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Research Paper

Investigation of the Potential of Thymex Plus in Hematological and Platelet Modulation in Myocardial Infarction Rats

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ABSTRACT

Background: Myocardial infarction (MI) is a common cardiovascular disease (CVD) caused by an imbalance between the high demand for blood and the heart's ability to supply it. For the first time, the present study investigated the effects of Thymex Plus (TYM), a herbal medication containing thymol extract and honey, on platelet-related indices, red cell distribution width (RDW) to platelet counts (PLT) ratio, and hemogram changes induced by isoproterenol (ISO) in a rat model .

Methods: : A total of 18 male Wistar rats were divided into three groups for the study. (I) Control, with no intervention; (II) ISO + Saline, receiving ISO (85 mg/kg, s.c.) on days 1 and 2, followed by 1.5 mL normal saline (oral) on days 3–7; and (III) ISO + TYM, receiving ISO (85 mg/kg, s.c.) on days 1 and 2, followed by 1.5 mL TYM (oral) on days 3–7. After the treatment period, blood samples were collected to evaluate hemogram parameters, including hemoglobin (Hb), hematocrit (HCT), red blood cell (RBC) and reticulocyte counts, RBC indices, PLT, and RDW-to-PLT ratio (RPR).

Results: In the ISO group, Hb, HCT, RBC, PLT, and reticulocyte counts significantly decreased ($p<0.05$). The ISO-TYM group showed a non-significant increase in Hb and HCT, while PLT and mean corpuscular hemoglobin concentration (MCHC) levels increased significantly ($p<0.05$). The RDW percentage and RPR ratio rose considerably in the ISO group ($p<0.05$), and TYM treatment substantially reduced these parameters ($p<0.05$).

Conclusion: The TYM demonstrated significant protective effects in hemogram indices, such as PLT, RDW, RDW to PLT ratio, and reticulocyte count on ISO-induced MI in rats. These effects included improvements. The results of the present study enhanced the potential of TYM as a compound with hematological modulating capabilities. However, to clarify the precise mechanisms of these effects, further studies are recommended.

Keywords: Blood Platelets, Honey, Isoproterenol (ISO), Rats, Red Cell Distribution Width, Thymol, Wistar

Introduction

Myocardial infarction (MI) is a cardiovascular disease (CVD) that is an imbalance between myocardial oxygen demand and coronary blood supply. This disproportion contributes to the destruction of the myocardial tissue and the eventual destruction of cardiomyocytes, which together result in death [1]. Therefore, MI is recognized as one of the serious diseases and a potential cause for a high number of deaths across several countries [2]. Myocardial oxidative stress (OS) is associated with endothelial dysfunction, inflammation, and an imbalance in antioxidants, leading to impaired cardiac function. Inflammation and OS contribute to apoptosis, making them vital factors in the development of MI [3]. Excessive production of myocardial adrenergic receptors leads to inflammation of the heart muscle and the death of heart cells (myocytes). During this process, the levels of cyclic adenosine monophosphate (cAMP) rise, activating protein kinase A. As a consequence of this activation, L-type calcium channels are phosphorylated, which eventually increases and leads to the occurrence and development of MI [4]. Some mechanisms in the pathogenesis of MI include OS, apoptosis, and inflammation. The negative impact of OS on cardiac function occurs through decreased activity of antioxidant enzymes, such as catalase, superoxide dismutase, and glutathione peroxidase. Reactive oxygen species (ROS) induce lipid peroxidation, which generates malondialdehyde, as

well as the elution of pro-apoptotic toxins onto the mitochondrial membrane [5]. Heart failure includes various complex clinical syndromes resulting from abnormal alterations in cardiac structure and/or function, which lead to dysfunction of either ventricular systolic or diastolic function [6]. The main symptoms include dyspnea, fatigue, and fluid retention, such as pulmonary congestion, systemic blood stasis, and peripheral edema [7]. The OS and inflammation increase in chronic heart failure. Dysfunction of cardiac mitochondria is an indicator of heart failure and one of the leading causes of OS. It negatively impacts cellular components, including the mitochondria, creating a vicious cycle [8,9]. A complete blood count is a commonly used laboratory test that includes a white blood cell (WBC) count, red blood cell (RBC) count, platelet count (PLT), and morphological indices, like red cell distribution width (RDW) [10]. It was stated that inflammatory processes and activation of neurohormonal and adrenergic systems profoundly affect erythrocyte maturation due to disturbances in erythrocyte membrane homeostasis, which increases the levels of RDW [11].

The RDW is a quantitative measure that indicates the variation in the volume of erythroid cells and is typically used in hematology to assist in diagnosing anemia [12]. Population-based studies suggest that RDW can predict mortality in CVDs and other acute or chronic conditions, like MI and heart failure [13,14]. Platelets play a crucial role in the pathophysiology of MI, as they activate endothelial cells and promote fibrin formation, ultimately leading to the formation of a thrombus within the coronary vasculature. They are involved in thrombogenesis and release mediators that amplify local inflammation. Additionally, platelet count has been linked to the severity of MI, as well as to increased risks of death and reinfarction [15-17]. The RDW-to-PLT ratio (RPR) combines two independent parameters and is a new index that reflects the severity of inflammation [18]. RPR has been established as a reliable prognostic marker in CVDs [19]. Iron deficiency anemia is a common complication in chronic diseases [20]. Anemia is a significant comorbidity in heart failure, impairing exercise tolerance, lowering quality of life, and contributing to worse clinical outcomes. Iron deficiency is considered a primary cause of anemia, as iron is crucial for optimal hematopoiesis (blood cell production) [21]. Erythroblasts and reticulocytes are the main contributors to hemoglobin (Hb) synthesis [22]. Iron deficiency causes resistance to hematopoietic growth factors, including erythropoietin, and interferes with the differentiation and maturation of all types of hematopoietic cells [23]. Isoproterenol (ISO) is a synthetic catecholamine and ß-adrenergic agonist that is commonly used for the management of bronchial asthma, allergic emergencies, ventricular bradycardia, status asthmaticus, cardiac arrest, and in glaucoma [24]. High ISO concentrations produce cytotoxic reactive free radicals during autoxidation, which injure and necrose cardiac muscle [25]. Subcutaneous ISO injection is commonly used in studies of MI to explore the cardioprotective effects of natural and synthetic agents. The ISO induces lesions in rat hearts, serving as a reliable model for studying heart attacks in humans [26]. The β-adrenoreceptors found in reticulocytes and mature erythrocytes are of the β2 subtype. ISO significantly enhances adenylate cyclase activity in reticulocytes, increasing the synthesis of cAMP. Reticulocytes are more sensitive to ISO than mature erythrocytes, showing a 6 to 9-fold increase in adenylate cyclase activity. As these cells mature into erythrocytes, they become unable to generate cAMP in response to ISO, despite the presence of β-adrenergic receptors, indicating a functional uncoupling of the receptor from the enzyme during erythroid maturation [27,28].

The individual ingredients of Thymex have been well established to have antioxidant and anti-inflammatory activities. So far, the synergistic effect of these ingredients, in relation to MI, has not been thoroughly investigated. The synergistic antioxidant action of thymol and honey, with anti-inflammatory and wound-healing effects, could represent a novel approach to regulating hematological variables in CVDs. According to recent studies, the combined effects of thymol and honey may enhance cardioprotection by reducing OS and inflammation, both of which are major pathophysiological drivers of MI [29, 30].

The present research aimed to investigate the possible protective role of a natural combination, Thymex Plus (TYM), created from thymol and honey, against blood-related alterations, such as total reticulocyte and PLT, and the RPR, in MI rats. The ISO model is considered the conventional method for inducing MI in rat models [31]. This study primarily emphasizes the hematological alterations that result from implementing this model, rather than directly assessing cardiac damage within the context of this research.

Materials and Methods

The rats used in the experiment were 18 male Wistar rats, aged 6-8 months and weighing 200-250g. They were obtained at the breeding institution in the Laboratory Animal Research Institute. Rats were maintained in the same environmental conditions in terms of temperature (20-24°C), humidity, and the light/dark cycle of 12/12 hours. These animals had free access to food and water and received regular lab animal pellets. All injections and blood sampling were performed at the same time of day (between 8:00 and 10:00 a.m.) to minimize the influence of circadian variations on hematological parameters. The rats were

randomly divided into three experimental groups (six rats per group) to acclimate them before the start of the study.

Ethical considerations

All animal procedures were performed following the institutional and national guidelines (ARRIVE guidelines) for animal care and approved by the Animal Research Ethical Committee of Semnan University of Veterinary Medicine, Iran (Ethics Code: IR.SU.REC.1402.10).

Study design

Plasma biochemical indices, including urea, uric acid, Rats were randomly divided into three groups as follows:

Group I: Control group; in this experimental group, no intervention was performed.

Group II: ISO group; the rats received subcutaneous injections of ISO (Sigma-Aldrich) at a dosage of 85 mg/kg of body weight on days 1 and 2, with a 24-hour interval (Murugesan et al., 2011). Subsequently, on days 3, 4, 5, 6, and 7, they were administered 1.5 ml of normal saline orally.

Group III: ISO and TYM Group (ISO-TYM); the rats received subcutaneous injections of ISO at a dosage of 85 mg/kg of body weight on days 1 and 2, with a 24-hour interval. Following this, on days 3, 4, 5, 6, and 7, they were orally given 1.5 mL of TYM by gavage. The TYM is formulated from thyme extract (*Thymus vulgaris*) and honey. Each 5 mL of the syrup contains approximately 1.1 mg of total phenolic compounds (calculated as thymol), 0.2 g of honey, and 653 mg of thyme extract.

Cardiac blood sampling

Animals were subjected to anesthesia through intraperitoneal administration of ketamine at a dosage of 80 mg/kg body weight, in conjunction with xylazine at a dosage of 10 mg/kg body weight. Euthanasia was confirmed by observing the cessation of both cardiac activity and respiratory movements, per ARRIVE guidelines. Blood samples were collected on day 7, immediately after the final treatment administration, under anesthesia and euthanasia procedures as described. Following this procedure, 4 ml of blood was extracted from the heart of each rat utilizing a syringe. Of the collected blood, 2 ml was placed in a clotting activator test tube, while the remaining 2 ml was placed in a test tube containing EDTA. In this study, a cell counter (Celltac α VET; MEK-6550) was utilized to measure blood cellular indices, and the test tubes containing EDTA were employed for this purpose. The clotting activator test tubes were centrifuged for 10 min at 3000 rpm (Behsan, HB-200) to measure biochemical blood indices. Afterward, the separated plasma was transferred to a microtube and stored in a freezer. Finally, biochemical indices were assessed manually using the appropriate kits.

Hematological examination

Hematological indices were measured, including Hb, WBC count, RBC count, hematocrit (HCT), PLT count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), RDW, and the RPR. Reticulocytes were manually counted on peripheral blood smears stained with new methylene blue. Their percentage per 100 RBCs was calculated, and the absolute count was determined using the formula: Absolute reticulocyte count (× 103/µL) = Reticulocyte% × RBC count (× 106/µL) × 10.

Data analysis

The selection of a sample size of six animals per group was based on findings from previous research investigating hematological alterations in rat models of MI induced by ISO [8]. A post-hoc power analysis confirmed that this sample size provided over 80% power to detect statistically significant differences in key parameters ($p<0.05$). The Shapiro-Wilk test was used to assess the normality of the data. For data that did not follow a normal distribution, group comparisons were performed using the Kruskal-Wallis test, with results reported as median and interquartile range (IQR). A p-value of less than 0.05 was considered statistically significant. All parameters passed the normality test (Shapiro-Wilk); therefore, one-way ANOVA followed by Tukey's post hoc test was employed for statistical comparison. To evaluate the robustness of our statistical findings, effect sizes (Cohen's d) were calculated for the key group comparisons. Furthermore, a post hoc power analysis was performed to evaluate the statistical power to detect moderate to significant effects based on the determined effect sizes. This analysis was based on a sample size of six rats per group.

Results

Figure 1 presents box plots of hematological parameters of three groups of the study: control, ISO, and ISO-TYM. p-values for statistical comparisons between these groups are provided above each box, indicating that the observed differences are statistically significant. Hb ($p=0.012$), RBC count ($p=0.038$), and HCT ($p=0.050$) all showed significant or borderline significant decreases in the ISO group compared to the control group. Although these values improved significantly in the TYM-treated group, none of the changes reached statistical significance compared with the ISO group. The PLT levels also dropped significantly in the ISO group compared with the control ($p=0.041$); however, TYM treatment did not result in a statistically significant recovery ($p=0.057$).

Reticulocyte count decreased significantly in the ISO group compared to the control (p=0.014), and this rise was even more pronounced in the ISO-TYM group, which demonstrated significantly higher values than both the ISO (p=0.021) and control (p=0.003) groups. The RDW and the RPR were both significantly elevated in the ISO group compared to the control (p<0.05). Treatment with TYM significantly lowered these values compared to the ISO group (p<0.05). To further evaluate these findings, the effect sizes (Cohen's d) were calculated. The post-hoc power analyses were performed for the key comparisons: ISO vs Control, with an effect size of 1.20 (large) and a power of 0.47. ISO-TYM vs ISO, with an effect size of -0.32 (small-to-negligible), with a power of 0.08. A comparison between ISO-TYM and the control has created an effect size of 1.42 (considerable effect); power was 0.60. These findings suggest that the research had sufficient power to measure large effect sizes, especially in the comparison between ISO-TYM and the control, regardless of the small sample size.

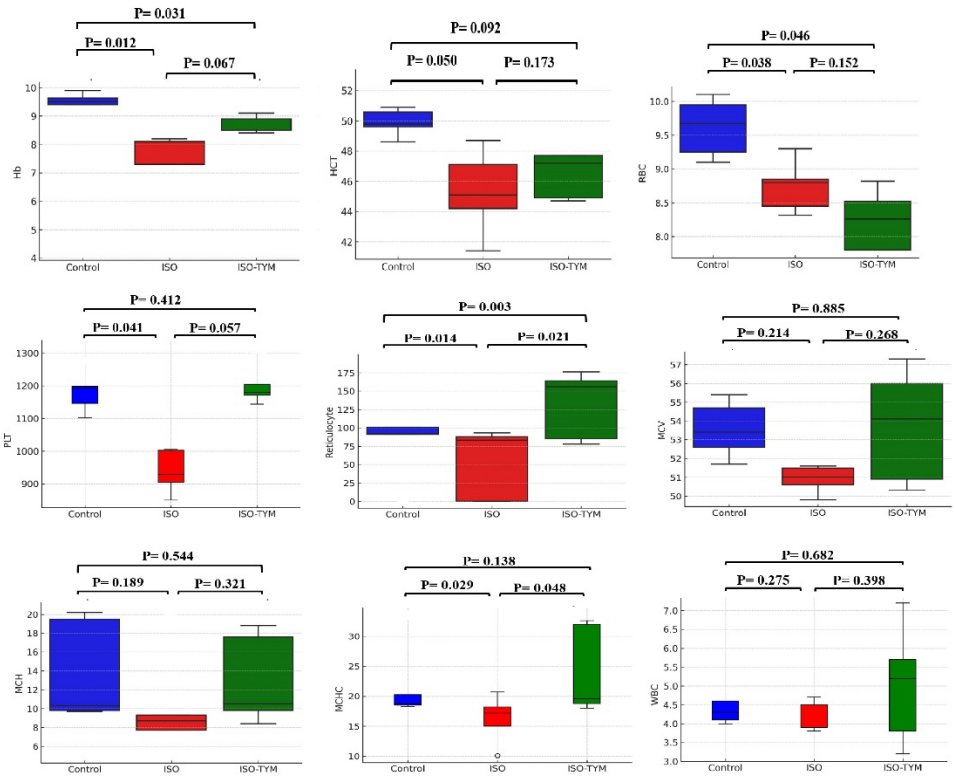

Figure 1. Box plots illustrating Hb, HCT, RBC, RET, and PLT indices, and RPR across the three study groups. In the box plot, the data points represent individual measurements, while the box indicates the interquartile range (IQR), with the median marked by the central line of the box. The p-values indicate the statistical significance of differences between groups. All parameters passed the normality test (Shapiro-Wilk); therefore, one-way ANOVA followed by Tukey's post hoc test was employed for statistical comparison.

Table1. Comparison of mean RDW and RPR across the three study groups

Group	RDW (%)		RDW/PLT	
	Mean	SD	Mean	SD
Control	11.51[b]	0.23	0.98[b]	0.05
ISO	12.10[a]	0.51	1.28[a]	0.12
ISO-TYM	11.66[b]	0.48	1.03[b]	0.19

Different superscript letters (a, b) indicate statistically significant differences between groups (p<0.05). Statistical comparisons were performed using one-way ANOVA followed by Tukey's post hoc test. Specifically, 'a' denotes a significant difference versus control, and 'b' denotes a significant difference versus the ISO group. All parameters passed the normality test (Shapiro-Wilk); therefore, one-way ANOVA followed by Tukey's post hoc test was used for statistical comparison.

Discussion

In the present study, the hematological effects of TYM, a combination of *Thymus vulgaris* and honey, were investigated in a rat model of ISO-induced MI. The findings show that TYM significantly reversed ISO-induced anemia, increasing Hb, HCT, and RBC levels, which were otherwise decreased in the rats. These results are consistent with previous studies demonstrating the protective roles of thymol and

carvacrol, major constituents of *Thymus vulgaris*, in reducing OS and inflammation, which have central effects on the pathophysiology of MI [29]. Studies on carvacrol in people with cardiac disease have reported its therapeutic benefits against MI, cardiac hypertrophy, hypertension, arrhythmias, and various cardiovascular pathologies, which are explained by its antioxidant and anti-inflammatory effects [33]. Additionally, research on the industrial dye tartrazine showed that thymol and carvacrol can prevent the production of toxins resulting from heme degradation and oxidation processes [34]. Thymol and carvacrol inhibit heme degradation and the breakdown of the porphyrin ring, thereby preserving the structure of Hb by maintaining its secondary and tertiary structures, which helps prevent oxidative damage. In the present study, TYM (containing thymol) compensated for the ISO-induced reduction in Hb, increasing Hb levels in treated rats [35]. Moreover, analysis of fish fed thymol revealed significant increases in Hb, HCT, RBC, and white blood cell counts, indicating that thymol increases blood oxygen-carrying capacity and has an immunomodulatory effect [36]. These findings align with the results obtained in the current experiment, supporting the thesis that thymol can be used to treat anemia.

The anemia induced by ISO in rats, reflected by decreases in Hb, HCT, and RBC, was improved with TYM treatment, leading to an increase in Hb and HCT, along with higher reticulocyte counts. Thymol may help reduce the adverse effects of erythrocyte damage by inhibiting OS, reducing cell volume, and preventing energy depletion that leads to RBC death. It allows thymol to prevent microcirculatory disturbances and may play a role in supporting recovery from anemia [37]. Unlike earlier studies that showed higher reticulocyte counts in anemic heart patients, reticulocytosis was not observed in the MI rats after a week. However, TYM induced reticulocytosis in group III, suggesting it could help improve hematological parameters [38]. Studies suggest that honey can also help raise Hb levels in pregnant women who lack iron, especially when combined with iron supplements [39]. Acacia honey appears to aid the body in producing more RBCs and increasing Hb levels [40]. In rats with lead-induced anemia, honey slowed the progression of anemia by increasing iron levels in the blood and stimulating the bone marrow [41]. However, a study in Pakistan found that rats fed acacia honey had lower Hb levels [42]. Nevertheless, honey's beneficial qualities suggest that it could help alleviate anemia, particularly in patients with heart conditions.

Research has demonstrated that elevated RDW is an independent predictor of poor prognosis in coronary heart disease and is associated with higher mortality in acute myocardial infarction (AMI) patients [43]. The RDW reflects inflammation, which plays a critical role in the onset and progression of AMI [44]. In this study, RDW was increased in rats with MI; however, TYM treatment significantly lowered it. Our findings revealed that TYM effectively modulates hematological parameters in a rat model of ISO-induced MI. It aligns with previous studies on thymoquinone, a key component of thymol, which have shown that it reduces OS, inflammation, and myocardial necrosis [45, 46]. Thymol enhances heart contraction by reducing OS, lowering heart rate, and protecting the myocardium. It even lowers the risk of CVDs by balancing lipids and preventing further harm to the heart. Furthermore, thymol augmented myocardial protection by inducing the expression of Bcl-2 (an antiapoptotic gene) and suppressing the expression of Bax (a pro-apoptotic gene) in rats' hearts, which could also contribute to minimizing cell apoptotic death [47]. Although the present study revealed numerous findings regarding the impact of TYM on hematological parameters in an MI model, we focused only on these parameters. Although assessment of alterations in hematological indices is informative, combining the analysis of cardiac-related biomarkers and histopathology assays may provide deeper insights into the cardioprotective effect of TYM. This exploration was limited to the changes in hematology as a preliminary circumstance of the potential of TYM. It would also be important for future research to integrate cardiac biomarkers, such as troponins and creatine kinase-MB, with histopathological analysis to assess myocardial injury, the inflammatory and repair mechanisms that follow.

Conclusions

The TYM demonstrated significant protective effects in hemogram indices, such as PLT, RDW, RPR, and reticulocyte count, on ISO-induced MI in rats. These effects included some improvements. The results of this study enhanced the potential of TYM as a compound with hematological modulating capabilities. However, to clarify the precise mechanisms of these effects, further studies are recommended.

Limitations

The present study mainly examined hematological changes induced by ISO. Direct assessments of myocardial injury, such as cardiac histopathology, measurement of cardiac biomarkers (troponins, CK-MB), and cardiac function tests, were not performed. Therefore, findings on MI and the protective effects of TYM are indirect and require further specialized cardiac studies. Although plasma samples were collected for biochemical analyses, data on OS and inflammatory markers are omitted from this report. Future research is needed to clarify the mechanistic pathways of TYM's cardioprotective effects.

Data Access and Responsibility

The authors confirm that this article contains original work and accept full responsibility for its content.

Ethical Considerations

All animal procedures were performed following the institutional and national guidelines (ARRIVE guidelines) for animal care and approved by the Animal Research Ethical Committee of Semnan University of Veterinary Medicine, Iran (Ethics Code: IR.SU.REC.1402.10).

Authors' Contributions

Mahmood Ahmadi-hamedani: Writing – original draft, Project administration, Formal analysis, Data curation, Conceptualization. Keivan Keramati: Review & editing, Project administration, Supervision, Conceptualization. Sina Adib: Methodology, Conceptualization. Leila Mohammadnezhad Nasrabadi: Methodology.

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Conflict of Interests

The authors declare that there is no conflict of interest.

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