

Effect of Pomegranate Peel Extract Alternatives to Oxytetracycline on Growth Performance and Physiological Homeostasis in Rabbits

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Abstract

The current study focused on evaluation of pomegranate peel extract (PPE) and the oxytetracycline as antioxidant and antiapoptotic potentialities on New Zealand White rabbits (NZW) performance, physiological homeostasis, hemato-biochemical indices and stabilized DNA structure resembling in 8-hydroxy-2-deoxyguanosine (8OH2dG) level. For this purpose, four groups (each one compromise of 6 animals) of weaned NZW rabbits aged four weeks were randomly divided as follows: The 1st group preserved as normal control (C) treated with tap water; 2nd group (OXY) treated with daily oral dose of Oxytetracycline 200 mg/kg BW/day; 3rd group (PPE) treated with daily oral dose of 130 mg/kg BW/day of PPE; 4th group OXY + PPE treated with daily oral dose of 100 mg/kg BW/day of OXY + 65 mg/kg BW/day of PPE. The experiment lasted for 8 weeks. Concerning growth parameters, results showed that treatment with PPE and its combination with OXY enhanced body weight and ameliorate the negative effect on liver and kidney function with minimal side effects. In addition, PPE elevate antioxidant parameters. However, OXY decreases the growth parameters (live body weight and body weight gain), total protein, albumin, globulin and A/G ratio levels and induces markedly increases in AST, ALT, creatinine, cortisol, and liver 8OH2dG concentrations. In conclusion, present study aimed to investigate the common side effects of oxytetracycline when compared with natural pomegranate peel extract and suggests that PPE and its combination with OXY at half dose of each ameliorate side effects of oxytetracycline, accelerate body weight and normalize physiological homeostasis.

Keywords: Pomegranate peel extract, Oxytetracycline, Antioxidants, New Zealand White rabbits.

Introduction

Oxytetracycline (OXY) is a type of antibiotic called a tetracycline which commonly used as antibiotic for the treatment of Anthrax, Chlamydia, Cholera, Lyme disease, Typhus, Relapsing Fever, Tularemia, Malaria, Plaque, Syphilis, Respiratory infection, Mycoplasma, Rickettsiae, Streptococcal infection and Acne¹. High doses of OXY are generally regarded as toxic; they produce a fairly large number of adverse effects, some of which can be life threatening (Brunton *et al.*, 2005). Several lines of evidence show that OXY produces severe microvesicular steatosis of the liver in human and it has been reported that excessive dose of OXY produce hepatic damage (Saraswat *et al.*, 1997). Oxytetracycline works by interfering with the ability of bacteria to produce essential proteins. Without these proteins, the bacteria cannot grow, multiply and increase in numbers. Oxytetracycline therefore stops the spread of the infection and the remaining bacteria are killed by the immune system or eventually die. Oxytetracycline is also used to treat flare-ups of chronic bronchitis, due to its activity against the bacteria usually responsible, Haemophilus influenzae (Kahsay *et al.*, 2013).

The pomegranate (*Punica granatum*), is used in several systems of medicine for a variety of ailments. The synergistic action of the pomegranate constituents appears to be superior to that of single constituents. In the past decade, numerous studies on the antioxidant, anticarcinogenic, and anti-inflammatory properties of pomegranate constituents have been published, focusing on treatment and prevention of cancer, cardiovascular disease, diabetes, dental conditions, erectile dysfunction, bacterial infections and antibiotic resistance, and ultraviolet radiation-induced skin damage. Other potential applications include infant brain ischemia, male infertility, Alzheimer's disease, arthritis, and obesity (Julie Jurenka, 2008). Negi *et al.* (2013) and Imbabi *et al.*, (2021)

showed that the pomegranate peel extracts have both antioxidant and antimutagenic properties and may be exploited as bio preservatives in food applications and nutraceuticals. Pomegranate peel extract contains substantial amounts of polyphenols such as tannins, ellagic acid and gallic acid. It has been used in preparation of tinctures, cosmetics, therapeutic formulae and food recipes (Nasr *et al.*, 1996). Guo *et al.* (2003) found that pomegranate peel had highest antioxidant activity among the peel, pulp and seed fractions of 28 kinds of fruits commonly consumed in China.

The aims of present study were to investigate the common side effects of oxytetracycline (OXY) in comparing with natural remedy pomegranate peel extract (PPE).

Materials and methods

1. Experimental animals and management:

A total of twenty-four weaned NZW were used in this study. Rabbits were obtained from a local farm (Nahya), Egypt. This study was carried out in summer during the period from 01/06/2018 to 30/07/2018. Rabbits were supplied with adequate standard diet pellets purchased from IBEX company and water provided *ad libitum*. After adaptation period (3 days), the experimental treatment started directly with animals aged about 32 days with average body weight of 500 ± 25g. Animals were housed in cages with wire-mesh bases constructed of galvanized steel. Dimensions of cages were 60 × 40 × 40 cm. All animals were housed in a room with controlled lighting (14 h/day), ambient temperature ranged from 16 to 20°C, relative humidity from 55 to 65% and natural ventilation. These animals were supplied with adequate standard diet pellets ingredient composition designed from Nutrition Requirement Center (N. R. C. 1998). The animals were randomly divided into four groups each one comprise 6 animals. The 1st group of rabbit served as normal control

(C) treated with tap water; 2nd group (OXY) treated with daily oral dose of oxytetracycline 200 mg/kg BW/day; 3rd group (PPE) treated with daily oral dose of 130 mg/kg BW/day of PPE **Parmar and Kar (2008)**; 4th group (OXY + PPE) treated with daily oral dose of 100 mg/kg BW/day of OXY + PPE (65 mg/kg BW/day). The experiment lasted for 8 weeks, and treatments were done at the 1st three days of the eight spontaneous weeks.

3.2. Pomegranate (*Punica granatum*) peel extract:

Pomegranates were obtained from local market and authenticated before extracted in the Department of Botany, Faculty of Agriculture at Moshtohor, Benha University. The peels were air dried and milled using a laboratory mill to pass a 1.0 mm-size, and then dried again in a cabinet oven with air circulation at 60°C for 16h then kept in refrigerator prior to extraction. PP was extracted according to the method of **(Panovska et al., 2005)**. Briefly, 1.5 kg of dry powder was extracted with 15L of ethanol 70% in a screw-capped flask and shaken at room temperature for 24 h. The extracts were centrifuged at 5000 rpm for 10 min while the residue was re-extracted under the same conditions twice and filtered through funnel with filter paper (Whatman No.1). The extract concentrated under reduced pressure to obtain dried powders and stored at 4 - 20°C until use.

3.3. Drugs:

3.3.1. Oxytetracycline:

Oxytetracycline was purchased from Adwia Pharmaceuticals, Cairo, Egypt. All chemicals and kits used in this study were analytical grade. Rabbits were orally received oxytetracycline at a dose of 200 mg/kg body weight according to **(Jayanthi and Subash, 2010)**.

3.4. The studied traits:

3.4.1. Growth performance:

The initial body weight (BW) was measured for each rabbit in different groups after the adaptation period (at 32 days of age) and every two weeks throughout the experimental period to calculate the average daily weight gain.

3.4.2. Hematological and biochemical parameters:

Venous blood samples from individual animals in each group were withdrawn from the marginal ear vein which visualized and dilated by a warm-wash cloth before sampling. The samples were taken using gauge butterfly catheter according to **(Moore, 2000)**. Blood samples were withdrawn from each animal group at the end of treatment (at 92 days of age). Serum was separated and kept at -20°C in Eppendorf test-tubes until subsequent analysis according

to **(Svobodová et al., 1991)**. Hemoglobin was determined by spectrophotometer according to **(Drabkin and Austin, 1932)**. Serum total protein and albumin were determined according to **Gornall et al. (1949)** and **Doumas et al. (1971)** respectively. However, serum globulin was calculated by subtracting albumin values from total protein of each corresponding sample. The Albumin to Globulin ratio (A/G) was calculated by dividing A/G values. Aspartate aminotransaminase (AST) and alanine aminotransaminase (ALT) were determined calorimetrically according to the method of **(Reitman and Frankel, 1957)**. Creatinine was determined spectrophotometrically according to the method of **(Schirmeister et al., 1964)**. 8hydroxy²deoxyguanosine was determined by HPLC according to **(Abd-Elrazek and Ahmed-Farid, 2017)**.

3.4.3. Antioxidant parameters:

The thiols compounds of oxidized and reduced glutathione (GSH) were detected by High Performance Liquid Chromatography (HPLC) using the method of **(Jayatilleke and Shaw, 1993)**. Glutathione (oxidized and reduced) reference standard purchased from Sigma Chemical Co. Malondialdehyde (MDA) standard was prepared according to **(Karatepe, 2004)**. The samples were analyzed according to **(Karalas et al., 2002)**.

3.4.4. Hormones analysis:

For determination of serum cortisol by ELISA (Enzyme Linked Immunosorbant Assay), the kit was obtained from Zoetis, New Jersey, USA, all procedures were conducted according to **(Olayemi, 2007)**.

Statistical analysis:

Statistical analysis of the obtained data was performed using the General Linear Model (GLM) produced by Statistical Analysis Systems Institute **(SAS, 2004)**. Significant differences among means were evaluated using **(Duncan, 1955)**. The following linear model was applied for body weight, body weight gain and all tissue and blood parameters measured after rabbit's decapitation (MDA, GSH, 8OH2dG, AST, ALT, protein fraction, creatinine, cortisol and hemoglobin):

$Y_{ij} = \mu + \alpha_i + e_{ij}$, Y_{ij} = Observation measured, μ = Overall mean, α_i = Effect of the i^{th} treatment, e_{ij} = Experimental error assumed to be randomly distributed with $IND \approx (0, \sigma^2 e)$

Results:

Table 1. Effect of OXY compared with PPE and their combination on body weight and body weight gain of weaned New Zealand White rabbit during experimental period:

Treatment (T)	Body weight (g) after 8 weeks of treatment	Body weight gain (g/day) at 4-12 weeks
Control	1840.8 ^b	22.17 ^b
OXY	1791.5 ^b	21.27 ^b
PPE	1924.3 ^a	23.58 ^a
OXY + PPE	1994.6 ^a	24.86 ^a
MSE	25.36	0.45

- Data are expressed as Mean \pm MSE for 6 rabbits/ group.

- ^{a,b} Means having different superscript in the same column are significantly different at $P < 0.05$.

- OXY: Oxytetracycline (200 mg/kg BW/day), PPE: pomegranate peel extract (130 mg/kg BW/day), OXY + PPE: 100 mg OXY/kg BW/day + 65 mg PPE/kg BW/day.

Table 1 show the effect of OXY compared with PPE and their combination on body weight and body weight gain after 8 weeks of age. PPE and their combination with OXY enhanced significantly ($P < 0.05$)

the final rabbit body weight and the average body weight after 8 weeks of age compared with OXY and control groups. However, OXY treated group did not show any

significant changes compared with control group after 8 weeks of age for each parameter.

Table 2. Effect of OXY compared with PPE and their combination on blood biochemical and hematological parameters of weaned New Zealand White rabbit during experimental period:

Parameters	Treatment (T)				MSE
	Control	OXY	PPE	OXY + PPE	
Total protein (g/dL)	7.23	7.14	7.30	7.21	0.05
Albumin (g/dL)	4.20	4.24	4.23	4.24	0.04
Globulin (g/dL)	3.02	2.90	3.07	2.97	0.07
A/G ratio	1.40	1.47	1.39	1.45	0.04
AST (U/L)	39.97 ^b	53.21 ^a	39.97 ^b	41.28 ^b	1.17
ALT (U/L)	34.35 ^b	42.28 ^a	33.74 ^b	35.27 ^b	1.09
Hemoglobin (g/dL)	13.81 ^a	13.62 ^a	12.67 ^b	13.59 ^a	0.18
Creatinine (mg/dL)	0.75 ^b	0.87 ^a	0.76 ^b	0.75 ^b	0.02

- Data are expressed as Mean \pm MSE for 6 rabbits/ group.

- ^{a,b} Means having different superscript in the same row are significantly different at $P < 0.05$.

- OXY: Oxytetracycline (200 mg/kg BW/day), PPE: pomegranate peel extract (130 mg/kg BW/day), OXY + PPE: 100 mg OXY/kg BW/day + 65 mg PPE/kg BW/day, AST: Aspartate aminotransaminase, ALT: Alanine aminotransaminase.

The obtained results of hematological and biochemical parameters of weaned NZW rabbits are shown in Table 2. PPE and their combination with OXY show no serious variations ($P > 0.05$) in any of the estimated hematological parameters in compared with OXY group. In contrast, PPE

and their combination with OXY showed a significant decrease ($P < 0.05$) in hemoglobin, ALT, AST and creatinine concentrations in compared with OXY group. However, OXY group show no serious variations ($P > 0.05$) in any of the estimated hematological parameters in compared with control group. On the contrary, OXY showed a significant increase ($P < 0.05$) in ALT, AST and creatinine concentrations in compared with control group.

Table 3. Effect of OXY compared with PPE and their combination on different liver and kidney antioxidant parameters of weaned New Zealand White rabbit during experimental period:

Treatment (T)	Antioxidant variables			
	MDA (nmol/g) tissue	GSH (μ mol/g) tissue	8OH2dG (pg/g) tissue	Cortisol (μ g/dL)
Control	16.90 ^{ab}	4.26 ^{ab}	143.55 ^b	1.42 ^b
OXY	20.43 ^a	3.30 ^b	171.41 ^a	1.80 ^a
PPE	16.90 ^{ab}	4.96 ^a	143.27 ^b	1.62 ^{ab}
OXY + PPE	15.63 ^b	4.63 ^a	143.33 ^b	1.38 ^b
MSE	1.32	0.33	4.59	0.1

- Data are expressed as Mean \pm MSE for 6 rabbits/ group.

- ^{a,b} Means having different superscript in the same column are significantly different at $P < 0.05$.

- OXY: Oxytetracycline (200 mg/kg BW/day), PPE: pomegranate peel extract (130 mg/kg BW/day), OXY + PPE: 100 mg OXY/kg BW/day + 65 mg PPE/kg BW/day, MDA: Malondialdehyde, GSH: Glutathione, 8OH2dG: 8-hydroxy-2-deoxy guanosine.

Effect of treatments administration on liver and kidney antioxidant capacity in different rabbit groups are shown in Table 3. Rabbit groups administrated by PPE and their combination with OXY showed positivity higher levels ($P < 0.05$) of GSH antioxidant compared with OXY and control groups. In turn, the level of MDA, cortisol and 8OH2dG concentrations in the tissue of respective rabbit groups administrated by OXY was markedly high ($P < 0.05$) compared with control group.

Discussion:

The results indicate that OXY treatment decreased body weight, immunological parameters and increase oxidonitrositive parameters. Hematological results revealed reduction in oxygen carrying capacity hemoglobin and

increase hormonal stress marker (cortisol). Also, OXY decrease liver and kidney function. These results reflect the hepatic damage caused by OXY treatment. The increase in serum AST levels mirrors the injury of cell membrane and leakage of cytoplasmic enzymes to the blood (Janbaz *et al.*, 2004). Moreover, the reduction in serum albumin and total protein concentrations indicates failure of protein synthesis by hepatocytes (Zimmerman, and Seeff, 1970). These functional alterations were long-established histopathologically. The hepatic structural changes prompted by OXY were diffuse hepatocytic vacuolation, mononuclear cell infiltrates in portal areas and hepatic necrosis. OXY induced hepatic damage may be due to inhibition of β oxidation of free fatty acids and lipoprotein secretion in liver and increased cholesterol and triglyceride biosynthesis (Ibrahim and Abdel-Daim, 2015). Neither antibiotics nor OXY produced a clinical evidence of toxicity in rats.

Pomegranate peel extract (PPE) treatment appeared to be beneficial in weaned rabbit's terms of accelerated body

weight, average body weight, immunological parameters, and increase oxidonitrositive parameters. Also, reduced liver and kidney alteration accelerated by OXY. The consumption of PP under hot conditions helps the animal to improve body weight and decrease oxidative stress through antioxidant properties of pomegranate peel. Digestive disorders of weaned rabbits were prevented by pomegranate peel, moreover severity of diarrhea was not observed by pomegranate peel inclusion in the experiment (Zeweil *et al.*, 2016 and Imbabi *et al.*, 2021). The protective effect of PPE in recovering the induced reduction in hepatic function in the current study is indicated by the significant reduction in ALT and AST activities. PPE decreased 8OH2dG concentration which is due to reduce the RNA-damaging effect of doxorubicin, H₂O₂ and spermine (Fimognari *et al.*, 2008). The mechanism of anticholinesterase activity of PPE may be due to antioxidant power of its bioactive compounds such as flavonoids (Amri *et al.*, 2017). The main aim of this stud was to evaluate the protective effects of PPE against OXY side effects in weaned male rabbits. These protective effects might depend on decreased MDA levels and increase endogenous antioxidant activity, which implied anti-oxygenation activity may be the possible mechanism of PPE in liver and kidney (Wei *et al.*, 2015). The increased levels of aminotransferase are the results of leakage from damaged hepatic cells and are used as markers of liver injury. These results provided evidence that the PPE able to improve hepatic-steatosis in rabbits.

Conclusion

In conclusion, present study suggests that PPE and its combination with OXY at half dose of each ameliorate side effects of oxytetracycline on liver and kidney functions, accelerate body weight and normalize physiological homeostasis.

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تأثير مستخلص قشر الرمان مقارنةً بالأوكسي تتراسيكلين والخليط بينهما على أداء النمو والإتزان الفسيولوجي في الأرناب

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أجريت الدراسة لمعرفة تأثير مستخلص قشر الرمان مقارنةً بالمضاد الحيوي أوكسي تتراسيكلين والخليط بينهما على أداء الأرناب البيضاء النيوزيلندية، ودراسة تأثيرهما على الإتزان الفسيولوجي، والمؤشرات البيوكيميائية وتأثيرهما على خلايا الكبد والكلية ووظائفهما. ولهذا الغرض، تم تقسيم الأرناب إلى أربعة مجموعات (كل منها يحتوي على 6 حيوانات) ويبلغ عمرها حوالي أربعة أسابيع وقسمت عشوائياً كالتالي: المجموعة الأولى (كنترول) غُذيت على علف قياسي + ماء بدون أية معاملات، المجموعة الثانية: (أوكسي) غُذيت على علف قياسي + أوكسي تتراسيكلين (200 ملجم/ كجم وزن جسم) يومياً، المجموعة الثالثة: (مستخلص قشر الرمان) غُذيت على علف قياسي + مستخلص قشر الرمان (130 ملجم/ كجم وزن جسم) يومياً، المجموعة الرابعة: (أوكسي + مستخلص قشر الرمان) غُذيت على علف قياسي + نصف الكمية من الأوكسي تتراسيكلين ومستخلص قشر الرمان 100 ملجم أوكسي تتراسيكلين/ كجم وزن جسم + 65 ملجم مستخلص قشر الرمان/ كجم وزن جسم يومياً. أظهرت النتائج زيادة في مقاييس النمو عند المعاملة بمستخلص قشر الرمان وبدائله مع الأوكسي تتراسيكلين حيث أدت لزيادة وزن الجسم وتحسين وظائف الكبد والكلية مع خفض الآثار الجانبية للمضاد الحيوي إلى الحد الأدنى. كما أظهرت المعاملة بمستخلص قشر الرمان إلى زيادة تركيز مضادات الأكسدة. وعلى العكس، أدت المعاملة بالأوكسي تتراسيكلين إلى انخفاض معدلات النمو (الوزن الحي وزيادة وزن الجسم)، البروتين الكلي، الألبومين، الجلوبيولين ومعدل الألبومين/الجلوبيولين وأدى أيضاً لارتفاع تركيزات AST، ALT، الكرياتينين، الكورتيزول، وزيادة معدل تكسير الـ DNA في الكبد بشكل ملحوظ.

الخلاصة، من خلال نتائج الدراسة نستنتج أن مستخلص قشر الرمان وبدائله مع المضاد الحيوي أوكسي تتراسيكلين يقلل من الآثار الجانبية للأوكسي تتراسيكلين على وظائف الكبد والكلية ويعيد الإتزان الفسيولوجي مما يعود بالكفاءة على الأداء الإنتاجي والفسيولوجي للأرناب.

الكلمات الدالة: مستخلص قشر الرمان، أوكسي تتراسيكلين، المضادات الحيوية، الأرناب البيضاء النيوزيلندية.