

Hematological Findings Associated with the Use of Licorice and Silymarin in Cisplatin Treated Rats

Randa, m. Abdel hamed^{1*}, Abdulla, O. A. M.², Omnia E. Kilany²

¹*Veterinarian in the university hospital of Suez Canal University.*

²*Department of clinical Pathology, Faculty of Veterinary Medicine, Suez Canal University*

Abstract

The purpose of this study was to assess the effect of licorice and silymarin supplementations on some hematological parameters in cisplatin treated albino rats.

A total of 72 normal male albino rats' weight 150 -200 gm. The rats were allowed for acclimation for one week at the animal shelter. The rats were divided randomly into six groups, each with 12 rats. Group (1): normal control group and fed with commercial balanced diet. Group (2): licorice extract orally treated group for 6 weeks at a rate of 2 gm/kg body weight. Group (3): silymarin orally treated group at a rate of 100mg/kg every day for six weeks. Group (4): served as hepatotoxic group treated by injection of cisplatin (CP) intraperitoneally in a dose of 1.5 mg/kg body weight every two weeks for three weeks starting from the 4th week of the experiment. Group (5): received licorice extract orally treated group at a rate of 2 gm/kg body weight for 6 weeks. and injected cisplatin intraperitoneally in a dose of 1.5 g/kg body weight repeated twice a week for 6 weeks starting from the 4th week of the experiment. Group (6): received silymarin orally treated group at a rate of 100mg/kg daily for 6 weeks. and injected cisplatin intraperitoneally in a dose of 1.5 mg/kg body weight every two weeks for six weeks starting from the 4th week of the experiment.

The purpose of this study was to investigate the effects of oral administration of licorice and silymarin extracts for 6 weeks on some hematological parameters in cisplatin treated albino rats. These effects were explored by measuring hematological parameters.

Group injected with cisplatin revealed decrease RBCs count, Hb concentration, and values of PCV, MCV, MCH and MCHC. When compared with normal control group, there is microcytic hypochromic anemia associated with leukocytosis, neutrophilia, eosinophilia, and lymphopenia, also thrombocytopenia is recorded. All these parameters were improved in treated (licorice and silymarin) CP intoxicated groups compared with non-treated CP intoxicated group.

The findings of this study showed that, administration of licorice and silymarin are effective when taken orally for 6 weeks, they alleviate the changes recorded in the hematological parameters induced by cisplatin injection.

Keywords:

Cisplatin, Hematology, Licorice, Silymarin, Rats.

Introduction

Cisplatin (cis-diaminedichloroplatinum) is an inorganic compound used in the treatment of malignancies of various sorts (*Wang et al., 2004*). Cisplatin binds to the DNA of cancer cells, causing them to die. It also causes an increase in reactive oxygen species and a decrease in antioxidant status, both of which lead to increased cytotoxicity (*Liao et al., 2008*). As a result, because cisplatin can harm a range of normal tissues, its clinical use is restricted (*Florea and Büsselberg, 2011*). Cisplatin's clinical efficacy in the treatment of cancer is undeniable, yet it has serious adverse effects (nephrotoxic and hepatotoxic) while intrinsic or acquired resistance limits its application in high doses (Yoshida et al., 2009).

Licorice plant (*Glycyrrhiza glabra*) has been proven to provide clinical benefits in the treatment of a variety of ailments in this regard (*Hu et al., 2009 and Al-Razzuqiet al., 2012*). Treatment with licorice extract, in particular, was found to protect rats' livers from the toxicity of cisplatin (*Huo et al., 2011*). Glycyrrhizic acid, the main bioactive component

of licorice extract, has been shown to reduce the incidence of hepatic cell cancer in cisplatin-treated mice (*Shiota et al., 1999*).

Recently, Silymarin have been used in some experimental studies for cisplatin nephrotoxicity prevention (*Turgut et al., 2008 and Mansour et al., 2006*). *Abdelmeguid et al. (2010)* studied the effect of silymarin, as a natural flavonoid with potent antioxidant properties on cisplatin induced liver injury, as well as the mechanism of the possible protection afforded by silymarin.

The purpose of this study was to observe if oral administration of licorice and silymarin extracts could protect rats against cisplatin-induced alteration in some hematological parameters.

Materials and methods

A total of 72 albino rats, with initial body weight ranging from 150-200g were used. Rats were purchased from Animal Vaccine Institute, Helwan. All animals were housed in a controlled laboratory conditions at 20-25°C and 50% humidity in a 12-hour light/dark cycle, as well as unlimited food and water. The study techniques followed institutional

rules for the use of laboratory animals, and all animals received human care.

They were allowed for two weeks acclimatization period before starting the experiment.

Plant:

Licorice root extract was obtained from Dongtai Hanfangyuan Biological Technology Co, Ltd, China.

Chemicals:

1-Cisplatin

Cisplatin (CDDP) was bought from Egyptian International Medical in the form of a vial (1 mg/ml). Co, Ltd, Egypt.

2-Silymarin

(Hepaticum suspension), was obtained from Medical union pharmaceuticals (MUP). Co, Ltd, Egypt.

Experimental design:

After acclimatization rats were divided randomly into six groups. Each group consisting of 12 rats.

1st Group: Served as control group. They were not given any therapy.

2nd Group: Licorice treated group, orally received Licorice extract by gastric gavage at a rate of 2gm/ kg body weight swiftly and efficiently for six weeks (*Faried et al., 2016*).

3rd Group: Silymarin treated group, orally received Silymarin by gastric gavage in a dose of 100 mg/kg swiftly and efficiently for six weeks (*Kabel et al., 2013*).

4th Group: Served as hepatotoxic group, they were given an intraperitoneal injection of cisplatin at a dose of 1.5 mg/kg body weight

twice a week for three weeks starting from the 4th week of the experiment (*Faried et al., 2016*).

5th Group: Received licorice extract orally by gastric gavage in a dose 2 gm/ for 6 weeks, one weighed kg of body weight and injected cisplatin intraperitoneally in a dose of 1.5 mg/kg body weight twice a week for three weeks beginning in the 4th week of the experiment.

6th Group: Received silymarin orally by gastric gavage in a dose 100mg/kg daily for 6 weeks and injected cisplatin intraperitoneally in a dose of 1.5 mg/kg body weight repeated twice a week for three weeks, starting from the 4th week of experiment.

Sampling: -

Blood sampling: -

Blood samples were taken 2 times, the first time after 4 weeks, and the second at the end of the experimental period (6 weeks). Retro orbital venous blood samples were drawn from 10 hours fasted rats under effect of tetrahydrofuran inhalation anesthesia. Blood samples were taken using capillary microtubes veins in inner canthus of the eye of mice - into EDTA tube for hematological studies.

Hematological parameters

evaluation: -

Included RBCs count, Hb concentration, PCV value, MCV value, MCH value, MCHC value were performed by using Sysmex KX-21N (hematology analyzer).

Analytical statistics:

A one-way analysis of variance was used to evaluate the data in this study (ANOVA) for all tested groups according to Snedecor and Cochran, (2006). Means separations were done by Duncan's multiple range tests according to Duncan, (1955). The present SPSS 20 for Windows was used to analyse the data. At a probability threshold of 0.05 (P 0.05), the results are considered significant.

Results

Effect of cisplatin and protective agents (licorice and silymarin) on hematological parameters at 4 and 6 weeks.

Erythrogram:

Licorice and silymarin administration produced a non-significant variation in Erythrogram when compared to control group while RBCs, Hb, PCV, MCV, MCH, and MCHC levels in the cisplatin-treated group were significantly lower than in the normal control group, there was microcytic hypochromic anemia

manifested by the significant decreases in MCV and MCHC. Moreover, pre-treated groups (5 &6) showed an improve in RBCs, Hb, PCV, MCV, MCH and MCHC levels when compared with the cisplatin group. As demonstrated in table (1).

Leukogram and platelets count:

The groups that gastric intubated with licorice and silymarin alone showed no significant change when compared with normal control group. While cisplatin treatment induced significant increase in WBCs, neutrophils, monocytes, and basophils while, significant decreases in lymphocytes and platelets count in respect to the control groups were recorded. Moreover, group pre-treated with licorice and silymarin (5&6) showed decreased WBCs, neutrophil, monocytes and basophils while, there was increase in lymphocytes and platelets count in respect to the toxic groups as illustrated in table (2).

Table 1: Erythrogram of different experimental groups at 4 and 6 weeks.

Parameter	Group Duration	Control	Licorice	Silymarin	Cisplatin	Licorice + Cisplatin	Silymarin + Cisplatin
Hb (g/dl)	At 4 weeks	13.96 ^a ±0.14	13.87 ^a ±0.04	13.72 ^b ±0.08	8.32 ^c ±0.038	12.45 ^b ±0.04	12.10 ^b ±0.12
	At 6 weeks	14.21 ^a ±0.17	14.00 ^a ±0.09	14.00 ^a ±0.061	8.32 ^c ±0.09	13.00 ^a ±0.10	12.92 ^b ±0.15
PCV (%)	At 4 weeks	42.03 ^a ±10.07	41.68 ^a ±0.56	41.10 ^a ±0.46	28.27 ^c ±0.29	37.37 ^b ±0.15	36.3 ^b ±0.63
	At 6 weeks	42.63 ^a ±0.52	41.92 ^a ±0.22	42.00 ^a ±0.52	25.52 ^c ±0.29	38.92 ^b ±0.33	38.77 ^b ±0.46
RBCs (10 ⁶ /µl)	At 4 weeks	6.79 ^a ±0.16	6.70 ^a ±0.04	6.74 ^a ±0.07	4.73 ^c ±0.65	6.17 ^b ±0.01	6.04 ^b ±0.03
	At 6 weeks	6.82 ^a ±0.09	6.71 ^a ±0.01	6.84 ^a ±0.08	4.50 ^c ±0.06	6.46 ^b ±0.06	6.46 ^b ±0.08
MCV (fl)	At 4 weeks	61.89 ^a ±0.31	62.05 ^a ±0.2	60.93 ^a ±0.97	52.84 ^b ±0.03	60.54 ^a ±0.48	60.09 ^a ±0.68
	At 6 weeks	62.51 ^{ab} ±0.97	62.76 ^a ±0.39	61.34 ^{ab} ±0.33	54.80 ^c ±0.73	60.22 ^b ±0.65	60.01 ^b ±0.49
MCH (pg)	At 4 weeks	20.55 ^a ±0.22	20.68 ^a ±0.07	20.30 ^a ±0.32	17.09 ^b ±0.24	20.15 ^a ±0.17	20.03 ^a ±0.23
	At 6 weeks	20.82 ^a ±0.22	20.90 ^a ±0.13	20.44 ^{ab} ±0.22	18.39 ^c ±0.24	20.08 ^{ab} ±0.17	20.00 ^a ±0.15
MCHC (g/dl)	At 4 weeks	33.22 ^a ±0.11	33.32 ^a ±0.00	33.23 ^a ±0.10	29.43 ^b ±0.33	33.33 ^a ±0.00	33.30 ^a ±0.03
	At 6 weeks	33.33 ^a ±0.00	33.20 ^a ±0.18	33.28 ^a ±0.05	229.61 ^b ±0.33	35.33 ^a ±0.00	33.33 ^a ±0.02

Means of the interaction between the studied factors carrying at (P-value0.05), different superscripts are statistically different.

Table 2: Leukogram and Platelet count of different experimental groups at 4 and 6 weeks.

Parameter	Group Duration	Control	Licorice	Silymarin	Cisplatin	Licorice + Cisplatin	Silymarin + Cisplatin
WBCs (10 ³ /µL)	At 4 weeks	10.82 ^d ±0.16	11.19 ^d ±0.08	11.08 ^d ±0.01	17.33 ^a ±0.09	13.27 ^{bc} ±0.05	13.50 ^b ±0.49
	At 6 weeks	11.12±0.07	11.12±0.03	11.14 ^d ±0.15	17.82 ^a ±0.079	14.19 ^{bc} ±0.06	14.10 ^b ±0.31
Lymphocytes (10 ³ /µL)	At 4 weeks	6.38 ^a ±1.53	6.69 ^a ±0.01	6.63 ^a ±0.01	4.73 ^a ±0.060	5.20 ^b ±1.007	5.25 ^b ±0.12
	At 6 weeks	6.64 ^a ±0.03	6.67 ^a ±0.02	6.59 ^a ±0.04	5.03 ^a ±0.03	6.13 ^b ±0.01	6.02 ^b ±0.00
Neutrophils (10 ³ /µL)	At 4 weeks	3.30 ^c ±1.62	3.27 ^c ±0.02	3.17 ^c ±0.01	5.77 ^a ±0.03	4.21 ^b ±0.99	4.34 ^b ±0.20
	At 6 weeks	3.24 ^c ±0.02	3.20 ^c ±0.03	3.28 ^c ±0.01	5.87 ^a ±0.02	4.19 ^b ±0.01	4.17 ^b ±1.66
Eosinophils (10 ³ /µL)	At 4 weeks	0.82 ^a ±0.03	0.88 ^a ±0.01	0.87 ^a ±0.01	0.64 ^a ±0.02	0.50 ^a ±0.02	0.52 ^a ±0.03
	At 6 weeks	0.91 ^a ±0.01	0.93 ^a ±0.01	0.90 ^a ±0.01	0.62 ^a ±0.03	0.49 ^a ±0.01	0.57 ^a ±0.36
Monocytes (10 ³ /µL)	At 4 weeks	0.22 ^c ±0.01	0.24 ^c ±0.03	0.24 ^c ±0.03	3.47 ^a ±0.02	1.60 ^b ±0.01	1.62 ^b ±0.03
	At 6 weeks	0.22 ^c ±0.03	0.23 ^c ±0.03	0.24 ^c ±0.03	3.57 ^a ±0.02	1.63 ^b ±0.01	1.61 ^b ±0.37
Basophils (10 ³ /µL)	At 4 weeks	0.10 ^c ±0.003	0.11 ^c ±0.023	0.17 ^c ±0.003	2.72 ^a ±0.006	1.76 ^b ±0.015	1.77 ^b ±0.012
	At 6 weeks	0.11 ^c ±0.01	0.09 ^c ±0.02	0.13 ^c ±0.01	2.73 ^a ±0.04	1.75 ^b ±0.01	1.73 ^b ±0.02
Platelet count (10 ³ /µL)	At 4 weeks	907.00 ^a ±1.16	908.10 ^a ±2.06	909.94 ^a ±0.06	630.33 ^d ±5.49	721.33 ^c ±9.35	785.67 ^b ±0.67
	At 6 weeks	915.66 ^a ±4.71	911.67 ^a ±0.33	911.18 ^a ±0.67	653.00 ^d ±1.72	741.67 ^c ±9.28	783.00 ^b ±1.53

Means of the interaction between the studied factors carrying at (P-value0.05), different superscripts are statistically different.

Discussion

The hematopoietic system is one of the most sensitive systems in humans and animals for assessing the effects of toxins and medications (*Lijuv et al., 2013*). Chemotherapeutic medications are usually cytotoxic, meaning they kill cancer cells while, also destroying the immune system. Bone marrow cells, depending on their proliferative nature, are extremely sensitive to cytotoxic substances and vulnerable to DNA damage, especially undifferentiated populations (*Shaymaa et al., 2017*). Inhibition of cell proliferation is one of the major causes of cisplatin induced myelotoxicity (*Basu et al., 2015*). The reduction in the erythrogram, leukogram and platelet values in the present study might be due the effect of cisplatin on bone marrow.

Moreover, licorice and silymarin treated groups didn't show significant changes in RBCs, Hb, PCV, MCV, MCH and MCHC levels when compared with the control. The findings of this investigation revealed that oral administration of silymarin has no significant influence on haematological parameters, which is consistent with the findings of another study (*Shaymaa et al., 2017*). Cisplatin is a strong cytotoxic agent that has been linked to severe side effects in various body organs, including hepatotoxicity, nephrotoxicity, and bone marrow suppression. The

impact of CP treatment on haematological parameters was investigated. When compared to normal control animals, CP caused a substantial decrease (P0.05) in Hb, RBCs and total platelet count over the course of the experiment (*Rajendrakumar et al., 2020*). *Ramya et al. (2013)* showed similar changes in blood parameters after cisplatin treatment. *Karale and Kamath (2017) and Lin et al. (2018)*.

Anemia and CP therapy were found to have an etiological link. Different mechanisms, such as the death of bone marrow cells or the rise in osmotic fragility of RBCs, could explain such a link. As a result, CP poisoning may cause anemia by suppressing hematopoietic tissue activity, impairing erythropoiesis, and hastening RBC breakdown due to increased RBC membrane permeability (*Hassan et al., 2010*). According to *Nowis et al. (2007)*, cisplatin injection decreased erythropoietin, a haemopoietic growth factor, causing haematological parameters to change. CP generates oxidative stress in human platelets and lymphocytes, according to *Olas et al. (2005)*, which could affect their function. Results of this study revealed that, pre-treated by licorice extract can mitigate all the adverse effects of cisplatin on hematological parameters. (*Iztleuov et al., 2021*) also obtained similar results that rats were intoxicated by Gamma irradiation the emptying of the bone

marrow, which is defined by a decrease in the level of cellular elements in the blood and bone marrow cellularity by 41%, 50%, and 25%, led to a noticeable and lasting shift in the peripheral blood picture. In comparison to the control group, 42 percent, 35 percent, and 46 percent improved. When compared to the data of the irradiation group, prophylactic and therapeutic use of the medicine "licorice oil" resulted in significant increases in the number of cellular components in the peripheral blood and bone marrow cellularity of 25%, 34%, 19%, 39%, 33 percent, and 37%, respectively. Erythrocytes, hemoglobin, hematocrit, leukocytes, and platelets were all measured. (*Mettler and Voelz, 2002*). When compared to the levels in the irradiated animals, the usage of "Licorice oil" before and after irradiation resulted in an increase in the number of erythrocytes, hemoglobin, hematocrit, leukocytes, and platelet content. In comparison to the data from the irradiated animals, the cellularity of the bone marrow increased by 37%. All of this points to a hemostimulant effect. The phyto-preparation's hemostimulating impact can be linked to increased proliferation, the activity of surviving stem cells, and migration from the peripheral blood and thymus to the bone marrow (*Suleimenova et al., 2021*). Research by *Razina (2006)* found that, the monoammonium salt of

glycyrrhizic acid, glyceram, increases granulopoiesis and erythropoiesis in hemodepressed mice.

The current study's findings showed that oral administration of silymarin alone has no discernible impact on hematological parameter. This agrees with the result of *Shaymaa et al. (2017)*, but after injection of 7.5 mg/kg cisplatin there was a reduction in RBCs, at both the 8th and 13th days of the trial, the cisplatin-treated group exhibited a substantial detrimental effect on haematological parameters, and pretreatment with silymarin had successfully alleviated these haematological disturbances. The previous findings revealed that anemia in the cisplatin-treated group could be explained by cisplatin's cytotoxic action on bone marrow cells or by cisplatin-induced enhanced RBC osmotic fragility (*Nasr, 2014*). Anemia caused by cisplatin intoxication can be caused by either decreasing hematopoietic tissue function or by hastening RBC death due to increased RBC membrane permeability (*Nasr, 2014*). *Adaramoye et al. (2008)* mentioned that the apoptotic impact of cisplatin on lymphocytes and platelets resulted in lymphopenia and thrombocytopenia in the cisplatin-treated group, resulting in a reduction in the amount of these cells in the blood. The observed leukocytosis in the cisplatin-treated group, on the other hand, could be

the result of infection and inflammation (*Markovic et al., 2011*).

Conclusion

Cisplatin used in the treatment of a wide range of malignant diseases has been associated with notable toxic effects on several organs. In this study, we have been able to show that cisplatin-induced alteration in some hematological parameters is reversible by licorice extract and silymarin supplementation.

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النتائج الدموية المرتبطة باستخدام عرق السوس والسيليمارين على الفئران المعالجة بالسيبيلاتين

رندا محمود عبد الحميد¹, اسامه محمد عبد الله², امنيه السيد كيلاني²

طبيب بيطرى فى مستشفى جامعه قناه السويس

قسم الباثولوجيا الاكلينيكيه كلية الطب البيطرى - جامعه قناه السويس

الملخص العربى

استهدفت هذه الرسالة دراسة تأثير إعطاء مستخلص العرقسوس والسيليمارين لمدة 6 اسابيع على الفئران المصابة بتسمم الكبد والكلى المحدث بالسيبيلاتين وقد أجريت هذه الدراسة على 72 جرذ التي تم تقسيمهم الى 6 مجموعات متساوية إشملت كل مجموعة على 12 جرذان و لم يلاحظ أي تغير في في صورة الدم في المجموعات التي تم إعطائها مستخلص العرقسوس أوالسيليمارين منفردين كما أظهرت صورة الدم إصابة الجرذان المسممة بالسيبيلاتين بفقر الدم من النوع صغير الخلايا منخفض الصبغ مع زيادة في كرات الدم البيضاء و نقصان في الصفائح الدموية في المجموعة السامة وهذا مقارنة بالمجموعة الطابطة. بينما أظهرت المجموعات المسممة السيبيلاتين والمعالجة بالمستخلصات النباتية تحسن في صورة الدم.