

Ameliorative effect of *Phoenix dactylifera* on adverse effects of Linezolid in rats

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Abstract

Linezolid is one of the oxazolidinone antibiotics that is used to treat methicillin resistant *Staphylococcus aureus* (MRSA) & vancomycin resistant *Staphylococcus aureus*. This study aimed to investigate the adverse effects of linezolid on bone marrow and, kidneys and their counteraction by using *Phoenix dactylifera* methanolic extract in rats. It was found that oral administration of linezolid (100 mg/kg body weight) for 14 successive days induced a significant decrease in hemoglobin content (7.88 ± 0.18 g/L) on the first day post-treatment, significant increase in serum urea (59.75 ± 0.85) and creatinine (1.89 ± 0.04) on the 14th day post-treatment. The concurrent oral administration of *Phoenix dactylifera* methanolic extract (1000 mg/kg body weight) and linezolid (100 mg/kg body weight) for the same period corrected the damaging effects of linezolid of the hemoglobin content, urea, creatinine of treated rats. It was concluded that methanolic extract of phoenix dactylifera clearly ameliorated these damaging effects of linezolid.

Key words: Phoenix dactylifera, Linezolid, urea, creatinine, brain and bone marrow

Introduction

The oxazolidinones represent a new synthetic class of anti-bacterial agents with activity against gram-positive organisms [1].

Studies have shown that the oxazolidinones LZD and eperzolid are active against MRSA, penicillin-resistant *Streptococcus pneumoniae*, and VRE [2]. Linezolid is entering phase III clinical trials as a therapeutic agent that is effective against skin infections, bacteremia, and pneumonia caused by gram-positive pathogenic bacteria, the antimicrobial activities of the oxazolidinones were first described by scientists at Dupont de Nemours Co., Inc, USA [3]. Resistance to linezolid is extremely rare [4].

Linezolid was discovered in the 1990s and first approved for use in 2000. It was the first commercially available 1, 3-oxazolidinone antibiotic, although others are in development. As a protein synthesis inhibitor, it stops the growth of bacteria by disrupting their production of proteins, that is, a bacteriostatic agent, not bactericidal. Although many antibiotics work this way, the exact mechanism of action of linezolid appears to be unique in that it blocks the initiation step of protein production, and not one of the later steps [5].

In Japan, the use of LZD for MRSA infections was approved in April 2006.

Because the mechanism of action of LZD differs from that of current protein synthesis inhibitors, it is considered to have no cross-resistance with existing antimicrobial agents [6]. Data on longer-term use are limited, but serious neuropathies (e.g., peripheral and optic neuropathies), myelosuppression, and hyperlactatemia have been observed [7], and are considered to be related to the inhibition of mitochondrial protein synthesis [8].

Phoenix dactylifera is also known as date palm. It is a monocotyledon plant within the palm tree family and they can be found mostly in the North Africa and Middle East region [9]. They are among a few plants that could survive the harsh arid environment and thus is highly regarded for the nutritional value that the palm tree fruit provides [9]. In these arid regions where foods are scarce, date palm serves as a good food source as they are rich in carbohydrates and they have even become a part of Arabian diet. Aside from a common food source, date palm fruits have been used traditionally to treat various types of ailments and it has been regarded that consumption of the fruit is good for health [10].

Traditional medicines are gaining importance and nowadays are being studied to find the scientific basis of their therapeutic actions. The use of herbal medicine has become increasingly popular worldwide

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especially in the Asian and African countries. The various parts of *Phoenix dactylifera* are widely used in traditional medicine for the treatment of various disorders which include memory disturbances, fever, and inflammation [11]. Muslims believe that ‘‘He who eats seven dates every morning will not be affected by poison or magic on the day he eats them’’ [12].

The aim of this study is to investigate the possible adverse effects of linezolid on different biological functions in rats, and to find out the possible role of *phoenix dactylifera* methanolic extract in counteracting these possible adverse effects.

Material and method

Drugs

- Linezolid ® (Global napi, Egypt), available as tablets (600 mg/tablet)
- Dose: 100 mg/kg b.wt
- Tween 80 (Al-Gomhoria Co. Ltd, Egypt).
- Methyl alcohol (Al-Gomhoria Co. Ltd, Egypt).

Phoenix dactylifera (Siwa oasis, Egypt).

Solubility It is moderately water-soluble (approximately 3 mg/mL), with a log P of 0.55 and soluble in 1% Tween 80 [13].

Phoenix dactylifera fruits: Dose: 1000 mg/Kg (as 25% solution) [14].

Experimental Animals

Forty eight male albino rats weighing 180-200 gm were used in this experiment. They were left to acclimatize in the laboratory of the Pharmacology Department for two weeks. They were given clean tap water ad libitum and balanced ration.

Methods

Method of methanolic extraction of *phoenix dactylifera* fruits

1 Kg of fresh fruits of PD and pits were prepared and the fresh PDFs seeds were removed. The known weight of FPDFs was soaked in 1 L methanol (79%) and left for three hours, then the mixture was blended in a stainless steel blender and the blended mixture was sieved twice by narrow mesh stainless

steel sieve and the sieved part was then added to 2 L of methyl alcohol 79%.The mixture was then filtered through sterile absorbed gauze. The residual part of dates was soaked in 3 liters of methanol 79% and left for 2 hours at 20°C, and then reblended and refrigerated using the clean gauze. The filtrate was added to the previous prepared filtrate and the residual non filtered part was weighed and discarded. The clean part of the supernatant was put in the rotary evaporator and adjusted to 42°C, then left for methanol to be evaporated. Finally, the resultant crude dates methanolic extract was then measured, weighed & kept in the laboratory refrigerator till needed to be administered orally to male albino rats.

Experimental design

Forty eight rats were distributed into four equal groups. (Each of 12 animals). The first group was left as control and was given tween 80 orally using the stomach tube daily for 14 consecutive days. The second group was given 0.5 ml of linezolid suspension 4% in tween 80 orally daily for 14 consecutive days. The third group received 0.5 ml of linezolid suspension 4% (100mg/kg body weight) followed by 1 ml of *Phoenix dactylifera* methanolic extract using the stomach tube daily for 14 consecutive days. The rats in the last group were given 1 ml of *Phoenix dactylifera* methanolic extract daily for 14 consecutive days.

Sampling: blood samples were collected in clean Wassermann tubes with EDTA as at 1st, 7th, and 14th day post treatment to be used for hematological studies. After that, rats were dissected out and femur bones were taken and kept on 10% formalin at the same periods to be used for histopathological study

Hematological studies

CBC was carried out according to Sysmex® automated cell counter [15].

Biochemical study

Determination of serum urea [16].
Determination of serum creatinine [17]

Histopathological studies

Histopathological examinations were carried out according to [18]. Sections were

stained with hematoxylin for 5-10 minutes, and then washed with running water for 5-10 minutes [19].

Statistical Analysis

Data were analyzed using computerized SPSS programs version 21 (2001). The results were expressed as Mean±S.E.M (Standard error of mean). The total variation was analyzed by performing one-way analysis of variance (ANOVA). Duncan test was used for determining significance. Probability levels of less than 0.05 were considered significant [20].

Results

1-Hematological results

Hemoglobin content

It was clear from Table (1) that the administration of LZD and MEPD and their combination for 14 days displayed non-significant changes during the entire period of the study compared with control group except with LZD alone after first day and its combination with MEPD after seven days post treatment which showed a significant decrease and increase ($P<0.05$) respectively compared to control group and revealed that the administration of various treatments daily for 14 days to male albino rats in their recommended doses afforded non-significant changes in TLC except with linezolid which afforded a significant increase ($P<0.05$) along the entire period of the study compared with control group.

Table (1): Effects of oral administration of Linezolid (100mg/Kg body wt), Phoenix dactylifera methanolic extract (1000 mg/kg body wt) and their combination given daily for 14 successive days on Hb content (g/L) and TLC (μ l) of rat. (Mean \pm SE) (n = 4)

Period Group	Hemoglobin content (g/L)			TLC (μ l)		
	Time post-treatment			Days Post -treatment		
	1 st day	7 th day	14 th day	1 st day	7 th day	14 th day
Control	12.93±0.36 ^b	12.93±0.3 ^b	13.40±0.6 ^a	9.60±1.20 ^b	9.60±1.20 ^b	11.33±0.59 ^b
LZD	7.88±0.18 ^c	15.30±0.4 ^a	13.10±0.1 ^a	17.83±0.5 ^a	17.78±0.7 ^a	15.40±0.76 ^a
LZD+ PD	13.55±0.27 ^{ab}	15.78±0.38 ^a	14.45±0.32 ^a	12.00±0.56 ^b	12.08±0.05 ^b	12.70±0.83 ^{ab}
PD	14.28±0.35 ^a	12.53±0.24 ^b	13.83±0.50 ^a	11.10±0.43 ^b	9.56±1.30 ^b	11.48±0.89 ^b

Means within the same column carrying different superscripts are significantly different at $P<0.05$.

Serum urea

Table (2) revealed that the oral administration of LZD and its combination with MEPD in their recommended doses and time elicited a significant increase in serum urea along the entire period of the study except after 14 days with the combination of both LZD and MEPD which showed a non-significant change compared with control group. Whereas, the administration of MEPD alone induced non-significant changes when compared with control group along the entire period of the study and a significant decrease when compared with LZD or its combination after 7th and 14th days post treatment. Also, it demonstrated that various treatments given daily for 14 days in their recommended doses

afforded a significant increase in serum creatinine after the first day post treatment except MEPD alone which produced a slight increase.

Whereas, various treatment induced non-significant changes when compared with control group except combination of LZD and MEPD which induced a significant decrease compared with control group and linezolid treated group. Whereas, after 14 days various treatments induced a significant increase when compared with control group except MEPD alone which induced a non-significant change with control group and a significant decrease when compared with LZD alone and its combination with MEPD.

Table 2. Effects of oral administration of Linezolid (100mg/Kg body wt), Phoenix dactylifera (1000 mg/kg b.wt) and their combination given for 14 successive days on serum urea and serum creatinine (mg/dl) of rat. (Mean \pm SE) (n=4):

	Serum Urea (mg/dl)			Serum Creatinine (mg/dl)		
	Time-post treatment			Time-post treatment		
	1 st day	7 th day	14 th day	1d	7d	14d
Control	27.00 \pm 0.71 ^b	27.00 \pm 0.71 ^b	45.50 \pm 1.04 ^{bc}	0.75 \pm 0.06 ^b	0.75 \pm 0.06 ^a	0.85 \pm 0.02 ^c
LZD	36.75 \pm 1.44 ^a	42.68 \pm 1.38 ^a	59.75 \pm 0.85 ^a	1.23 \pm 0.04 ^a	0.74 \pm 0.01 ^a	1.89 \pm 0.04 ^a
LZD+ PD	37.75 \pm 2.95 ^a	44.65 \pm 5.01 ^a	48.75 \pm 1.11 ^b	1.16 \pm 0.09 ^a	0.57 \pm 0.02 ^b	1.35 \pm 0.02 ^b
PD	31.00 \pm 2.12 ^{ab}	27.77 \pm 0.83 ^b	41.00 \pm 1.58 ^c	0.97 \pm 0.10 ^{ab}	0.75 \pm 0.06 ^a	0.96 \pm 0.05 ^c

Means within the same column carrying different superscripts are sig. different at P<0.05.

Histopathological results

Bone marrow

The bone marrow section of the control group showed numerous megakaryocytes with white and red blood cells. After seven days post-treatment the bone marrow section showed hypocellular bone marrow elements with linezolid alone. But the combination of both linezolid and methanolic extract of phoenix dactylifera, the bone marrow section showed moderate increase in the bone marrow elements and scattered fat cells. Whereas, normal bone marrow was normal cellularity and numerous megakaryocytes surrounded by white and red blood cell elements was observed as a result of treatment with Phoenix alone after the seventh day post-treatment (Figure 1A-D).

Brain

Normal brain tissue from control group showed normal neuron cells surrounded by neurological fibers with elongated vascular space filled with red blood cells. After one day post-treatment with linezolid, the brain tissue

showed aggregates of inflammatory cells surrounding dilated vascular space, while the group treated with the combination of linezolid and methanolic extract of phoenix dactylifera showed mild aggregates of inflammatory cells. Whereas, the group treated with methanolic extract of phoenix dactylifera revealed normal neuron cells and neurofillary material after the first day post-treatment (Figure 1E-H).

Kidney

The kidney section of the control group showed normal renal glomeruli and renal tubules. The renal tissue showed moderately dilated congested vascular space and mild aggregates of inflammatory cells in between glomeruli and renal tubules at day seven post-treatment with linezolid alone. Whereas, the combination of both linezolid and methanolic extract of phoenix dactylifera led to absence of inflammatory cells with the return of renal tissue to its normal state at day seven post-treatment. Whereas, 7 days post-treatment with phoenix dactylifera, the renal tissue showed normal structure (Figure 1I-L).

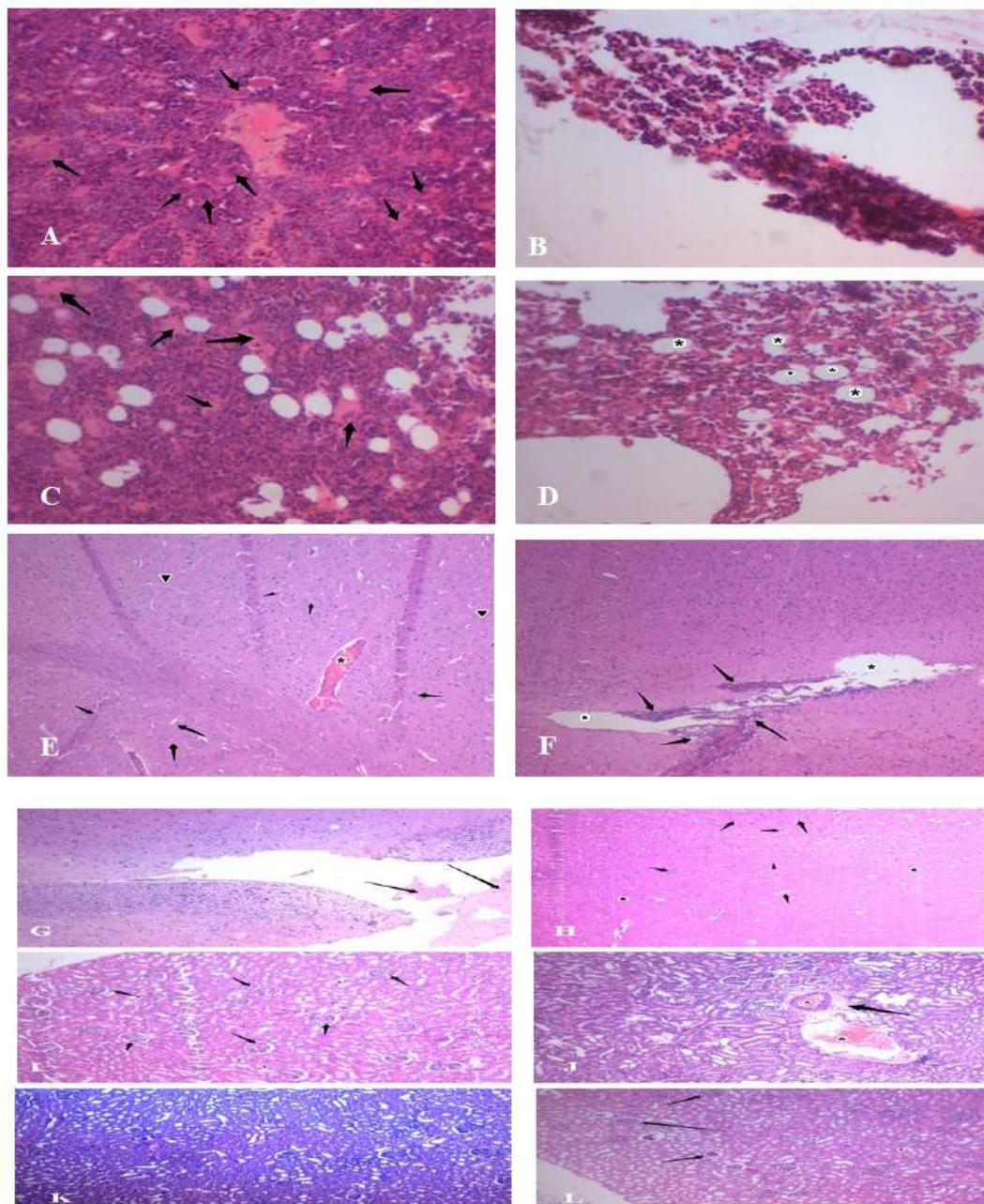


Figure 1 A. Photomicrograph of normal bone marrow of control group showing numerous megakaryocytes↑with white and red blood cells elements. (H & E X400). **B.** Photomicrograph of bone marrow from rats 7 days post-treatment treated with linezolid showing hypocellular bone marrow elements. (H & E X 400). **C.** Photomicrograph of normal bone marrow from rats one day post-treatment with phoenix showing normal cellularity of the bone marrow with numerous megakaryocytes↑surrounded by white blood cell and red blood cell elements. (H & E X 400). **D.** Photomicrograph of bone marrow treated with linezolid and phoenix 7 days post treatment showing moderate increase in the bone marrow elements with scattered fat cells * (H & E X 200). **E.** Photomicrograph of normal brain tissue from control group showing normal neuron cells↑surrounded by neurological fibers with elongated vascular space filled with red blood cells *. (H & E X 200). **F.** Photomicrograph of brain tissue treated with linezolid at the first day post treatment showing aggregates of inflammatory cells↑surrounding dilated vascular space *. (H & E X 200). **G.** Photomicrograph of brain tissue from rats treated with linezolid and phoenix at day one post-treatment showed mild aggregates of inflammatory cells↑. (H & E X 200). **H.** Photomicrograph of brain tissue from rats at day one post-treatment with phoenix showing normal neuron cells↑ and neurofibrillary material *. (H & E X 200). **I.** Photomicrograph of normal rat kidney of control group showing renal glomeruli↑and renal tubules *. (H & E X 200). **J.** Photomicrograph of kidney from rats seven days post-treatment with linezolid showing moderately dilated congested vascular space * and mild aggregates of inflammatory cells↑in between the glomeruli and tubules. (H & E X 200). **K.** Photomicrograph of kidney treated with linezolid and phoenix seven days post treatment showing normal glomeruli↑ and tubules * (H & E X 200). **L.** Photomicrograph of kidney treated with phoenix showing normal glomeruli↑and tubules *. (H & E X 200).

Discussion

Linezolid is an oxazolidinone antimicrobial drug active against antibiotic-resistant Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci [21]. Its high oral bioavailability provides a definite economic advantage compared with other MRSA therapeutic options, allowing earlier hospital discharge and reducing out-patient therapy cost. Linezolid is well-tolerated with nausea, vomiting, diarrhea and headache being the most commonly reported side effects. Bone marrow suppression and neuropathies may occur in patients taking this antibiotic for more than two weeks [22].

The present study was carried out to evaluate the adverse effects of therapeutic doses of linezolid in tween 80 for fourteen consecutive days on adult male albino rats (100 mg/kg bwt.) and to use the methanolic extract of *Phoenix dactylifera* fruits in a new trial to possibly counteract the undesirable effects of linezolid. Further approach was designed to study the pharmacological effects of these drugs on some hematological parameters. Histopathological picture and further approach for detecting any dysfunction in bone marrow femur bones was performed.

On Hb. content, a significant decrease was observed after one day post-treatment with linezolid similar results were previously recorded by Birmingham *et al.*, [23] and MacDougall and Chambers [24], who reported that one of the adverse effects induced by linezolid is anemia. The TLC was significantly increased during the entire period of the study which might be due to posterior leuco encephalopathy induced by linezolid [25]. Our findings were also incompatible with Ager and Gould [26] who recorded that oral administration of linezolid at a dose of 600 mg twice daily post-administration induced leucopenia and thrombocytopenia after 28 days in human. It needs further investigation to explain the cause of this leukocytosis. These findings were supported by the histopathological changes in the bone marrow which revealed hypocellularity reverting them to their normal state as concluded by Arshad *et al.*, [27] who reported that MEPD decreased TLC due to its anti-inflammatory effect.

The obtained results revealed that linezolid in its recommended doses and duration afforded a significant increase in serum urea and creatinine whereas phoenix dactylifera when given in combination with linezolid decreased these elevated levels significantly, reverting them to their normal control values. These results were supported by the histopathological study in this work which revealed that linezolid elicited degenerative changes in the kidney.

Effect of linezolid (100 mg/kg bwt.) orally administered to rats for 14 consecutive days on serum creatinine level showed a significant increase on the fourteenth day post treatment. These results were supported by our histopathological findings shown on the kidney sections. Also, our results agreed with those established by Natsumoto *et al.*, [28] who reported that linezolid increased serum creatinine level in patient received linezolid for 7 weeks and this may be contributed to that linezolid can cause interstitial nephritis after 3 days as reported by Nayak *et al.*, [29]. Upon administration of linezolid and *Phoenix dactylifera* combination, our recorded results showed a significant decrease in creatinine level, this suggested that *Phoenix dactylifera* fruits have nephroprotective effect as investigated by Al-Qarawi *et al.*, [30] who studied the effect of an extract of the flesh and pits of *Phoenix dactylifera* on gentamicin-induced nephrotoxicity in rats were effective in reducing the increased serum creatinine. Also, our results informed that linezolid caused a significant increase in the serum urea as shown in figure and table; these results agreed with Ahmed *et al.*, [31] who stated that linezolid mildly elevated urea fourteen days after administration in patients with renal impairment.

Our histopathological outcomes revealed in figure, methanolic extract of *Phoenix dactylifera* fruits returned the kidney to its normal state and treated its lesion, these results were in accordance with Lin *et al.*, [32] who concluded that the protection of *Phoenix dactylifera* seeds extract could be attributed to the total phenol/proanthocyanidin content, which can suppress the oxidative stress induced by xenobiotic-generating free radicals with the subsequent restoration of the

physiological and histological features of the susceptible organs.

Our histopathological findings on the brain section showed aggregates of inflammatory cells and that may be due its high penetration through CSF [33] and may be contributed to the axonal damage to sensory neurons that occurs after linezolid exposure [34]. Linezolid and *Phoenix dactylifera* combination showed mild aggregates of inflammatory cells. This result agreed with Agbon *et al.*, [35] who concluded that *Phoenix dactylifera* fruits have neuroprotective effect due to its anti-oxidant properties.

Conclusion

The current study revealed the oral administration of the therapeutic dose of linezolid to male albino rats for fourteen consecutive days resulted in damaging effects on the bone marrow. It was evident that the concurrent oral administration of *Phoenix dactylifera* methanolic extract (1000 mg/kg bwt.) with linezolid (100 mg/kg bwt.) clearly counteracted the bone marrow damaging effects of linezolid.

Conflict of interest

The authors declare that they have no conflict of interest.

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الملخص العربي التأثير الوقائي لخلصة التمر على الآثار الجانبية للينزوليد في الجرذان

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إستهدفت هذه الدراسة دراسة الآثار الجانبية للينزوليد كأحد أحدث المضادات الحيوية من مجموعة الأوكسازوليدونونات وكذلك تسلط الضوء على الدور الوقائي المحتمل للمستخلص الكحولي للتمر لهذه الآثار الجانبية. تم إجراء هذا البحث على عدد ثمانية و أربعون من الجرذان البيضاء، تم تقسيمهم إلى أربع مجموعات بواقع اثني عشر جرذا لكل مجموعة. (أ): المجموعة الضابطة التي تم تجريعها ٥. مل ١% توين ٨٠ خالي من اي دواء عن طريق الفم باستخدام أنبوبة المعدة. المجموعة (ب): تم تجريعها لينزوليد ٥. مل (١٠٠ مجم/كجم من وزن الجرذان) معلق على ١% توين ٨٠ لمدة ١٤ يوما متوaslًا مرة واحدة يوميًا. المجموعة (ج): تم تجريع الجرذان بعقار اللينزوليد ٥. مل (١٠٠ مجم/كجم من وزن الجرذان) مصحوبا بجرعة خلاصة التمر الميثانولية بجرعة ١ مل مذاب في ماء مقطر يحتوي على (١٠٠٠ مجم/كجم من وزن الجرذان) عن طريق الفم مرة واحدة يوميا لمدة ١٤ يوما متوaslًا. المجموعة (د): تم تجريع الجرذان بجرعة خلاصة التمر الميثانولية بجرعة ١ مل مذاب في ماء مقطر يحتوي (١٠٠٠ مجم/كجم من وزن الجرذان) عن طريق الفم مرة واحدة يوميا لمدة ١٤ يوما متوaslًا. إنه في اليوم الأول والسابع و الرابع عشر بعد توقف اعطاء الدواء، تم ذبح أربعة جرذان من كل مجموعة من أجل تجميع عينات من الدم لكل جرذ على حدة من الأوعية الدموية بالرقبة. تم تجميع عينة الدم في أنبوبة تحتوي على إديتا من أجل إجراء الدراسة على صورة الدم. تم تشريح الجرذان بعد تجميع عينات الدم وتم أخذ عظمي الفخذ (نخاع العظام) من أجل إجراء دراسات نسج مرضية عليها. تم حفظ الأعضاء المجمعة في حاويات تحتوي على ١٠% فورمالين متعادل لكي تكون جاهزة لعمل الشرائح النسج مرضية. بالنسبة للتأثير على العدد الكلي لكريات الدم البيضاء فإن جميع العلاجات عندما اعطيت بنفس الجرعات والمدد لم تحدث أي تأثير معنوي في عدد كريات الدم البيضاء طوال فترة التجربة فيما عدا اللينزوليد الذي أحدث زيادة معنوية طوال فترة التجربة مقارنة بالمجموعة الضابطة. أما بالنسبة للتأثير على تركيز الهيموجلوبين فإن إعطاء اللينزوليد بمفرده و خلاصة التمر و خليط منهما عن طريق الفم لمدة ١٤ يوما متوaslًا لم يؤدي إلى إحداث أي تغيير معنوي طوال فترة التجربة فيما عدا اللينزوليد بعد اليوم الأول وخليط منه مع خلاصة التمر بعد اليوم السابع من نهاية العلاج حيث أحدث نقصا و زيادة معنوية على التوالي مقارنة بالمجموعة الضابطة. في اليوم الأول بعد توقف إعطاء اللينزوليد، أظهر الفحص زيادة ملحوظة في عدد الصفائح الدموية وكرات الدم البيضاء وفي اليوم السابع بعد توقف إعطاء اللينزوليد أوضح الفحص زيادة معنوية في عدد كرات الدم الحمراء و زيادة معنوية في نسبة الهيموجلوبين وكذلك زيادة معنوية في عدد الصفائح وكرات الدم البيضاء. أدى اعطاء اللينزوليد بالجرعات المكرره لذكور الجرذان لمدة ١٤ يوما متتالية الى حدوث زيادة معنوية في مستوى اليوريا طوال فترة التجربة ، كما اظهر اللينزوليد نفس التأثير السابق عند اليوم الاول والرابع عشر بعد نهاية العلاج. أدى إعطاء اللينزوليد بالجرعة المكررة والمدة المكررة إلى إحداث زيادة معنوية في مستوى الكرياتينين بالمصل بعد اليوم الأول والرابع عشر من نهاية العلاج وإلى إحداث تأثير غير معنوي بعد اليوم السابع من نهاية العلاج مقارنة بالمجموعة الضابطة. بينما أدى اعطاء التمر مع اللينزوليد الى احداث نقص معنوي في يوريا المصل مقارنة بمجموعة اللينزوليد. كما أظهر اعطاء التمر مع اللينزوليد بالتزامن الى احداث نقص معنوي في مستوى كرياتينين المصل عند اليوم الرابع عشر من نهاية العلاج. أدى اعطاء اللينزوليد الى احداث بعض التغيرات التحطيمية في أنسجة المخ والكلى ونخاع العظام واختفت هذه التغيرات التحطيمية عندما أعطيت خلاصة التمر مع اللينزوليد. ونستخلص من هذه الدراسة أن اعطاء اللينزوليد بالجرعات والمدة المكرره أدى إلى إحداث تغيرات تحطيمية نخاع العظام وأن اعطاء خلاصة التمر مع اللينزوليد أدى إلى اختفاء هذه التأثيرات. لذا فإننا ننصح بإعطاء خلاصة التمر مع اللينزوليد طوال فترة العلاج.