

The Promotive Effects of *Punica granatum* Seed Extract on Hematological, Cardiovascular, and Reproductive Biomarkers in Rabbits

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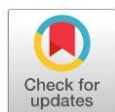
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ABSTRACT

Objective: Pomegranate seeds, which constitute approximately 3% of the fresh fruit, are a by-product of pomegranate juice. They contain significant levels of essential minerals (Zn, Na, Fe, Mn, Cu, and Se) and vitamins (A, B1, B2, C, and E). Beside they are rich in crude protein and crude fat. However, during the production of this fruit juice they are often discarded as waste. This research aimed to investigate the effect of *Punica granatum* seed extract on hematological parameters, cardiac enzymes and reproductive hormone levels in rabbits. Also, the promotive role in enhancement of sex hormone in local rabbit breeds was investigated.

Methods: The experiment was conducted over March 11 – May 1, 2024 at the Faculty of Medical Laboratory Technique, University of Al-Zahrawi, Karbala, Iraq. During the experiment, male rabbits were employed. Totally ten adult male rabbits were randomly assigned into two equal groups, each consisting of five animals. They were housed in cages under same condition. Group-1 served as control and treated with ad libitum access to water and standard diet. Group-2 was treated with extract of *Punica granatum* (pomegranate) seeds. The statistical analysis of the data of the experiment was measured by using the Using T-test for experiment using IBM SPSS program ($p < 0.05$).

Results: Treatment with pomegranate seed extract significantly enhanced several hematological and hormonal parameters ($p < 0.05$), including elevated counts of white blood cells, red blood cells, packed cell volume, and platelet, as well as increased concentrations of key reproductive hormones compared to the control group. In contrast, it was observed that the treatment of *Punica granatum* seed extract significant decrease the concentration of cardiac injury biomarkers (troponin and creatine phosphokinase), whereas hemoglobin levels remained unaffected.

Conclusion: The findings suggest that pomegranate seed extract can promote the production of red blood cells and platelets and help hematopoiesis. Pomegranate seed extract helps strengthen the heart muscle and reduce the level of specific cardiac enzymes. It also contributed to raising the levels of progesterone, estradiol, and the hormones FSH and LH.

Keywords: Cardiac biomarkers, hematological parameters, *Punica granatum*, rabbit, reproductive hormones

1. INTRODUCTION

Punica granatum L. has received increasing attention in recent years due to its diverse nutritional spectrum and its pronounced antioxidant properties [1,2]. *Punica granatum* based products are widely used in the pharmaceutical and cosmetic fields. Because of its rich content regarding vitamins, polyphenols, and bioactive compounds such as punicalic acid [3–5]. For instance, punicalic acid which is a unique conjugated polyunsaturated fatty acid which acid plays a role in a variety of physiological functions. It is often used as a by-product of juice processing and is widely used in syrups, health products and processed foods [6,7].

Pomegranate seeds are a valuable source of anthocyanins, tannins, flavonoids, fatty acids and sterols [8, 9]. Pomegranate (*Punica granatum*) is considered to be one of the most extensively studied medicinal plants, and its rich phytochemical components. Therefore, it was attracted great attention from researchers. Special attention is paid to such compounds as ellagotannins, flavonoids and anthocyanins, which have pronounced biological activity [10,11]. Pomegranate and products based on it are valued not only for their nutritional value. A number of studies have shown that they have a wide range of pharmacological properties. Among the identified effects are anxiolytic, cardioprotective, antidepressant, hypoglycemic, hypolipidemic, as well as antiviral, antibacterial, antioxidant, anti-inflammatory and even antitumor effects [12–17]. Such effects are largely explained by the presence of biologically active substances in the composition of pomegranate. In particular, an important role is played by vitamin C, quercetin, β -glucan and polyphenols, which are involved in the regulation of many physiological processes [18,19]. Experimental results confirm the positive effect of pomegranate seed extracts (PS) on blood parameters in local breeds of male rabbits [20]. Additionally, an increase in serum protein levels of rats was reported [21]. In another study, the effects of *Punica granatum* extract on blood parameters, coagulation and platelet activity in healthy white rabbits was investigated and they reported that the extract increased erythrocyte and hemoglobin levels, slowed coagulation and reduced platelet aggregation. These findings point to pomegranate's hematopoietic and cardioprotective effects [13]. Numerous studies demonstrated the positive effects of pomegranate and its derivatives on the cardiovascular system, particularly in improving the function of platelets, endothelial cells, and macrophages [22]. Esmailzadeh et al. [23] noted that *Punica granatum* L. (pomegranate) has the ability to lower blood lipids, thereby helping to prevent cardiovascular and other chronic diseases. DiSilvestro et al. [24] demonstrated that pomegranate extract contributes to a reduction in arterial pressure and affects the vascular response to various catecholamines. Furthermore, Nigris et al. [25] highlighted the promising properties of pomegranate juice in reducing the risk of coronary heart disease, atherosclerosis and vascular disorders. Its intake may have anti-atherosclerotic effects in humans, mainly due to its significant antioxidant properties, which help protect blood vessels from oxidative damage [26].

The aim of this study was to investigate the effects of pomegranate seed extract on hematological parameters, cardiac biomarkers, and reproductive hormone levels in rabbits, with a particular focus on its possible role in promoting reproductive function in local breed animals.

2. MATERIALS AND METHODS

2.1. Ethical Approval

This study was approved by the Local Ethics Committee of the Faculty of Veterinary Medicine (Approval number: UOK.VET.2024.088). The experiment was conducted between March 11 and May 1, 2024 at the Faculty of Medical Laboratory Techniques, Al-Zahrawi University, Iraq.

2.2. Experimental Animals and Experimental Design

All animals were housed in individual cages under similar environmental conditions and given ad libitum access to standard commercial pelleted feed and clean tap water for the duration of the experiment. Before starting the experiment, all rabbits were examined for injuries, deformities or signs of disease. Only healthy animals were included in the study. A total of 10 healthy adult male rabbits (domestic cross breed; weighing 1-1.5 kg, 6-11 months of age) were randomly divided into two equal groups (n=5):

Group 1 (Control): Fed only with standard pellet feed and clean tap water.

Group 2 (Treatment): In addition to standard feed and water, an aqueous extract of *Punica granatum* seeds (1kg/10L) administered by gavage at a rate of 1 ml per day for 50 days.

2.3. Preparation of Aqueous Extract of *Punica granatum* Seeds

The aqueous extract of *Punica granatum* seeds was prepared adapted from previous study [27]. The method used is as follows:

1. One kilogram of *Punica granatum* seeds powder was weighed and added to 10 liters of distilled water (1:10 ratio). The mixture was allowed to stand for 72 hours using cold extraction (infusion method).
2. The mixture was then stirred thoroughly for 4 hours on a hot plate at 25-30 °C using a magnetic stirrer.
3. The mixture was filtered using Whatman No.1 filter paper.
4. The solvent was removed from the resulting filtrate using a rotary evaporator. Thus, a completely soluble herbal product with a dark brown-black color and dense consistency was obtained.
5. The resulting plant extract was weighed, divided into portions and placed in dark glass bottles and hermetically sealed. Stored at 4 °C.
6. The extract was used within a maximum of three months from the date of preparation.

2.4. Blood Sampling Procedure

Blood collection was performed as previously described by Mahdi et al. [28], following the protocol approved by the Local Ethics Committee of the Faculty of Veterinary Medicine. At the end of the experiment, 3 ml of blood was collected directly from the heart of each rabbit under light anesthesia.

Blood samples for hematologic analyses were collected in tubes containing anticoagulant. For biochemical analyses, blood samples were collected in gel tubes without anticoagulant, centrifuged at 3000 rpm for 20 minutes, serum was separated and used in laboratory tests.

2.5. Complete blood count (CBC) analysis

The measurement was carried out automatically after a blood sample was collected and put into the URIT-2900 apparatus.

2.6. Troponin and Creatine Phosphokinase Analysis

The serum sample for the determination of troponin and creatine phosphokinase levels was placed in a DC-40 Mindray device (Mindray Medical, Shenzhen, China) and measurements were performed automatically.

2.7. Estradiol (E2), Progesterone, Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) Analysis

After serum samples were collected, they were placed in a DC-40 Mindray device (Mindray Medical, Shenzhen, China) and hormone levels were measured automatically.

2.8. Statistical Analysis

The data obtained from the experiment were analyzed using SPSS 20.0. The normality of the data distribution was assessed using the Shapiro-Wilk test. The statistical analysis of the data of the experiment was measured by using the Using T-test for experiment using IBM SPSS program ($p < 0.05$).

3. RESULTS

In the group treated with *Punica granatum* extract, significant increases were observed in all hematologic parameters except hemoglobin (Hb) level compared to the control group (Table 1). In the treatment group, erythrocyte (RBC) count, leukocyte (WBC) count, hematocrit (PCV) ratio and platelet count increased statistically significantly ($p < 0.05$). On the other hand, there was no significant difference in hemoglobin level between the two groups. These findings suggest that *Punica granatum* extract may have supportive effects on the hematologic system and promote blood cell production.

Table 1. The Effect of *Punica granatum* seed extract on hematologic parameters (n=5)

Parameter	Control group Mean ± SE	Treated group Mean ± SE	p-value
RBCs count (cell/mL*10 ⁶)	4.96 ± 0.27 ^b	5.82 ± 0.11 ^a	0.031
WBCs count (cell/mL*10 ³)	3.90 ± 0.43 ^b	6.61 ± 0.09 ^a	0.001
Hemoglobin (Hb) (g/dl)	11.97 ± 0.59 ^a	13.10 ± 0.38 ^a	0.53
Packed Cell Volume PCV (%)	38.34 ± 0.43 ^b	42.50 ± 1.61 ^a	0.04
Platelet count (103/μL)	127.37 ± 26.79 ^b	288.17 ± 16.92 ^a	0.0009

Uppercase letters denote significant differences between treatment groups for each measured parameter

Punica granatum extract administration led to significant decreases in some biochemical parameters related to cardiac function (Table 2). In the treatment group, troponin and creatine phosphokinase (CPK) levels were significantly decreased compared to the control group ($p < 0.05$). These decreases suggest that *Punica granatum* extract may reduce the damage that may occur in heart cells and may have a cardioprotective effect.

Table 2. The Effect of *Punica granatum* seed extract on biochemical parameters related to heart function) (n=5)

Parameter	Control group Mean ± SE	Treated group Mean ± SE	p-value
Troponin concentration (ng/L)	19.09 ± 5.51 ^a	5.82 ± 1.40 ^b	0.03
Creatine phosphokinase (U/L)	461.2 ± 32.78 ^a	267.6 ± 21.44 ^b	0.001

Uppercase letters denote significant differences between treatment groups for each measured parameter

Significant increases were observed in all reproductive hormones in the *Punica granatum* extract treated group compared to the control group (Table 3). Estradiol (E2), progesterone, follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels were significantly increased in the treatment group ($p < 0.05$). These findings suggest that *Punica granatum* extract may increase the release of reproductive hormones by stimulating the endocrine system and may potentially contribute positively to fertility.

Table 3. The Effect of *Punica granatum* seed extract on reproductive hormones (n=5)

Parameter	Control group Mean ± SE	Treated group Mean ± SE	p-value
Estradiol (E2) (pg/mL)	12.20 ± 0.86 ^b	30.62 ± 2.42 ^a	0.042
Progesterone (ng/mL)	0.26 ± 0.05 ^b	2.04 ± 0.60 ^a	0.045
Follicle Stimulating Hormone (IU/L)	0.68 ± 0.07 ^b	1.40 ± 0.20 ^a	0.033
Luteinizing Hormone (IU/mL)	0.72 ± 0.09 ^b	1.60 ± 0.15 ^a	0.006

Uppercase letters denote significant differences between treatment groups for each measured parameter

4. DISCUSSION

Blood parameters in rabbits can be affected by many factors such as diet, environmental conditions, disease status, housing density and exposure to environmental pollutants [29]. In this study, red blood cell count, hemoglobin level and hematocrit ratio increased significantly in the group given pomegranate extract. These findings suggest that pomegranate seed extract could enhance red blood cell formation or protect them from the destruction which was induced by oxidative stress.

Hemoglobin and red blood cells are essential for carrying oxygen from the lungs to body tissues. Plants rich in polyphenols are known to help strengthen red blood cells. Since they make them more resilient to oxidative stress [30]. The polyphenols, vitamins, minerals, and antioxidants in pomegranate seed extract may contribute to its protective effects. Because, these components are also reported to boost immunity and promote the production of white blood cells [31]. The results of our study align with those of Abatenh et al. [32] and Jadoh [1820]. They also observed an increase in leukocyte counts in rabbits fed a diet containing pomegranate extract.

Consumption of pomegranate juice was shown to boost antioxidant capacity in red blood cells and protect hemoglobin from oxidation [33,34]. Similarly, hemoglobin and hematocrit levels were increased in this study. This could be linked to the antioxidants in pomegranate seed extract. Since, they contribute to reduce red blood cell breakdown.

Numerous studies have demonstrated the antioxidant and protective effects of pomegranate and its components on the cardiovascular system. These effects include reducing oxidative stress and improving the functions of macrophages, endothelial cells and platelets [4]. In this study, pomegranate seed extract reduced troponin and creatine phosphokinase levels, consistent with findings reported by Kabir et al. [35]. Various parts of the pomegranate—like the peel, seeds, root, and rind—have shown different pharmacological effects in studies. While the fruit is generally safe, the root and rind could have toxic alkaloids [36]. Properly prepared and carefully dosed pomegranate seed extracts may help promote heart health.

In the present study, rabbits treated with PS showed significant increases in serum FSH and LH levels. This response may be associated with the flavonoids in PS. Because they are believed to stimulate steroid hormone production [37,38]. One study suggested that flavonoids could lead to increased levels of LH and FSH by regulating GnRH secretion [39]. Pomegranate is a rich source of antioxidants like tannins, phenols, and flavonoids, which may support FSH production by reducing oxidative stress [40]. Additionally, pomegranate may help lower stress hormone levels and potentially enhance LH production by affecting hormone release in the hypothalamus [41]. These findings support the common belief that pomegranate consumption is associated with enhanced fertility.

5. CONCLUSION

This study showed that pomegranate seed extract positively impacted blood, heart, and hormone markers in male rabbits. The extract group had higher red and white blood cell counts, hematocrit, and platelets, along with lower troponin and CPK levels. The levels of hormones such as estradiol, progesterone, FSH and LH also increased significantly, however, hemoglobin levels remained unchanged. These findings suggest that pomegranate seed extract may have blood-promoting, heart-protective and some reproductive hormone-enhancing effects. However, new studies with larger sample groups are needed to reveal the mechanism of these effects more clearly. In addition, issues such as dose-response relationship, effects in different animal species, long-term safety, bioavailability and standardization of the extract should be investigated in detail.

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Conflicts of Interest: The authors declare that there are no conflicts of interest related to this study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement: The study was approved by the Local Ethics Committee of the Faculty of Veterinary Medicine (Approval No: UOK.VET.2024.088).

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