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Investigation the Cytotoxic Effect of Erythromycin and the Potential Protective Role of Vitamin C in Male White Rats

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P A P E R I N F O

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A B S T R A C T

The study aimed to demonstrate the side effects of certain drugs currently used as antibiotics. The research examined the effects of erythromycin at both the cellular and molecular levels, as well as the potential protective role of vitamin C. A total of 25 male white rats *Mus musculus* were used in the experiment for 14 days**.** The study was conducted in the laboratory of the College of Science University of Babylon in May 2024 **.**The animals were divided into five groups, with five rats in each group. The first group was the control group, while the second and third groups received the drug at concentrations of (15, 30) mg/kg, respectively, as treatment groups. The fourth and fifth groups were dosed with the drug at the aforementioned concentrations along with vitamin C at a concentration of (100) mg/kg as protective groups.
The results of the experiment showed structural abnormalities in chromosomes, including deletions in the treated groups (G2, G3), specifically in dicentric chromosomes. Additionally, breaks and ring chromosomes were observed in the treated groups compared to the control group. However, the results of the protective groups (G4, G5) showed a significant reduction in the rates of these abnormalities. The results also indicated a significant decrease in the proportion of non-fragmented DNA, and a significant increase in the mean DNA fragmentation was recorded in groups (G2, G3), while no such observation was made in groups (G4, G5). High DNA fragmentation was found only in group (G3), which received a concentration of (30) mg/kg, but this was not observed in the other experimental groups**.**

1. INTRODUCTION

Erythromycin a drug from the macrolide group, is characterized by its broad-spectrum effect against bacteria and is considered more effective than penicillin. Therefore, it is used in the treatment of many infections [1]. Erythromycin is part of a large therapeutic group composed of more than 13 compounds or drugs that were first extracted over six decades ago in the 1950s. However, it quickly showed many drawbacks, including side effects for patients, poor solubility in water (H_2O), and instability in gastric acids, all of which lead to reduced bioavailability and limited therapeutic effectiveness [2]. Despite the side effects associated with erythromycin treatment, such as nausea, abdominal cramps, and hepatotoxicity, among others, it is still used in pharmacies. However, these drawbacks have limited its oral use [3]. Many studies and research have been conducted on erythromycin to overcome these disadvantages, eventually leading to modifications in the chemical structure of the drug for safer use and increased effectiveness against microbial infections [4]. The use of dietary supplements in alternative medicine as adjuvants to chemical drugs aims to reduce side effects on the body or enhance their effectiveness. One of the compounds used alongside certain drugs, including erythromycin, is vitamin C [5]. Vitamin C, also known as ascorbic acid, is a water-soluble vitamin found in fresh foods, particularly citrus fruits and vegetables. It is important for the body's functions and for protecting the mucous membranes in the respiratory tract, shielding them from infections and microbial inflammation. It was discovered in the early 20th century [6]. Vitamin C acts as a cofactor or substrate for many neurotransmitters and enzymes, participates in collagen synthesis, serves as an antioxidant, protects the

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heart from stress, and improves iron absorption in the intestines [7]. Vitamin C is a micronutrient with multiple roles, particularly in electron donation. It is a powerful natural antioxidant and an enzyme cofactor, contributing to the body's immune system and acting as a protective agent against the toxicity of many compounds and drugs used today. Vitamin C accumulates in immune phagocytic cells, which helps increase ROS (reactive oxygen species) in immune complexes, thus killing microbes. Additionally, vitamin C plays a role in regulating gene expression [8].

The comet assay, also known as the single-cell gel electrophoresis (SCGE) test, is a tool used to detect any damage or degradation of DNA molecules. It is also employed in assessing the effects of certain substances at the genetic level. This test is considered one of the most versatile, rapid, and accurate methods for obtaining results. It is a highly sensitive and fast-responding technique for detecting single and double-strand breaks in DNA, which are caused by various physical and chemical factors in eukaryotic cells [9].

2. MATERIALS AND METHODS

2.1. Experimental Animals

A total of 25 male white rats *Mus musculus* were used in the experiment, with ages ranging between 10-12 weeks and weights ranging from 215-265 grams. The rats were fed a diet consisting of a mixture of various grains, supplemented with powdered milk.

2.2. Experimental Design

The rats were divided into five groups as follows:

1. First Group (Control Group): Consisted of 5 rats, which were given a saline solution at a concentration of 0.5 ml.
2. Second Group (Therapeutic Group): Consisted of 5 rats, which were given erythromycin at a concentration of 15 mg/kg.
3. Third Group (Therapeutic Group): Consisted of 5 rats, which were orally administered erythromycin at a concentration of 30 mg/kg.
4. Fourth Group (Protective Group): Consisted of 5 rats, which were given erythromycin at a concentration of 15 mg/kg along with vitamin C at a concentration of 100 mg/kg.
5. Fifth Group (Protective Group): Consisted of 5 rats, which were given erythromycin at a concentration of 30 mg/kg along with vitamin C at a concentration of 100 mg/kg.

The concentrations for the drug and the vitamin were determined as follows:

- The dosage of vitamin C was calculated based on a previous reference [10].
- The dosage of erythromycin was determined according to pharmacokinetic data [11]. The experiment lasted for two weeks.

2.3 Sample Collection

The rats were Animal sacrificing , and a blood sample of 5 ml was collected via cardiac puncture for testing. The blood was placed in specialized tubes and centrifuged at 4000 rpm to separate the serum, which was then stored at 4°C. Afterward, the animals were dissected to collect bone marrow samples from the femur and sternum for genetic testing.

2.4 Tests

1- Comet Assay

The comet assay was used to measure DNA damage using the OX Select Comet Assay kit. All required reagents and materials were prepared in advance, including comet agarose gel (Comet LM Agarose), Green Stain Solution, antifade solution, alkaline unwinding solution, and electrophoresis buffer for the assay. The procedure was carried out according to the steps outlined in a reference [12]. A ready-made software program on the computer was used to perform the necessary calculations for each sample [13].

2- Chromosomal aberration test

Slides were prepared after carefully dissecting the animal. After preparation, the slides were stained with a 2% methylene blue solution for 12 minutes. The slides were examined using an oil immersion lens [14], and non-dividing cells were counted according to the mitotic index using the following formula:

$$\text{Mitotic Index (MI)}=\frac{Number\ of\ Dividing\ Cells}{Total\ Number\ of\ Cells}\times 100$$

2.5 The Statistical Analysis

The statistical analysis of the experiment was conducted according to the completely randomized design to study the effect of the drug efficacy and the protective role of Vitamin C in male white mice using the tow-way analysis variance and LSD test for significant difference to show the significance of the difference between the arithmetic means of the experimental variables. All statistical analyses were conducted using the ready statistical program 25. SPSS.V.

3. RESULTS

3.1 Effect Of Erythromycin And The Protective Role Of Vitamin C On Chromosomal Aberration Rate

The results shown in **Table 1** indicate a significant increase ($P<0.05$) in the appearance of chromosomes that experienced deletions in the third group, which was administered erythromycin at a concentration of 30

mg/kg, compared to the control group. In contrast, the fifth, fourth, and second groups did not show a significant difference in chromosomal deletion. The results also revealed a significant increase in the presence of dicentric chromosomes, especially in the third group compared to the first (control) group, while no significant differences ($p>0.05$) were observed in the second, fourth, and fifth groups regarding dicentric chromosomes. There was a noticeable increase in the occurrence of acentric chromosomes in the therapeutic group that received erythromycin at a concentration of 30 mg/kg. However, the fourth and fifth protective groups were not affected by the drug, while the second group, which received 15 mg/kg, showed a lower rate of acentric chromosomes compared to the third group and the control.

When observing **TABLE 1**, the fourth, second, and fifth groups did not show significant differences in the appearance of ring chromosomes compared to the control group.Yet, the therapeutic third group recorded significant differences in the appearance of ring chromosomes at a probability level of ($p<0.05$) compared to the control group. The results showed the presence of chromosome breaks in the therapeutic groups that received erythromycin at both concentrations (30 and 15 mg/kg) compared to the protective and control groups. **Table 1** indicated a statistical difference in the overall chromosomal abnormalities between the first (control), second, and third groups. In contrast, no significant differences were observed in the fourth and fifth protective groups when compared to the control.

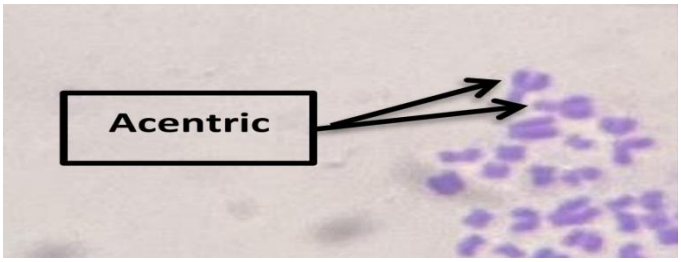
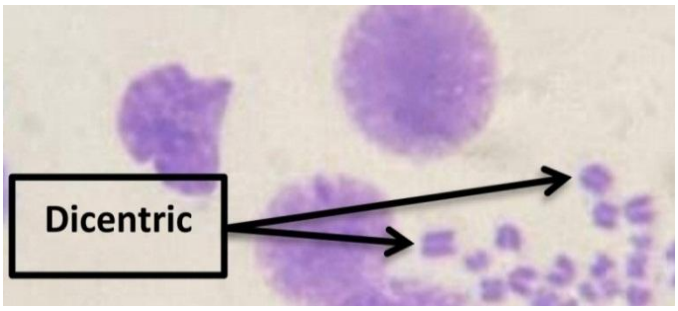
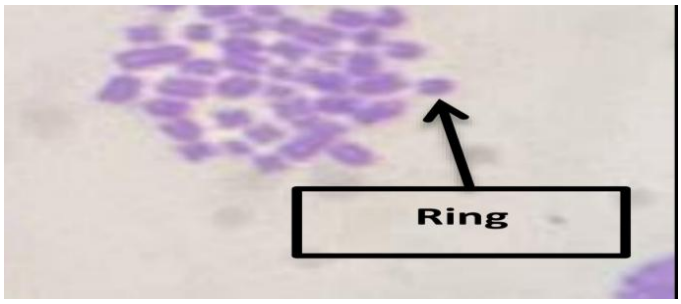


Figure 1. Acentric chromosome in metaphase of bone marrow cells in white mice of the second treatment group (magnification 1000x)



. **Figure 2**. Dicentric chromosome in metaphase of bone marrow cells in white mice of the therd treatment group (magnification 1000x)



. **Figure 3.** Ring chromosome in metaphase of bone marrow cells in white mice of the therd treatment group (magnification 1000x)

TABLE 1. Effect of Erythromycin and The Protective Role of Vitamin C on Chromosomal Aberration Rate

Groups	Deleted Chromosome Percentage	Dicentric Chromosome Percentage	Acentric Chromosomes	Ring Chromosome	Broken Chromosomes	Total Aberrations
Control Group(G1)	B 0.191±0.0826	B 0.250±0.047	BC 0.070±0.385	B 0.0790+0.066	C 0.168+0.059	C 1.09+0.157
Erythromycin G2(15mg/kg)	AB 0.320+0.871	B 0.299+0.073	AB 0.429+0.122	B 0.181+0.105	B 0.263+0.076	B 1.095+0.157
Erythromycin G3(30mg/kg)	A 0.328+0.162	A 0.604+0.108	A 0.521+0.212	A 0.308+0.104	A 0.320+0.821	A 2.015+0.372
Vitamin C G4(100mg/kg) Erythromycin 15mg/kg	B 0.282+0.091	B 0.0.372+0.142	C 0.312+0.086	B 0.231+0.048	C 0.175+0.041	C 1.056+0.308
Vitamin C G5 (100mg/kg) Erythromycin 30mg/kg	B 0.221+0.209	B 0.432+0.082	BC 0.452+0.021	B 0.105+0.082	C 0.176+0.072	BC 0.782+0,112
p-value	0.018	0.011	0.007	0.001	0.002	0.004
LSD	**0.236**	**0.138**	**0.134**	**0.208**	**0.098**	**0.363**

3.2 Effect Of Erythromycin And The Protective Role Of Vitamin C On Dna Damage Rates

The results in **Table 2** show a significant decrease in the percentage of intact DNA in the treatment groups (G2 and G3), whether the erythromycin concentration was 15 mg/kg or 30 mg/kg. Meanwhile, the results of the groups that received vitamin C along with the drug as a protective factor showed a significant decrease in the percentage of fragmented DNA compared to the second and third groups, and the control group. Table (2) indicates a significant increase in the average DNA fragmentation in the groups that received the drug alone (15 mg/kg and 30 mg/kg). In contrast, no significant differences were observed in the average DNA fragmentation in the two protective groups compared to the control group when the animals were given both the vitamin and the drug together. The results of **Table 2** showed no significant difference in the high DNA strand breakage rates in groups G2, G4, and G5 compared to the control. However, a significant difference in DNA strand breakage was observed in the third group, which received the drug at a concentration of 30 mg/kg, compared to the control group.

TABLE 2. Effect of Erythromycin and the protective role of Vitamin C on DNA damage rates

Groups	Unbroken DNA	low DNA breakage	moderate DNA breakage	High DNA breakage
Control Group(G1)	A 50.062±3.321	A 40.113±3.923	D 6.449±0.982	C 6.023±1.217
Erythromycin G2(15mg/kg)	C 39.732±40.032	B 36.321±2.821	B 12.926±2.821	A 13.331±1.298
Erythromycin G3(30mg/kg)	D 36.682±1.802	B 35.706±1.382	A 17.023±2.621	A 14.092±0.872
Vitamin C G4(100mg/kg) Erythromycin 15mg/kg	B 45.492±0.802	A 41.728±0.662	D 8.023±1.203	C 7.231±0.931
Vitamin C G4(100mg/kg) Erythromycin 30mg/kg	C 42.807±1.682	A 37.992±1.348	C 11.122±1.601	B 9.235±0.786
p-value	0.001	0.002	0.003	0.001
LSD	**3.162**	**2.742**	**2.523**	**5.982**

4. DISCUSSION

The Effect of Erythromycin and the Protective Role of Vitamin C on Chromosomal Aberration Rates. The results of the experiments indicated cytotoxicity due to erythromycin, particularly in groups two and three, which received the drug alone at concentrations of 15 and 30 mg/kg. This outcome is consistent with findings from study [15], which reported that erythromycin caused chromosomal aberrations, with a significant increase in structural deviations in human lymphocyte chromosomes. Additionally, study [16] highlighted growing concerns regarding the drug's impact on embryos in pregnant women, particularly in the form of structural abnormalities in sister chromatids. These abnormalities serve as an indicator of genetic safety after exposure to the drug during pregnancy, especially given that fetal and neonatal cells are sensitive to teratogenic effects. A study [17] conducted on pregnant mice treated with erythromycin (a macrolide family drug) at various doses during late pregnancy revealed a reduction in cell proliferation, changes in the morphology of fetal testes, and deviations in cellular functions. Exposure to different concentrations of orally administered erythromycin poses a risk to epithelial cells in the intestine, as study [18] demonstrated that

drug accumulation in food at certain concentrations affects the permeability of the intestinal epithelial layer. Acute exposure increased cytotoxicity and caused changes in embryonic gene expression related to the production of adhesion proteins, suggesting that these gene expression alterations are associated with the drug's immune activation and compensatory mechanisms in the intestinal epithelium.

The results of the study showed that the protective groups, which received vitamin C along with the drug, produced outcomes different from those of the second and third therapeutic groups. Statistical analyses revealed no significant differences in chromosomal abnormalities, aligning with study [19], which highlighted the protective role of vitamin C in reducing structural DNA damage caused by the genotoxic and cytotoxic effects of erythromycin. Moreover, study [20] demonstrated a reduction in chromosomal structural damage when vitamin C was used as a protective agent alongside macrolide treatments. Study [21] mentioned that vitamin C enhances the efficacy of enzymes involved in DNA methylation, thereby maintaining genome stability due to its antioxidant properties and its role in promoting the activity of the TET enzyme family. These enzymes, with the assistance of vitamin C, help regulate and demethylate harmful methylation, ensuring genomic stability.

The Effect of Erythromycin and the Protective Role of Vitamin C on DNA Damage Rates

Our current study noticed a significant increase in DNA fragmentation rates, particularly in groups two and three, which received erythromycin alone without vitamin C. These results are consistent with study [22], which showed that the drug causes genotoxicity resulting in DNA fragmentation, especially in conjunction with strong oxidative agents and cellular degeneration. This effect is attributed to intracellular reactions that lead to chromatin condensation and ultimately programmed cell death. Additionally, the drug has mitochondrial toxic effects due to increased oxidative stress and DNA fragmentation in epithelial and fibroblast cells [23]. Study [24] highlighted the drug toxicity of macrolides, specifically clarithromycin (a member of the macrolide family), and its inhibitory effect on CYP3A5 (a genetic variant in humans responsible for metabolizing drugs and related molecules in the body). In some volunteers who took the drug orally, results showed inhibition of the gene expression studied due to drug accumulation after the treatment period. In a study conducted by [25], mice were administered telithromycin, and the comet assay revealed DNA damage in lymphocytes and structural harm to the DNA, confirming the genotoxicity of these drugs. The current study results indicate that vitamin C acts as a protective agent against DNA damage caused by erythromycin, as noted in study [26]. This study highlighted the vitamin's role in preventing partial DNA fragmentation by directly reducing the damage caused by ROS molecules, which can harm proteins and DNA in cellular environments. Comet assay analyses revealed no significant differences in DNA damage between the groups receiving both the drug and vitamin C when compared to the control group. This finding aligns with study [27], which emphasized vitamin C's protective role against DNA damage from harmful mutations due to its antioxidant properties and its ability to neutralize free radicals causing oxidative stress.

5. CONCLUSIONS

Erythromycin affects the structural integrity of chromosomes, with its impact varying according to the doses administered. Combining erythromycin with Vitamin C can mitigate its side effects on chromosomal structures. The drug induces DNA damage by causing fragmentation of the double-stranded DNA. Vitamin C exhibits a protective effect, safeguarding DNA from structural aberrations induced by erythromycin. A dose of 30 mg/kg of erythromycin administered to mice results in the most pronounced genetic effects.

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Arabic Abstract

هدفت الدراسة إلى بيان التأثير المحتمل لبعض أنواع العقاقير المستخدمة حالياً كمضادات حيوية. تناول البحث الآثار الجانبية التي يسببها عقار الإريثرومايسين على المستويين الخلوي والجزيئي، ودور فيتامين C كعامل وقائي محتمل. استخدمت في التجربة ذكور الفئران البيضاء لمدة 14 يومًا، قُسمت الحيوانات إلى خمس مجموعات بواقع 5 فئران في كل مجموعة. المجموعة الأولى كانت مجموعة السيطرة، بينما تلقت المجموعتان الثانية والثالثة العقار بتركيز (15، 30) mg/kg على التوالي كمجموعات علاجية. أما المجموعتان الرابعة والخامسة فقد جُرعتا بالعقار بتركيز المذكور مع فيتامين C بتركيز (100) mg/kg كمجموعات وقائية. أظهرت نتائج التجربة حدوث تشوهات تركيبية في الكروموسومات تمثلت بوجود حذف (Deletion) في المجموعتين العلاجيتين (G2، G3) في الكروموسومات ذات مركزين (Dicentric)، بالإضافة إلى ظهور تكسر وكروموسوم حلقي (Ring) في المجموعات العلاجية مقارنة مع مجموعة السيطرة. بينما سجلت نتائج المجموعتين الوقائيتين (G4، G5) انخفاضًا معنويًا في نسب حدوث التشوهات المذكورة. بينت النتائج انخفاضًا معنويًا في نسب الـ DNA غير المتكسر، وسجلت أيضًا ارتفاعًا ذا قيمة معنوية في متوسط تكسر الـ DNA للمجموعتين (G2، G3)، بينما في المجموعتين (G4، G5) لم يُلاحظ ذلك. وُجد أن هناك تكسرًا عاليًا في الحمض النووي للمجموعة (G3) فقط التي جرعت بتركيز (30) mg/kg، ولم يُلاحظ هذا في باقي المجموعات التجريبية.