ARC Journal of Nephrology
Volume 4, Issue 1, 2019, PP 7-12
www.arcjournals.org

Comparison of the Hyperdehydrogenasemic Effects of Erythropoietin and U-74389G on Lactate Dehydrogenase Levels

C. Tsompos[1*], C. Panoulis[2], K. Toutouzas[3], A. Triantafyllou[4], CG. Zografos[5], K. Tsarea[6], M. Karamperi[6], A. Papalois[7]

[1]*Department of Gynecology, General Hospital of Thessaloniki "St. Dimitrios" Thessaloniki, Hellas*

[2]*Department of Obstetrics&Gynecology, Aretaieion Hospital, Athens University, Athens, Attiki, Hellas*

[3]*Department of Surgery, Ippokrateion General Hospital, Athens University, Athens, Attiki, Hellas*

[4]*Department of Biologic Chemistry, Athens University, Athens, Attiki, Hellas*

[5]*Department of Surgery, Ippokrateion General Hospital, AthensUniversity, Athens, Attiki, Hellas*

[6]*ExperimentalResearch Centre ELPEN Pharmaceuticals, S.A. Inc., Co., Pikermi, Attiki, Hellas*

[7]*Experimental, Educational and Research Centre ELPEN European University Cyprus, School of Medicine*

Corresponding Author:** ***C. Tsompos*, Department of Gynecology, General Hospital of Thessaloniki "St. Dimitrios" Thessaloniki, Hellas, Greece.* ***Email:*** *Tsomposconstantinos@gmail.com*

Abstract

Aim: *This study calculated the effects on lactate dehydrogenase (LDH) levels, after treatment with either of 2 drugs: the erythropoietin (Epo) and the antioxidant lazaroid (L) drug U-74389G. The calculation was based on the results of 2 preliminary studies, each one of which estimated the certain influence, after the respective drug usage in an induced ischemia reperfusion (IR) animal experiment.*

Materials and Methods: *The 2 main experimental endpoints at which the serum LDH levels (LDHl) were evaluated was the 60th reperfusion min (for the groups A, C and E) and the 120th reperfusion min (for the groups B, D and F). Specially, the groups A and B were processed without drugs, groups C and D after Epo administration; whereas groups E and F after the L administration.*

Results: *The first preliminary study of Epo presented a non significant hyperdehydrogenasemic effect by 2.39%±3.19% (p-value=0.4430). The second preliminary study of U-74389G presented a significant hyperkinasemic effect by 9.72%±2.62% (p-value=0.0005). These 2 studies were co-evaluated since they came from the same experimental setting. The outcome of the co-evaluation was that L is 4.051881-fold [4.04778 - 4.055986] more hyperdehydrogenasemic than Epo (p-value=0.0000).*

Conclusions: *The anti-oxidant capacities of U-74389G ascribe 4.051881-fold more hyperdehydrogenasemic effects than Epo (p-value=0.0000).*

Keywords: *ischemia; erythropoietin; U-74389G; Lactate Dehydrogenase levels; reperfusion*

1. INTRODUCTION

The lazaroid U-74389G (L) may be not famous for its hyperdehydrogenasemic [1] capacity (p-value=0.0005). U-74389G as a novel antioxidant factor, implicates exactly only 260 published studies. The ischemia reperfusion (IR) type of experiments was noted in 18.84% of these studies. A tissue protective feature of U-74389G was obvious in these IR studies. The U-74389G chemically known as 21-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-pregna-1,4,9(11)-triene-3,20-dione maleate salt is an antioxidant complex, which prevents the lipid peroxidation either iron-dependent, or arachidonic acid-induced one. Animal kidney, liver, brain microvascular endothelial cells monolayers and heart models were protected by U-74389G after IR injury. U-74389G also attenuates the leukocytes; down-regulates the proinflammatory gene; treats the endotoxin shock; produces cytokine; enhances the mononuclear immunity; protects the endothelium and presents antishock property.

Erythropoietin (Epo) even if is not famous for its hyperdehydrogenasemic action (p-value=0.4430), it can be used as a reference drug for comparison with U-74389G. Although Epo is met in over 30,786 published biomedical studies, only a 3.60% of them negotiate the known type of IR experiments. Nevertheless,

Epo as a cytokine, it is worth of being studied about its effects on lactate dehydrogenase (LDH) levels too. This experimental work tried to compare the effects of the above drugs on a rat induced IR protocol. They were tested by calculating the serum LDH levels (LDHl) alterations.

2. MATERIALS AND METHODS

2.1. Animal Preparation

The Vet licenses under 3693/12-11- 2010 & 14/10-1-2012 numbers, the granting company and the experiment location are mentioned in preliminary references [1, 2]. The human animal care of Albino female Wistar rats, the 7 days pre-experimental *ad libitum* diet, the non-stop intra-experimental anesthesiologic techniques, the acidometry, the electrocardiogram, the oxygen supply and post-experimental euthanasia are also described in preliminary references. Rats were 16 – 18 weeks old. They were randomly assigned to six (6) groups consisted in N=10. The stage of 45 min hypoxia was common for all 6 groups. Afterwards, reperfusion of 60 min was followed in group A; reperfusion of 120 min in group B; immediate Epo intravenous (IV) administration and reperfusion of 60 min in group C; immediate Epo IV administration and reperfusion of 120 min in group D; immediate U-74389G IV administration and reperfusion of 60 min in group E; and immediate U-74389G IV administration and reperfusion of 120 min in group F. The dose height assessment for both drugs are described at preliminary studies as 10 mg/Kg body mass.

Ischemia was caused by laparotomic clamping the inferior aorta over renal arteries with forceps for 45 min. The clamp removal was restoring the inferior aorta patency and reperfusion. After exclusion of the blood flow, the protocol of IR was applied, as described above for each experimental group. The drugs were administered at the time of reperfusion; through inferior vena cava catheter. The LDHl were determined at 60th min of reperfusion (for A, C and E groups) and at 120th min of reperfusion (for B, D and F groups). Along, due to a strong relation was rised between LDHl values with animals' mass (p-value=0.0044), the predicted LDHl values were used.

2.2. Statistical Analysis

Table 1 presents the (%) hyperdehydrogenasemic influence of Epo regarding reoxygenation time. Also, Table 2 presents the (%) hyperdehydrogenasemic influence of U-74389G regarding reperfusion time. Chi-square tests were applied using the ratios which produced the (%) results per endpoint. The outcomes of chi-square tests are depicted at Table 3. The statistical analysis was performed by Stata 6.0 software [Stata 6.0, StataCorp LP, Texas, USA].

Table1. *The (%) hyperdehydrogenasemic influence of erythropoietin in connection with reperfusion time*

Hyperdehydrogenasemia	±SD	Reperfusion time	p-value
0.08%	±21.69%	1h	0.9904
4.42%	±19.28%	1.5h	0.3549
8.77%	±15.18%	2h	0.1509
-4.42%	±20.74%	reperfusion time	0.3721
2.39%	±3.19%	interaction	0.4430

Table2. *The (%) hyperdehydrogenasemic influence of U-74389G in connection with reperfusion time*

Hyperdehydrogenasemia	±SD	Reperfusion time	p-value
12.63%	±19.21%	1h	0.0663
17.46%	±16.74%	1.5h	0.0001
22.30%	±12.79%	2h	0.0003
-3.49%	±15.87%	reperfusion time	0.4103
9.72%	±2.62%	interaction	0.0005

Table3. *The U-74389G / erythropoietin efficacies ratios on serum lactate dehydrogenase levels after chi-square tests application*

Odds ratio	[95% Conf. Interval]		p-values	Endpoint
142.9228	142.7153	143.1307	0.0000	1h
3.944068	3.941078	3.947061	0.0000	1.5h
2.543149	2.538475	2.547832	0.0000	2h
1.2677226	1.2664672	1.2689792	0.0000	reperfusion
4.051881	4.04778	4.055986	0.0000	interaction

3. RESULTS

The successive application of chi-square tests revealed that U-74389G enhanced the LDHl by 142.9228-fold [142.7153 - 143.1307] more than Epo at 1h (p-value=0.0000), by 3.944068-fold [3.941078 - 3.947061 more than Epo at 1.5h (p-value=0.0000), by 2.543149-fold [2.538475 - 2.547832] more than Epo at 2h (p-value= 0.0000), more by 1.2677226-fold [1.2664672 - 1.2689792] (p-value=0.0000) without drugs and by 4.051881-fold [4.04778 - 4.055986] more than Epo whether all variables have been considered (p-value=0.0000).

4. DISCUSSION

The unique available study investigating the hyperdehydrogenasemic effect of U-74389G on LDHl was the preliminary one[1]. Although the most famous activities of neuroprotection and membrane-stabilization properties, it accumulates in the cell membrane, protecting vascular endothelium from peroxidative damage but hardly penetrates the blood-brain barrier. It elicits a beneficial effect in ototoxicity and Duchenne muscular dystrophy. It increases γgt, superoxide dismutase (SOD) and glutathione (GSH) levels in oxygen-exposed cells. It treats septic states and acts as immunosuppressant in flap survival. It prevents the learning impairments, it delays the early synaptic transmission decay during hypoxia improving energetic state of neurons. It shows antiproliferative properties on brain cancer cells and is considered as a new promising anti inflammatory drug for the treatment of reperfusion syndrome in IR injuries.

The same authors confirmed [2] the short-term hyperdehydrogenasemic effect of Epo preparations in non iron deficient individuals. Kumarasinghe G et al assessed [3] a percentage functional recovery of 18-month BD hearts stored in Celsior supplemented with glyceryl trinitrate + erythropoietin + zoniporide, equivalent to that of 3-month hearts and found it significantly improved compared with 18-month hearts stored in Celsior alone ($p < 0.01$ to $p < 0.001$), with reduced lactate dehydrogenase release ($p < 0.01$) to protect older hearts against IRI and improve graft function. Zhang Q et al found[4] that the Huang-Lian-Jie-Du-Tang (HLJDT) preconditioning significantly ameliorated the neurological deficient score of rats subjected to middle cerebral artery occlusion on neurons under oxygen and glucose deprivation. Joshi D et al treated [5] by a nonhematopoietic helix-B peptide of EPO (ARA 290) the ischemic myotubes in vitro with a significantly decreased number of lactate dehydrogenase release (ischemia vs ischemia plus ARA 290 by 1.52-fold, $P < .01$) in both ischemic and control muscle fiber in skeletal muscle obtained from humans after critical limb ischemia. Kumaş M et al resulted [6] in the decline of LDH enzyme level ($p<0.001$) as a necrosis marker after berberine (BRB) administration in a streptozotocin (STZ)-induced diabetic rat model. Cheng B et al verified [7] by increased expression of Bcl-2 the reduction of serum LDH activity levels after ebselen administration in myocardial ischemia-reperfusion (I/R) injury in a rat model. Zhang L et al found that alprostadil treatment significantly reduced [8] serum LDH activity ($P<0.05$) in myocardial I/R of rats. Pisarenko O et al enhanced [9] recovery of cardiac function with reduced glutathione ($\{(GS^-)_2Fe^+(NO^+)_2\}^+$, (DNIC-GS) and reduced LDH release in the coronary effluent at reperfusion of isolated working hearts in male Wistar rats. Peterson DR et al exhibited a significant reduction in LDH release into the incubation medium by 2.4-fold [$P =0.02$] compared[10] with controls in cultured embryonic cardiomyocytes (H9c2) cells coincubated with gamma-L-glutamyl-L-cysteine (γGlu-Cys) during ischemia-reperfusion. Meng X et al showed[11] that 12.5 μg/mL extract of Radix Scrophulariae (RSAE) inhibited LDH leakage both in vitro and in vivo; inhibiting I/R-induced neurological deficits and reduced loss of neurons in a middle cerebral artery occlusion/reperfusion (MCAO/R) model mice. Huang X et al found[12] that ophiopogonin D and shenmai injection exert protective effects on MI/R injury, including regulation of cardiac function, reduction of lactate dehydrogenase production and attenuation of myocardial infarct size. Chen J et al invented [13] that the levels of LDH in the rosiglitazone group were significantly decreased ($P<0.05$) than in hepatic ischemia reperfusion injury (HIRI) group. Leng Y et al found that diabetic hearts with excessive (highly selective histone deacetylase 6) HDAC6 activity and decreased acetylated- protein peroxiredoxin 1 (Prdx1) levels were more vulnerable to MI/R injury and investigated[14] whether tubastatin A (TubA), a HDAC6 inhibitor, could confer a protective effect in a rat model of in vitro MI/R. Zaki AM et al manifested[15] by depressed plasma lactate dehydrogenase (LDH) activities a marked improvement of hepatic function and

structural integrity compared with the hepatic I/R group after pretreatment with plumbagin. Parsa H et al noticed[16] that SD attenuated LDH in non-infarcted area and administration of bicuculline increased LDH; whereas bicuculline administration prior to acute sleep induction decreased SD effects on LDH in male Wistar rats compared with CONT. Sedighi M et al caused [17] significant decrease in serum cardiac troponin I, lactate dehydrogenase, and malondialdehyde levels, after cinnamomum zeylanicum (cinnamon) extract, 5 days after reperfusion in adult male Sprague-Dawley rats in an in vivo model of regional heart ischemia. He Z et al demonstrated[18] that acute kidney injury (AKI) model caused a remarkable increase in LDH, MDA, caspase 3 and cytochrome c (Cyt C) level, compared with the control group after the therapeutic effect of BAPTA-AM (1,2-Bis(2-aminophenoxy) ethane-N,N,N,N-tetraacetic acid tetrakis(acetoxymethyl ester)) nanoparticle (BA-N) administration. Jin HX et al exhibited inhibited myocardial infarction size and LDH serum levels in rats orally administered[19] both with the MEK inhibitor PD0325901 and oleuropein compared with rats treated with oleuropein only which presented less inhibitions in myocardial I/R of rats. Shi A et al indicated [20] that pretreatment of cells with phenolic components of Gastrodia elata Blume (25 μg/ml) for 24 h significantly reduced H_2O_2-induced cell death through LDH assay in astrocytes of a rat model of middle cerebral artery occlusion. Zhang FW et al found [21] that the ω-3 polyunsaturated fatty acids (PUFAs) postconditioning I/R-ω group had significantly reduced levels of lactate dehydrogenase against ischemia-reperfusion (I/R) injury. Abou-Hany HO et al demonstrated [22] significantly declined serum lactate dehydrogenase (LDH) contents in unilateral renal ischemia reperfusion injury (URIRI) induced in rats after crocin [the main bioactive constituent of Crocus sativus extract] administration. Alva N et al measured[23] the level of tissue-damage indicators (alanine amino transferase, ALT; lactate dehydrogenase, LDH; and proteins) in aliquots of perfusate sampled at different time intervals after a brief cycle of hypothermic preconditioning in isolated IR rat liver.

According to above, table 3 shows that U-74389G has 4.051881-fold [4.04778 - 4.055986] more hyperdehydrogenasemic effect than Epo (p-value=0.0000) whether all variables have been considered (p-value=0.0000); a trend accentuated along time, in Epo non-deficient rats. A meta-analysis of these ratios from the same experiment, for 21 other seric variables, provides comparable results (table 4) [24].

Table4. *A U-74389G / erythropoietin efficacies ratios meta-analysis on 21 hematologic variableς (17 variables with balancing efficacies and 4 variables with opposite efficacies)*[24].

Endpoint / Variable	1h	p-value	1.5h	p-value	2h	p-value	Reperfusion 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
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
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
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
ALP	134.0033	0.0000	3.602703	0.0000	2.349961	0.0000	0.7205412	0.0000	3.701187	0.0000
AST	1.149264	0.0391	0.9347365	0.0000	0.6695775	0.0000	0.7631082	0.0000	0.8224656	0.0000
Mean	13.678620	0.0249	2.854616	0.0000	2.827506	0.0026	1.0829736	0.0128	3.3053484	0.0000

Endpoint / Variable	1h	p-value	1.5h	p-value	2h	p-value	Reperfusion time	p-value	interaction	p-value
Mean corpuscular hemoglobin concentrations	-0.2774225	0.0000	-0.5504722	0.0000	-0.8522433	0.0000	+3.044774	0.0000	-0.7793243	0.0000
Platelet crit	-0.2312044	0.0000	-0.6719365	0.0000	-1.330756	0.0886	+5.620077	0.0000	-0.9771515	0.0000
ALT	+0.5955473	0.0000	-1.157335	0.0000	+7.967324	0.0000	+0.4734427	0.0000	-0.6208232	0.0000
γGT	1	1.0000	+0.5367033	0.0000	-0.9428571	0.8982	+2.146813	0.0000	-0.2683513	0.0000
Mean	-0.4757810	0.0250	-0.9450332	0.0000	-0.6052695	0.2467	+2.0421598	0.0000	-0.5968125	0.0000

5. Conclusion

The anti-oxidant agent U-74389G was proved having 4.051881-fold [4.04778 - 4.055986] more hyperdehydrogenasemic effect than Epo whether all variables have been considered (p-value=0.0000); a trend accentuated along the short term time frame of the experiment in rats. A biochemical investigation remains about how U-74389G mediates in these actions.

References

[1] Tsompos C, Panoulis C, Toutouzas K, Triantafyllou A, Zografos G, et al. (2016) The Effect of the Antioxidant Drug "U-74389G" on Lactate Dehydrogenase Levels during Ischemia Reperfusion Injury in Rats. J Anal Pharm Res 3(1): 00043.

[2] C. Tsompos, C. Panoulis, K. Toutouzas, G. Zografos, A. Papalois. The effect of erythropoietin on lactate dehydrogenase levels during ischemia reperfusion injury in rats. Gazi M J. 2014; 25: 20-23.

[3] Kumarasinghe G, Gao L, Hicks M, Villanueva J, Doyle A, Rao P, Ru Qiu M, Jabbour A, Iyer A, Chew HC, Hayward CS, Macdonald P. Improved heart function from older donors using pharmacologic conditioning strategies. J Heart Lung Transplant. 2016 May; 35(5):636-46.

[4] Zhang Q, Bian H, Li Y, Guo L, Tang Y, Zhu H. Preconditioning with the traditional Chinese medicine Huang-Lian-Jie-Du-Tang initiates HIF-1α-dependent neuroprotection against cerebral ischemia in rats. J Ethnopharmacol. 2014 Jun 11; 154(2):443-52.

[5] Joshi D, Abraham D, Shiwen X, Baker D, Tsui J. Potential role of erythropoietin receptors and ligands in attenuating apoptosis and inflammation in critical limb ischemia. J Vasc Surg. 2014 Jul; 60(1):191-201, 201.e1-2.

[6] Kumaş M, Eşrefoğlu M, Karataş E, Duymaç N, Kanbay S, Ergün IS, Üyüklü M, Koçyiğit A. Investigation of dose-dependent effects of berberine against renal ischemia/reperfusion injury in experimental diabetic rats. Nefrologia. 2019 Jan 31. pii: S0211-6995(19)30004-9.

[7] Cheng B, Zhong JP, Wu FX, Li GL, Ruan QX, Luo G, Jiang H. Ebselen protects rat hearts against myocardial ischemia-reperfusion injury. Exp Ther Med. 2019 Feb; 17(2):1412-1419.

[8] Zhang L, Zhang Y, Yu X, Xu H, Sui D, Zhao X. Alprostadil attenuates myocardial ischemia /reperfusion injury by promoting antioxidant activity and eNOS activation in rats. Acta Cir Bras. 2018 Dec; 33(12):1067-1077.

[9] Pisarenko O, Studneva I, Timoshin A, Veselova O. Protective efficacy of dinitrosyl iron complexes with reduced glutathione in cardioplegia and reperfusion. Pflugers Arch. 2019 Jan 6.

[10] Peterson DR, Huang H, Peresada D, Sukowski EJ, White C, Stefanov G, Schweig L, Vazzalwar R. A Glutathione Precursor Reduces Oxidative Injury to Cultured Embryonic Cardiomyocytes. Am J Ther. 2018 Sep 18.

[11] Meng X, Xie W, Xu Q, Liang T, Xu X, Sun G, Sun X. Neuroprotective Effects of Radix Scrophulariae on Cerebral Ischemia and Reperfusion Injury via MAPK Pathways. Molecules. 2018 Sep 19; 23(9). pii: E2401.

[12] Huang X, Wang Y, Wang Y, Yang L, Wang J, Gao Y. Ophiopogonin D Reduces Myocardial Ischemia-Reperfusion Injury via Upregulating CYP2J3/EETs in Rats. Cell Physiol Biochem. 2018; 49(4):1646-1658.

[13] Chen J, Liu H, Zhang X. Protective effects of rosiglitazone on hepatic ischemia reperfusion injury in rats. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2018 Jul 28; 43(7):732-737.

[14] Leng Y, Wu Y, Lei S, Zhou B, Qiu Z, Wang K, Xia Z. Inhibition of HDAC6 Activity Alleviates Myocardial Ischemia/Reperfusion Injury in Diabetic Rats: Potential Role of Peroxiredoxin 1 Acetylation and Redox Regulation. Oxid Med Cell Longev. 2018 Jun 25; 2018:9494052.

[15] Zaki AM, El-Tanbouly DM, Abdelsalam RM, Zaki HF. Plumbagin ameliorates hepatic ischemia-reperfusion injury in rats: Role of high mobility group box 1 in inflammation,

oxidative stress and apoptosis. Biomed Pharmacother. 2018 Oct; 106:785-793.

[16] Parsa H, Faghihi M, Kardar GA, Imani A. Acute sleep deprivation induces cardioprotection against ischemia/ reperfusion injury through reducing inflammatory responses: the role of central GABA-A receptors. Gen Physiol Biophys. 2018 May; 37 (3):345-352.

[17] Sedighi M, Nazari A, Faghihi M, Rafieian-Kopaei M, Karimi A, Moghimian M, Mozaffarpur SA, Rashidipour M, Namdari M, Cheraghi M, Rasoulian B. Protective effects of cinnamon bark extract against ischemia-reperfusion injury and arrhythmias in rat. Phytother Res. 2018 Oct; 32(10):1983-1991.

[18] He Z, Tang H, You X, Huang K, Dhinakar A, Kang Y, Yu Q, Wu J. BAPTA-AM Nanoparticle for the Curing of Acute Kidney Injury Induced by Ischemia/Reperfusion. J Biomed Nanotechnol. 2018 May 1; 14(5):868-883.

[19] Jin HX, Zhang YH, Guo RN, Zhao SN. Inhibition of MEK/ERK/STAT3 signaling in oleuropein treatment inhibits myocardial ischemia/reperfusion. Int J Mol Med. 2018 Aug; 42(2):1034-1043.

[20] Shi A, Xiang J, He F, Zhu Y, Zhu G, Lin Y, Zhou N. The Phenolic Components of Gastrodia elata improve Prognosis in Rats after Cerebral Ischemia/Reperfusion by Enhancing the Endogenous Antioxidant Mechanisms. Oxid Med Cell Longev. 2018 Mar 22; 2018:764 2158.

[21] Zhang FW, Tong J, Yan YS, Chen QQ, Zhao XP. ω-3 Polyunsaturated Fatty Acid Postconditioning Protects the Isolated Perfused Rat Heart from Ischemia-Reperfusion Injury. Cardiorenal Med. 2018; 8(3):173-182.

[22] Abou-Hany HO, Atef H, Said E, Elkashef HA, Salem HA. Crocin reverses unilateral renal ischemia reperfusion injury-induced augmentation of oxidative stress and toll like receptor-4 activity. Environ Toxicol Pharmacol. 2018 Apr; 59:182-189.

[23] Alva N, Bardallo RG, Basanta D, Palomeque J, Carbonell T. Preconditioning-Like Properties of Short-Term Hypothermia in Isolated Perfused Rat Liver (IPRL) System. Int J Mol Sci. 2018 Mar 29; 19(4). pii: E1023.

[24] Tsompos C, Panoulis C, Toutouzas K, Triantafyllou A, Zografos GC, Tsarea K, Karamperi M, Papalois A. Comparison of the Hypertransferasemic Effects of Erythropoietin and U-74389G on Aspartate Aminotransferase Levels. Clin Res Hematol 2018; 1(2):1-7.

Citation: *C. Tsompos, C. Panoulis, K. Toutouzas, A. Triantafyllou, CG. Zografos, K. Tsarea, M. Karamperi, A. Papalois. Comparison of the Hyperdehydrogenasemic Effects of Erythropoietin and U-74389G on Lactate Dehydrogenase Levels. ARC Journal of Nephrology. 2019; 4(1):7-12.*