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Effect of Costus (*Saussurea lappa)* Root Aqueous Extract on Tamoxifen-Induced Hematotoxicity in Female Rats

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Eman Ali Faraj Hamouda

Department of Zoology, Factually of Arts and Sciences, University of Benghazi, Tocra, Libya
eali40411@gmail.com

Abstract

In recent years, traditional medicine has been used to treat various diseases such as anemia. One of these plants is *Saussurea lappa* .The objective of the study is to investigate the impact of an aqueous extract of *Saussurea lappa* root (AESL) on Tamoxifen-induced anemia in female albino rats. A total of twenty-four rats (180-190 g) were separated into 4 groups (n= 6 for each group).Group (1), normal control was received only normal saline solution. Group (2), administered orally AESL (200 mg/kg body weight. Group (3)، received orally tamoxifen (TAM, 40 mg/kg body weight). Group (4), given TAM concurrently with AESL.TAM was administered concurrently with AESL for 28 successive days. The results showed that TAM intoxication had led to significant depletion in, red blood cells count (RBCs), hemoglobin (Hb), mean corpuscular hemoglobin (MCH), hematocrit (HCT), white blood cells count (WBCs) and platelets in TAM intoxicated ratsversus control counterparts. No significant changes in mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) were observed in TAM intoxicated rats versus control ones .Oral intake of AESL concurrently with TAM markedly ameliorated the depletion in WBC, RBC, Hb, MCH, HCT and platelets when compared with TAM intoxicated rats.This investigation revealed that oral intake of AESL in parallel with TAM can protect against hematotoxicityrelated to TAM. This result may candidate the use

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of AESL in the treatment of blood cell disorder.
Keyword: Anemia, S*aussurea lappa*, Tamoxifen, Hb

تأثير المستخلص المائي لجذور نبات القسط الهندي علي التسمم الدموي المستحدث بعقار التامكسوفين في إناث الجرذان

إيمان علي فرج حموده
قسم علم الحيوان /كلية الأداب والعلوم –توكرة/ جامعة بنغازي– ليبيا
eali40411@gmail.com

الملخص

في السنوات الأخيرة، تم استخدام الطب التقليدي لعلاج أمراض مختلفة مثل فقر الدم. واحدة من هذه النباتات هي القسط الهندي. تهدف الدراسة لمعرفة مدى تأثير المستخلص المائي لجذور نبات القسط الهندي (***Saussurea lappa***) على التغيرات الدموية (السمية) المستحدثة بفعل عقار التامكسوفين في إناث الجرذان. تم إستخدام أربعة وعشرون جرذا (إناث) بوزن 180–190 جرام موزعين على أربعة مجاميع على التوالي، تحتوي كل مجموعة على ستة جرذان، المجموعة الأولى (الكنترول) تلقت فمويا بفعل الإنبوب المعدي محلول ملحي فقط، المجموعة الثانية (مجموعة القسط الهندي (**AESL**)، تلقت فمويا بفعل الإنبوب المعدي المستخلص النباتي لجذور القسط الهندي بتركيز 200 ملجم/ كيلو جرام من وزن الجسم، المجموعة الثالثة (مجموعة التامكسوفين) (**TAM**) تلقت فمويا بفعل الإنبوب المعدي عقار التامكسوفين على شكل معلق بتركيز 40 ملجرام/كيلو جرام من وزن الجسم، والمجموعة الرابعة (مجموعة التامكسوفين + المستخلص النباتي)، تلقت فيه الجرذان فمويا بفعل الإنبوب المعدي على التوالي عقار التامكسوفين ثم مباشرة المستخلص النباتي، استغرقت مدة الدراسة 28 يوم على التوالي لكل المعالجات المذكورة اعلاه. أظهرت النتائج أن التسمم بـ TAM قد أدى إلى انخفاض كبير في عدد كريات الدم الحمراء (**RBCs**) والهيموجلوبين (**Hb**) ومتوسط تركيز الهيموجلوبين في الكريات (**MCH**) و

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الهيماتوكريت **(HCT)** وعدد كريات الدم البيضاء **(WBCs)** والصفائح الدموية في الجرذان التي تعرضت للتسمم بـ TAM مقارنةً بنظرائها في مجموعة الكونترول لم تُلاحظ تغييرات ملحوظة في حجم الكريات الحمراء المتوسط **(MCV)** وتركيز الهيموغلوبين المتوسط في الكريات الحمراء **(MCHC)** في الجرذان المعرضة لتسمم التاموكسيفين مقارنةً بالجرذان الضابطة. أدى تناول المستخلص المائي لجذور نبات القسط الهندي(**AESL**) عن طريق الفم بالتزامن مع **TAM** إلى تحسين ملحوظ في نقص كريات الدم البيضاء، وكريات الدم الحمراء، والهيموغلوبين، ومتوسط حجم كريات الدم الحمراء، ونسبة الهيماتوكريت، والصفائح الدموية مقارنةً بالجرذان التي تعرضت لتسمم**TAM** .كشفت الدراسة أن تناول المستخلص المائي لجذور النبات عن طريق الفم بالتوازي مع **TAM**يمكن أن يحمي من السمية الدموية المرتبطة ب-**TAM**. قد تشير هذه النتيجة إلى إمكانية استخدام هذا المستخلص في علاج اضطرابات خلايا الدم.

الكلمات المفتاحية: أنيميا، تامكسوفين، سوشوريا لابا، هيموجلوبين.

Introduction

Hematological toxicity is commonly observed during the treatment with cytotoxic agents [1,2]. Tamoxifen (TAM) is a synthetic non-steroidal antiestrogen drug that is extensively employed in breast cancer chemotherapy [3]. According to reports, TAM causes several negative effects including myelosuppression, via decreasing in bone marrow activity, which then leads to a decline in red blood cells (RBCs), white blood cells (WBC), and platelets (PLT). (International Adjuvant Therapy Organization[4] , Wang et al. [5]Beside , previous investigation stated that TAM can alter the typical discoid shape of RBC and forming stomatocytes, suggesting that the drug may be inserted into the inner layer of the red blood cell membrane [6]. Furthermore, TAM can affect RBC via inducing the production of reactive oxygen species (ROS). ROS promote the oxidation of lipids and proteins in the erythrocyte membrane, as well as changes in cytoskeleton proteins, leading to RBC hemolysis [7]. In addition, some studies revealed

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that TAM has an eryptotic activity and can induce erythrocyte cell death [8,9] .In addition, previous studies documented that thrombocytopenia is a secondary side effect of TAM treatment in breast carcinoma patients [10]. Drug-induced thrombocytopenia is either immune mediated (increased destruction of platelets) or due to suppression of bone marrow (reduced formation of platelets) [11] .Nasiroglu et al [12] postulated that TAM could induce the production of antibodies target against the platelets. These antibodies bind to the platelet surface glycoproteins and destroy them [11]. Another report revealed that treatment with TAM is associated with reduced platelet function due to increased platelet nitric oxide, there by resulting in an increase in the bleeding time [13]. Therefore, TAM therapy can influence both the quality and the quantity of platelets in susceptible individuals [14]. It has recently reported that TAM can be responsible for leucopenia, when used as a hormonal treatment in breast cancer women [15]. Extended usage of tamoxifen was linked to bone marrow suppression according to International Adjuvant Therapy Organization [4]. Phytochemicals function as potent antioxidants by removing free radicals, boosting the intracellular antioxidant system, and inhibiting the proapoptotic signal pathway. Consequently, they possess a notable capacity to safeguard against oxidative harm induced by chemotherapy medications, along with the accompanying adverse consequences. *Saussurea lappa* (*S .lappa*) is a botanical plant renowned for its abundant concentration of antioxidants, which possess significant medicinal properties. [16]. *S. lappa*, often referred to as Saussurea costus, belongs to the Asteraceae family. The plant contains a variety of chemicals with therapeutic characteristics, including as trepans, alkaloids, anthraquinone, and flavonoids the roots of *S. lappa* received significant study for theirpotential biological activities. [17].

Several compounds have been identified in *S.lapp* roots, including costunolide, dihydrocostunolide, 12-methoxydihydrocostunolide , dehydrocostuslactone, lappadilactone8, hydroxydehydrocostus lactone,, reynosin, santamarine, caryophyllene oxide, Mycenae,

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octanoic acid, and p-cymene.[18] Costunolide, a sesquiterpene lactone, produced by the roots of *S. lappa*, demonstrates a broad range of biological actions, such as antioxidant, anti-inflammatory, anti-anemia, and anti-diabetic properties[19]. The objective of the current study is to investigate the potential effect of aqueous extract of *S.lappa* root (AESL) against hematotoxicity induced by TAM intoxication in female rats. The current research for the first time investigated the prophylactic impact of AESL versus TAM hematotoxicity.

Materials and Methods

Chemicals

Tamoxifen: Tamoxifen (tamoxifen citrate), trade name Nolvadex®, was manufactured by Astra Zeneca United Kingdom and packed as tablets by Astra Zeneca-UK .It was suspended in distilled water and orally given to the experimental animals at a dose level of 40 mg/kg body weight (equivalent to the rapeutic dose for human, daily for 28 days according to Paget and Barnes) [20] .

Plant material and extraction method for *Saussurea lappa*

S. lappa dry roots were obtained from medicinal plant market, Benghazi, Libya. To prepare the aqueous root extract, one Kg of *S.lappa* root was finely powdered, boiled for 30 minutes with 5 liters of distilled water and then filtered. The obtained extract was then lyophilized. For this investigation, the freeze-dried substance was weighed (about 35 g), and dissolved in water to get a final concentration of 50 mg/ml [16].

Animals and Treatment

Twenty four female albino rats (eight weeks age), weighing 180-190 g, were utilized for this work. The rats were bought from animal house, University of Benghazi Faculty of medicine. The animals were housed under controlled conditions (23-25 ºC, humidity 50-65%, 12 h dark/light cycles). Animals were given a diet with standard composition and water adlibitum. The animals were left for seven days for adaptation and then distributed into four groups, each of 6 rats.

Group I: Normal animals treated orally with normal saline

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only.

Group II: rats treated orally with SLRE (200 mg/Kg /day) for 28 Consecutive days [16].

Group III: Rats treated orally with a suspension of TMX (40 mg/Kg/day) for 28 consecutive days [21].

Group IV: rats received orally TMX (40 mg/Kg/day) concurrently with SLRE (200 mg/ Kg /day) for 28 consecutive days.

Sampling

At the end of the experimental period, the rats were subjected to ether vapour for an aesthesia, and the blood specimens were collected into EDTA sample bottle for a hematologicalassay.

Hematological parameters analysis

Total leukocyte count (WBC), erythrocyte count (RBC), hemoglobin concentration (Hb),Hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) and platelet count were measured using an automated hematologyanalyzer (Genrui KT-6400 Shenzhen, China).

Statistical analysis

The statistical analyses were done using SPSS (Version 26, SPSS Inc., and Chicago, USA). Using one-way ANOVA followed by the Duncan test as a post hoc to determine the statistically significant difference between groups. The data are presented as means ± SD, with significance set at $P< 0.05$.

Results

Effect of aqueous extract of *S. lappa* (AESL) on blood cell profile

Red blood cell (RBCs) indices

The present results demonstrated that, non significant variations in RBC indices (RBC count, Hb concentration, HCT %, MCV , MCH, and MCHC with respect to control counterparts were recorded in rats treated with the plant extract only versus control animals.

TAM administration induced alterations in RBC indices in rats as shown by the decreases in RBC count, Hb concentration, HCT %,

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and MCH with respect to control counterparts. The percentage changes for these parameters in TAM intoxicated rats from control ones were 25.3 %, -30 %, -28.5%, and -3% respectively. None marked variations in MCV and MCHC was found among different experimental groups. Oral administration of AESL concurrently with TAM , pronouncedly alleviated the deviations in RBCs count, Hb concentration, HCT %, and MCH in comparison to TAM intoxicated group ($p \leq 0.001$ for RBC , Hb and HCT , $p \leq 0.05$ for MCH) with percentage changes from control of - 4.7 %, -9.08%, -9.1% and -1.9% respectively (Table 1).

White blood cells (WBCs)

Table 2 shows the influence of AESL on WBC in TAM intoxicated rats. The table revealed that non-significant variation in WBC was recorded in rats treated with the plant extract only versus control animals. Marked depletion in these cell counts in TAM treated rats with respect to control ones ($p \leq 0.001$). The percentage change in WBC of TAM intoxicated rats with respect to control was – 69.1 % .Oral administration of AESL to TAM group, markedlymodulated the count of WBC versus TMX untreated group ($p \leq 0.001$) with percentage change from control of – 42%.

Platelets count

Table 3 illustrates the effect of AESL on platelet count in TAM intoxicated rats. The data showed that non-significant variation in platelet count was recorded in rats treated with the plant extract only versus control animals. Severe reduction in these cell counts in TAM treated rats with respect to control ones ($p \leq 0.001$). The percentage change in platelet count of TAM intoxicated rats with respect to control was – 90.88 %. Oral ingestion of AESL to TAM group, markedly reverse the platelet count to normal count.

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TABLE 1.Impact of AESL on RBCs indices in TAM- induced hematotoxicity in female rats

Parameters	Control	AESL	TAM	TAM+ AESL
RBC count (x 10^3)	6.75±0.32	6.7±0.34* [3]	4.85±0.18 [a]	6.43±0.21*
% change		- 0.74%	- 25.3 %	- 4.7 %
Hb g/dl	11.56±0.55	11.53±0.78*	8.1±0.55 [a]	10.51±0.66 [c*]
% change		- 0.25%	- 30%	- 9.08%
HCT %	38.55±2.04	38.46±3.2*	27.58±2.73 [a]	35.03±2.1 [c*]
% change		- 0.23%	- 28.5%	- 9.1%
MCV fl	56.73±0.57	57.21±2.3	56.50±3.68	56.10±1.00
% change		+ 0.84%	- 0.40%	- 1.11%
MCH pg	17.10 ±.16	17.10±0.36**	16.6±0.56[c]	16.76±0.21**
% change		0 %	- 3%	- 1.9%
MCHC g/dl	30.05±0.25	29.96±0.70	29.40±0.99	29.93±0.33
% change		- 0.30%	- 2.16%	- 0.40%

Values are expressed as mean ± SD of 6 rats. [a]p≤ 0.001, [c]p≤ 0.05 compared with control, *p≤0.001, **p≤ 0.05 compared with TAM. The percentage changes are calculated for different groups with respect to control group.

TABLE 2.Impact of (AESL) onblood WBCs in TAM - induced hematotoxicity in female rats

Parameters	Control	AESL	TAM	TAM+ AESL
WBC count ($x10^3$)	7.76±0.53 $x10^3$	**7.7±0.49* $x10^3$**	2.4±0.27[a] $x10^3$	4.5±0.60 [a*] $x10^3$
% change		- 0.77%	- 69.1%	42 %-

Values are expressed as mean ± SD of 6 rats.[a]p≤ 0.001compared with control *p≤0.001, compared with TAM. The percentage changes are calculated for different groups with respect to control group.

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TABLE 3.Impact of AESL on platelets count in TAM- induced hematotoxicity in female rats

Parameters	Control	AESL	TMX	TMX+ AESL
PLT count ($x10^3$)	947±98.36	959.5±140.2*	86.33±6.50 [a]	1098±237.50*
change%		+ 1.26%	- 90.88	+ 15.94 %

Values are expressed as mean ± SD of 6 rats.[a]p≤ 0.001 compared with control, *p≤0.001 compared with TAM. The percentage changes are calculated for different groups with respect to control group.

Discussion

Hematotoxicity is commonly observed during the treatment with cytotoxic agents[1,2].The current investigation showed that administration of TAM for 28 consecutive days to female rats caused significant alteration in RBC indices as observed by depletion in the mean values of RBCs count, Hb concentration , HCT %, and MCH with respect to control counterparts . The percentage changes for these indices in TAM intoxicated rats from control ones were 25.3 %, -30 %, -28.5%, and -3% respectively. The deficiency in the number of circulating RBC, Hb, or HCT (the volume of packed RBCs) may indicate that treatment with TAM greatly affect RBCs and induce anemia in rats. Similar finding has been obtained by Panchal et al [22].The depletion in RBC and their indices (Hb concentration, HCT %, and MCH) in response to TAM treatment may attribute to the ability of the drug to increase destruction of RBC and/or reducing RBC formation by bone marrow. Some reports revealed that treatment with TAM causes myelosuppression, via suppressing erythropoiesis, leading to a depletion in RBC production [4, 23].On the other hand, Silva et al [24],point to a prominent role of TAM in inducing defects in erythrocyte membrane shape and decreased mechanical stability, resulting in hemolytic anemia. In addition, previous study showed that TAM could affect RBC via inducing the production of reactive oxygen species (ROS). ROS promote the oxidation of lipids and proteins in the erythrocyte membrane,

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as well as changes in cytoskeleton proteins, leading to RBC Hemolysis [7].In addition, some investigation stated that TAM has an eryptotic activity and can induce erythrocyte cell death [7, 8].

In the present study, marked depletion in WBCs count in TAM treated rats was recorded with respect to control ones. The percentage change in WBCs of TAM intoxicated rats with respect to control was – 69.1 %. This result is aligns with a recent clinical investigation revealed that leucopenia is an important adverse event of TAM treatment in breast cancer patients [15]. Also earlier investigation demonstrated that TAM specifically targets neutrophils, lymphocytes, and basophils, resulting in a substantial reduction in the count of these white blood cells, suggesting the genotoxic impact of TAM therapy in leukocytes of breast cancer patients [25].Herein, a severe depletion in the count of blood platelets was noticed in rats intoxicated with TAM with respect to control counterparts. The percentage change in platelets of TAM intoxicated rats with respect to control was – 90.88 %.Similarly , it has reported that thrombocytopenia is secondary adverse effect to TAM therapy in patients with breast cancer [26] .TAM -induced thrombocytopenia can occur through an increased destruction of platelets and/or suppression of hematopoiesis, resulting in lower creation of platelets [11]. Nasiroglu et al [12], proposed that TAM could promote the generation of antibodies target against the platelets. These antibodies bind to the platelet surface glycoproteins and destroythem [11]. Another study demonstrated that treatment with TAM is connected with reduced platelet function due to increased platelet nitric oxide, there by resulting in an increase in the bleeding time [13].

Oral intake of AESL concurrently with TAM for 28 successive days pronouncedly alleviated the alterations in RBCs count, Hb concentration, HCT %, and MCH as well as WBCs and platelets count and in comparison to TAM intoxicated group. These results may indicate the protective impact of AESL against TAM induced hematotoxicity in rats. Kadhem [27], suggested that demonstrated of AESL mitigates the harmful impact of paracetamol by enhancing hematological parameters, including RBC count, Hb,

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PCV, MCV, MCH, MCHC and WBCs count. Li et al [28], suggested that *S .lappa* extract contains active amino acid, namely L-proline, L-ß-homo-tryptophan, and L-5-oxoprolinewhich can influence hematological parameters [28]. The plant's roots contains active compounds, such as sesquiterpene lactones as costunolide and dehydrocostus lactone, with many pharmacological activities , include antioxidant, immunostimulation, anti-inflammatory , anticancer, anti-ulcer, anemia treatment[29]. States that AESL with its antioxidant capabilities, it enhances the generation of different blood cells in the peripheral blood by suppressing oxidative stress on the DNA of hematopoietic stem and reducing lipid peroxidation, and hence protects the blood cells against oxidative cell damage [30].

Conclusion

From this study, it can be conclude that oral administration of AESL concurrently with TAM could mitigate the hemato-toxic impact of TAM as shown by increases in RBCs, Hb concentration, HCT (MCH), WBCs and platelets. This result may candidate the usage of AESL as a useful drug in the treatment of blood cells disorder related to drug toxicity**.**

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