrivar FF, Moghimi N, Tehrani FR. Cardiac function and tolerance to ischemia/reperfusion injury in a rat model of polycystic ovary syndrome during the postmenopausal period. Life Sci. 2020;262:118394. DOI:10.1016/j.lfs.2020.118394
10. HuZ, Jepps TA, Zhou L, Liu J, Li M, Abbott GW. Kcne4 deletion sex dependently inhibits the RISK pathway response and exacerbates hepatic ischemia-reperfusion injury in mice. Am J PhysiolRegulIntegr Comp Physiol. 2019; 316(5):R552-62. DOI:10.1152/ajpregu.00251.2018
11. Noroozzadeh M, Raoufy MR, Yarandi RB, Shahrivar FF, Tehrani FR. The effects of prenatal androgen exposure on cardiac function and tolerance to ischemia/reperfusion injury in male and female rats during adulthood. Life Sci. 2019;15;229:251-60. DOI:10.1016/j.lfs.2019.05.044
12. Gholami M, Abbaszadeh A, Baharvand P, Hasanvand A, Hasanvand A, Gharravi AM. Protective effects of persian honey, *Apis mellifera* MedaSkorikov on side effects of chemotherapy and ischemia/reperfusion induced testicular injury. J Complement Integr Med. 2018; 23;15(4). DOI:10.1515/jcim-2016-0035
13. Maldonado O, Ramos A, Guapillo M, Rivera J, Palma I, Gayosso IR, *et al.* Effects of chronic inhibition of Testosterone metabolism on cardiac remodeling after ischemia/reperfusion-induced myocardial damage in gonadectomized rats. Biol Open. 2019; 13;8(5). DOI:10.1242/bio.041905
14. Sekerci CA, Tanidir Y, Sener TE, Sener G, Cevik O, Yarat A, *et al.* Effects of platelet-rich plasma against experimental ischemia/reperfusion injury in rat testis. J Pediatr Urol. 2017;13(3):317. DOI:10.1016/j.jpurol.2016.12.016
15. Abdel-Gaber SA, Mohammed RK, Refaie MMM. Mechanism mediating the protective effect of diacerein in ischemia-reperfusion-induced testicular injury in rats. Life Sciences. 2018;209(15):57-62 DOI:.org/10.1016/j.lfs.2018.07.060
16. Tsompos C, Panoulis C, Triantafyllou A, Zografos CG, Gerakis E, Gerakis S, *et al.* Comparison of the Hypamylasemic Effects of Erythropoietin and U-74389G. J Bacteriol Mycol. 2020;7(4):1136.

Cite this article: Tsompos C, Panoulis C, Triantafyllou A, Zografos C, Zografos GC, Papalois A. Comparative Hypertestosteronemic Effects of the Erythropoietin and the U-74389G. Free Radicals and Antioxidants. 2024;14(1):27-31.