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Research Article

Age-Related Platelet and Coagulation Dysfunction: Vitamin E and Zinc Modulation via Antioxidant Mechanism

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Abstract

Background: Age-related changes in platelet function, coagulation, and oxidative balance impair hemostasis, contributing to delayed wound healing and other age-associated disorders. Micronutrients such as Vitamin E and Zinc, with established antioxidant and modulatory properties, may counteract these effects. This study investigated the impact of Vitamin E, Zinc, and their combination on platelet function, coagulation, and oxidative stress in young and older Wistar rats.

Methods: Sixty-four male rats were assigned to young (28-day) and older (90-day) groups, each subdivided into four subgroups: control, Vitamin E (200 mg/kg/day), Zinc (10 mg/kg/day), and Vitamin E + Zinc (200 mg/kg + 10 mg/kg/day). Supplements were administered orally for 28 days. Platelet indices, aggregation, prothrombin time, bleeding time, fibrinogen, and oxidative stress markers (MDA, SOD, CAT, GPx) were assessed.

Results: Older rats exhibited reduced platelet counts and plateletcrit, but elevated MPV, PDW, platelet aggregation, prothrombin time, bleeding time, fibrinogen, and MDA, alongside decreased SOD, CAT, and GPx ($p < 0.05$), consistent with age-related hemostatic and oxidative alterations. Vitamin E, Zinc, and particularly their combination, significantly improved platelet indices, reduced aggregation, bleeding time, fibrinogen, and MDA, while enhancing antioxidant enzyme activities ($p < 0.05$). The combined supplementation produced the strongest effects, indicating synergistic antioxidant mechanisms.

Conclusion: Vitamin E and Zinc supplementation, especially in combination, mitigates age-related platelet and coagulation dysfunction via antioxidant modulations. These findings highlight their potential as adjunct pharmacological agents for maintaining hemostatic balance and reducing complications associated with aging.

Keywords: *Aging Physiology; Platelet Function; Coagulation; Vitamin E; Zinc; Antioxidant Mechanism*

Introduction

Aging is associated with progressive alterations in platelet function, coagulation parameters, and oxidative balance, which collectively impair hemostasis and increase susceptibility to age-related disorders such as delayed wound healing, cardiovascular disease, and metabolic complications [1-3]. Platelet hyperactivity, elevated prothrombotic factors, and oxidative stress are major contributors to these changes, creating a heightened risk of thrombosis and impaired vascular repair [4,5].

Micronutrients with antioxidant properties, such as Vitamin E and Zinc, have been shown to modulate platelet function and maintain redox homeostasis [6,7]. Vitamin E, a lipid-soluble antioxidant, stabilizes cellular membranes and protects against lipid peroxidation, while Zinc serves as a cofactor for antioxidant enzymes, supporting endogenous defense systems [8-11]. Their combined effects may synergistically counteract age-related hemostatic and oxidative dysfunction.

However, the role of Vitamin E and Zinc in the context of age-related platelet and coagulation dysfunction is not fully elucidated. Most available studies have evaluated these micronutrients individually, with limited evidence regarding their combined influence on hemostatic balance and oxidative stress across different stages of aging. This knowledge gap hinders the development of targeted nutritional or pharmacological strategies for mitigating age-associated hemostatic complications.

Aim of the Study

This study aimed to evaluate the effects of Vitamin E, Zinc, and their combination on platelet indices, coagulation parameters, and oxidative stress markers in young (28-day) and older (90-day) Wistar rats. Findings from this work provide mechanistic insight into how these micronutrients may preserve hemostatic integrity during aging.

Materials and Methods

Animals and experimental design

Sixty-four male Wistar rats were used in this study. Animals were divided into two age groups: young (28 days old) and older (90 days old). Each age group was further subdivided into four subgroups (n = 8 per subgroup): Control, Vitamin E, Zinc, and Vitamin E + Zinc. Rats were housed under standard laboratory conditions (12h light/dark cycle, temperature 22 ± 2°C) with free access to standard feed and water. Experimental procedures conformed to the Guide for the Care and Use of Laboratory Animals and the Declaration of Helsinki (Helsinki, 2008). All efforts were made to minimize pain, stress, and suffering of animals.

Supplementation protocol

Zinc supplement was freshly prepared in distilled water each day and administered orally at a dose of 10 mg/kg body weight/day [11]. Vitamin E was supplied in liquid form and administered orally by gavage at a dose of 200 mg/kg body weight/day [12]. Animals in the combination group (Vit E + Zn) received both supplements concurrently at the same doses. Control rats received an equivalent volume of distilled water. All treatments were administered once daily for 28 consecutive days.

Blood collection and hematological parameters

At the end of the treatment period, rats were anesthetized with ketamine (100 mg/kg), and blood was collected via cardiac puncture into EDTA tubes. Platelet indices, including platelet count, mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT), were measured using an automated hematology analyzer [13-15].

Platelet aggregation assay

Platelet aggregation was assessed using a platelet aggregometer (Chrono-log Corporation, USA). Whole blood anticoagulated with sodium citrate was centrifuged at 200 × g for 10 minutes to obtain platelet-rich plasma (PRP). Platelet-poor plasma (PPP), obtained by centrifugation at 2,000 × g for 15 minutes, served as the reference blank. Aggregation was induced in PRP using adenosine diphosphate (ADP, 10 μM) at 37°C under constant stirring. Changes in light transmission were recorded for 6 minutes, and maximum aggregation (%) was calculated relative to PPP [15].

Coagulation parameters

Coagulation function was evaluated by determining: Prothrombin time (PT), Bleeding time (BT) and Plasma fibrinogen concentration was determined as described by [15].

Oxidative stress markers

Markers of oxidative stress were measured in plasma. Malondialdehyde (MDA) levels were determined as an index of lipid peroxidation. Antioxidant enzyme activities, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), were assayed spectrophotometrically following established protocols [16].

Statistical analysis

Data were expressed as mean ± Standard Error of the Mean (SEM). Statistical analyses were performed using GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA, USA). Comparisons among groups were made using two-way analysis of variance (ANOVA), followed by Bonferroni's post hoc test. A p-value < 0.05 was considered statistically significant.

Results

Platelet function

Compared to young controls, older control rats showed a significant reduction in platelet count (Figure 1a) and plateletcrit (Figure 1b), alongside increased mean platelet volume (MPV) (Figure 1c), platelet distribution width (PDW) (Figure 1d), and platelet aggregation (Figure 1e) ($p < 0.05$). Supplementation with Vitamin E (200 mg/kg/day), Zinc (10 mg/kg/day), or their combination improved platelet indices and significantly reduced platelet aggregation in older rats ($p < 0.05$). Among the supplemented subgroups, the combined Vitamin E + Zinc group showed the most pronounced normalization of platelet count, MPV, and PDW, approaching values comparable to young controls.

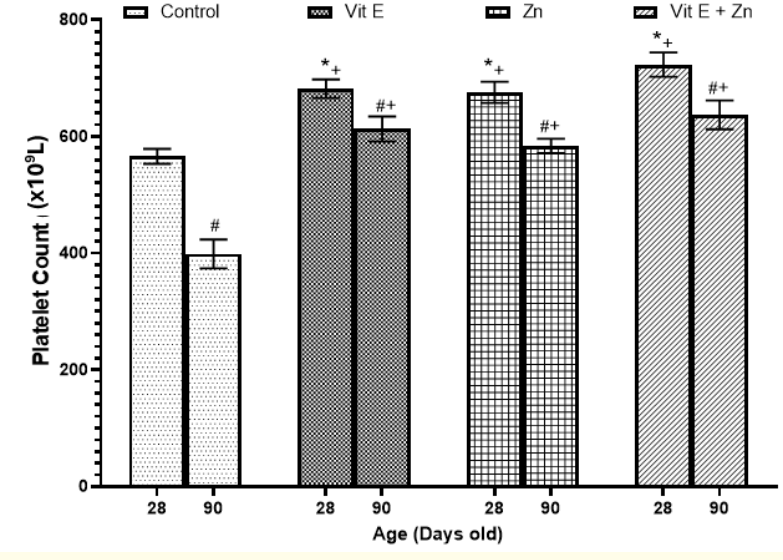

Figure 1a: *Effects of vitamin E and zinc on age-related variations in platelet count (x109/L).*

*Values expressed as mean ± SEM (standard error of mean). * and + significant difference (P < 0.05) when treated groups is compared with control 28 and 90 days old respectively; # significant difference between 28 and 90 days old within control, Vitamin E-treated (Vit E), Zinc-treated (Zn) and Vitamin E + Zinc-treated (Vit E + Zn) groups.*

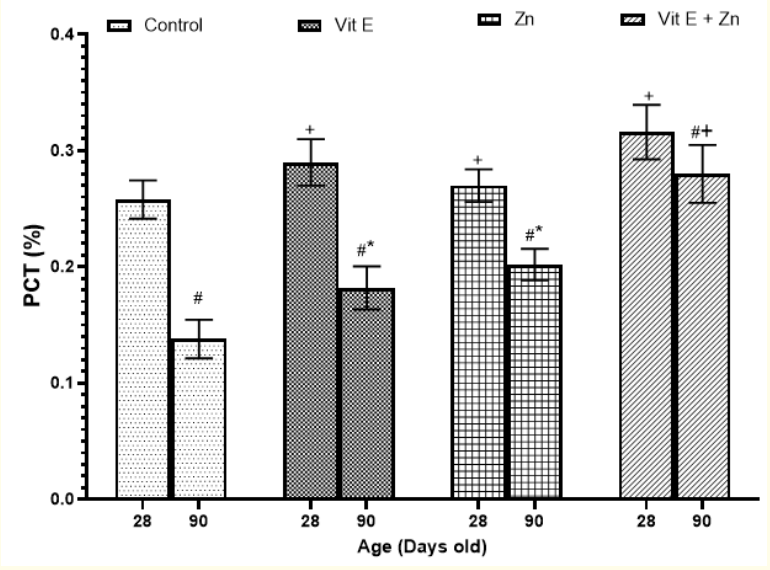

Figure 1b: *Effects of vitamin E and zinc on age-related variations in plateletcrit (PCT).*

*Values expressed as mean ± SEM (standard error of mean). * and + significant difference (P < 0.05) when treated groups is compared with control 28 and 90 days old respectively; # significant difference between 28 and 90 days old within control, Vitamin E-treated (Vit E), Zinc-treated (Zn) and Vitamin E + Zinc-treated (Vit E + Zn) groups.*

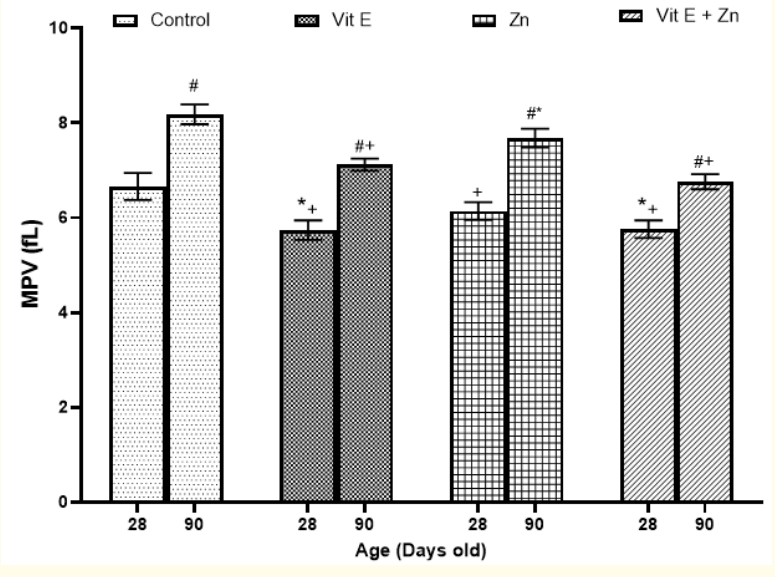

Figure 1c: *Effects of vitamin E and zinc on age-related variations in mean platelets volume (MPV).*

*Values expressed as mean ± SEM (standard error of mean). * and + significant difference (P < 0.05) when treated groups is compared with control 28 and 90 days old respectively; # significant difference between 28 and 90 days old within control, Vitamin E-treated (Vit E), Zinc-treated (Zn) and Vitamin E + Zinc-treated (Vit E + Zn) groups.*

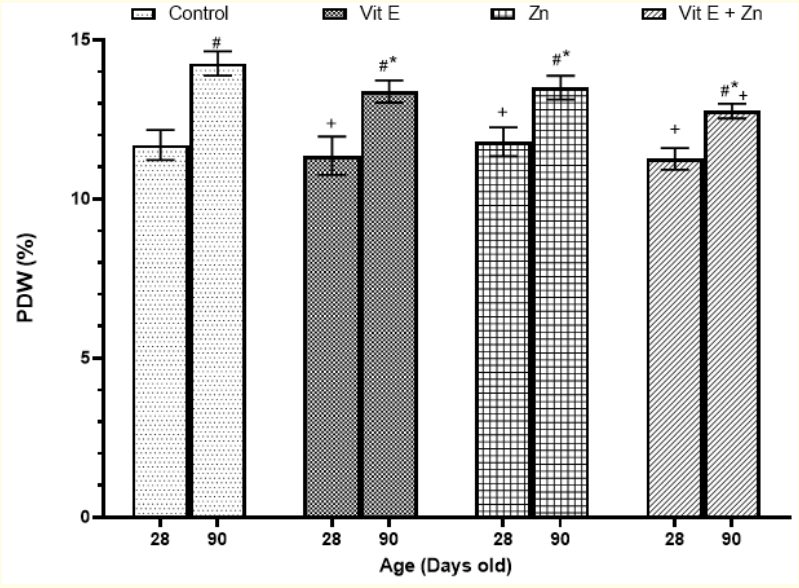

Figure 1d: *Effects of vitamin E and zinc on age-related variations in platelets distribution width (PDW). Values expressed as mean ± SEM (standard error of mean). * and + significant difference (P < 0.05) when treated groups is compared with control 28 and 90 days old respectively; # significant difference between 28 and 90 days old within control, Vitamin E-treated (Vit E), Zinc-treated (Zn) and Vitamin E + Zinc-treated (Vit E + Zn) groups.*

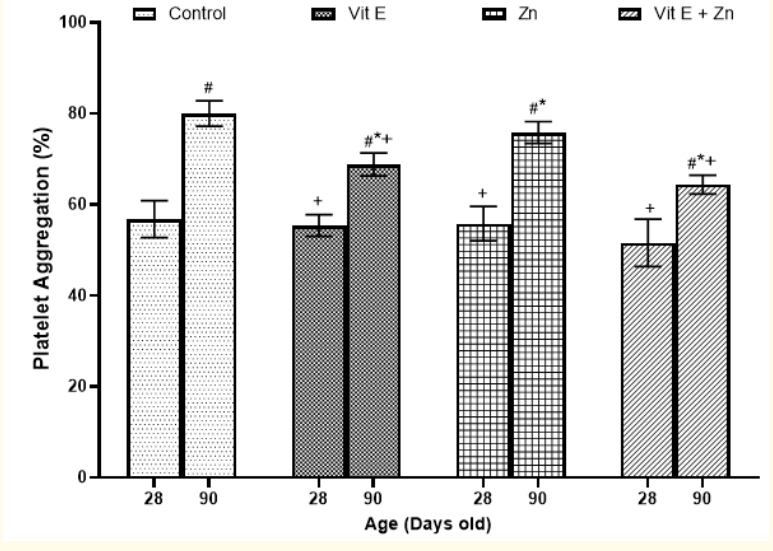

Figure 1e: *Effects of vitamin E and zinc on age-related variations in platelets aggregation. Values expressed as mean ± SEM (standard error of mean). * and + significant difference (P < 0.05) when treated groups is compared with control 28 and 90 days old respectively; # significant difference between 28 and 90 days old within control, Vitamin E-treated (Vit E), Zinc-treated (Zn) and Vitamin E + Zinc-treated (Vit E + Zn) groups.*

Coagulation parameters

Older control rats demonstrated prolonged prothrombin time (Figure 2a) and bleeding time (Figure 2b), as well as elevated fibrinogen levels (Figure 2c) compared to young controls ($p < 0.05$). Treatment with Vitamin E, Zinc, or their combination significantly reduced bleeding time and fibrinogen concentration in older rats ($p < 0.05$). Prothrombin time was also partially restored, with the combined supplementation group showing the closest values to those of young controls.

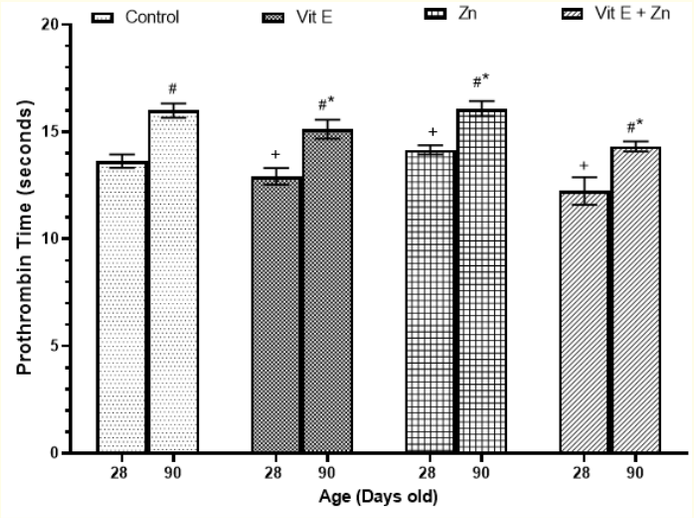

Figure 2a: *Effects of vitamin E and zinc on age-related variations in prothrombin time.*

*Values expressed as mean ± SEM (standard error of mean). * and + significant difference (P < 0.05) when treated groups is compared with control 28 and 90 days old respectively; # significant difference between 28 and 90 days old within control, Vitamin E-treated (Vit E), Zinc-treated (Zn) and Vitamin E + Zinc-treated (Vit E + Zn) groups.*

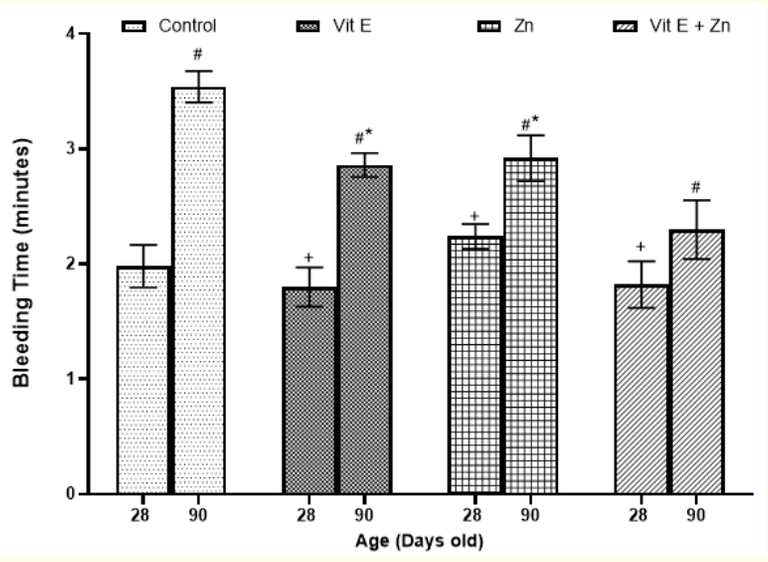

Figure 2b: *Effects of vitamin E and zinc on age-related variations in bleeding time.*

*Values expressed as mean ± SEM (standard error of mean). * and + significant difference (P < 0.05) when treated groups is compared with control 28 and 90 days old respectively; # significant difference between 28 and 90 days old within control, Vitamin E-treated (Vit E), Zinc-treated (Zn) and Vitamin E + Zinc-treated (Vit E + Zn) groups.*

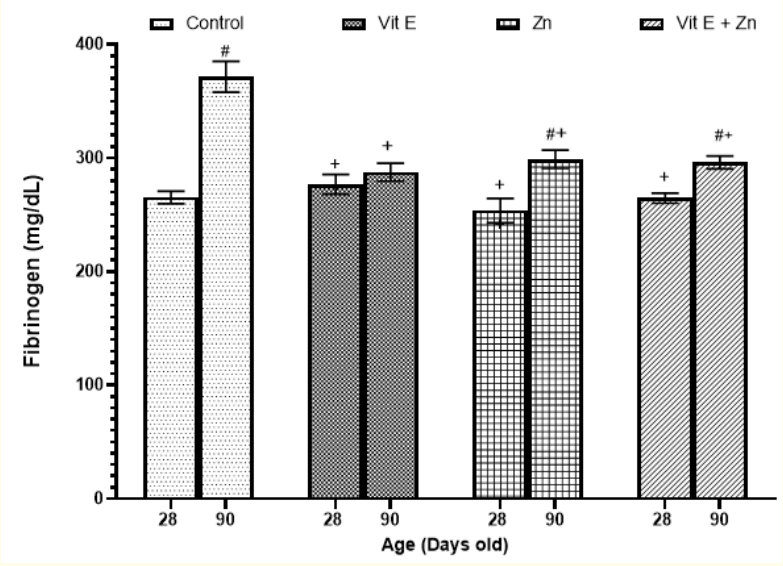

Figure 2c: *Effects of vitamin E and zinc on age-related variations in fibrinogen levels.*

*Values expressed as mean ± SEM (standard error of mean). * and + significant difference (P < 0.05) when treated groups is compared with control 28 and 90 days old respectively; # significant difference between 28 and 90 days old within control, Vitamin E-treated (Vit E), Zinc-treated (Zn) and Vitamin E + Zinc-treated (Vit E + Zn) groups.*

Oxidative stress markers

In older control rats, malondialdehyde (MDA) levels were significantly elevated, while activities of superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) were markedly reduced relative to young controls ($p < 0.05$). Supplementation with Vitamin E, Zinc, or both effectively reduced MDA concentrations and enhanced SOD, CAT, and GPx activities ($p < 0.05$). The Vitamin E + Zinc group demonstrated the greatest antioxidant effect, with enzyme levels significantly higher than in single-supplement groups and approaching those of young controls (Table 1).

Parameter	Age (days)	Control	Vit E	Zn	Vit E + Zn
MDA (nmol/mg protein)	28	5.21 ± 0.22	3.94 ± 0.18*	4.01 ± 0.19*	3.21 ± 0.15*
	90	6.87 ± 0.28#	4.95 ± 0.20+	5.02 ± 0.23+	3.79 ± 0.16+
SOD (U/mg protein)	28	12.3 ± 0.52	16.1 ± 0.61*	15.4 ± 0.58*	18.7 ± 0.65*
	90	9.6 ± 0.43#	13.8 ± 0.55+	13.2 ± 0.49+	16.9 ± 0.60+
CAT (U/mg protein)	28	45.2 ± 1.8	56.4 ± 2.1*	54.8 ± 2.0*	62.3 ± 2.2*
	90	37.6 ± 1.5#	49.1 ± 1.9+	47.2 ± 1.8+	58.7 ± 2.0+
GPx (U/mg protein)	28	7.8 ± 0.35	10.4 ± 0.42*	9.9 ± 0.40*	11.6 ± 0.45*
	90	6.1 ± 0.28#	8.9 ± 0.37+	8.4 ± 0.34+	10.7 ± 0.41+

Table 1: *Effects of Vitamin E, Zinc, and their combination on oxidative stress markers (MDA, SOD, CAT, GPx) in young (28-day) and older (90-day) Wistar rats.*

*Values expressed as mean ± SEM (standard error of mean). * and + significant difference (P < 0.05) when treated groups is compared with control 28 and 90 days old respectively; # significant difference between 28 and 90 days old within control, Vitamin E-treated (Vit E), Zinc-treated (Zn) and Vitamin E + Zinc-treated (Vit E + Zn) groups.*

Discussion

Our findings confirm that aging is accompanied by alterations in platelet function and coagulation activity, as reflected in the older (90-day) rats compared with younger (28-day) controls. Previous studies have shown that age is associated with enhanced platelet activation, increased thrombin generation, and impaired fibrinolysis, all of which contribute to a prothrombotic state [17–19]. The hyperactive platelet profile observed in this study may underlie the increased susceptibility of aging organisms to cardiovascular complications and delayed vascular repair.

Oxidative stress is a well-recognized driver of age-related hemostatic dysfunction. Excessive generation of reactive oxygen species (ROS) promotes lipid peroxidation of platelet membranes, impairs nitric oxide bioavailability, and activates redox-sensitive pathways involved in thrombogenesis [20,21]. The elevated oxidative imbalance observed in older rats in this study aligns with this paradigm and provides a mechanistic explanation for the concurrent alterations in platelet and coagulation parameters.

Vitamin E and Zinc supplementation attenuated age-associated changes in platelet and coagulation parameters, likely via complementary antioxidant mechanisms. Vitamin E, as a lipid-soluble antioxidant, protects platelet membranes from peroxidative damage and inhibits abnormal platelet aggregation [22,23]. Zinc, on the other hand, functions as a cofactor for antioxidant enzymes such as superoxide dismutase (SOD), stabilizes sulfhydryl groups, and supports endogenous defense systems [24,25]. Our results indicate that their combination produced greater protective effects than either agent alone, suggesting a synergistic interaction where Vitamin E directly scavenges lipid peroxyl radicals while Zinc enhances enzymatic detoxification of ROS.

The observed benefits of combined Vitamin E and Zinc may reflect both direct and indirect modulation of platelet and coagulation pathways. By preserving membrane integrity, reducing lipid peroxidation, and enhancing redox enzyme activity, these micronutrients may restore hemostatic balance in aging organisms. Importantly, this suggests that targeted antioxidant supplementation could mitigate age-related thrombotic risks and improve vascular repair processes. Although our study provides experimental evidence in rats, the findings may have translational relevance in the context of nutritional strategies for elderly populations at risk of coagulation abnormalities.

Limitations and Future Directions

Several limitations must be acknowledged. First, the study was conducted in rats, and extrapolation to human physiology requires caution given species-specific differences in platelet biology and coagulation pathways. Second, only short-term supplementation was assessed; long-term safety and efficacy of Vitamin E and Zinc co-administration remain to be established. Third, while oxidative stress markers were evaluated, detailed molecular analyses of signaling pathways (e.g., Nrf2/HO-1 axis, platelet adhesion receptors, and coagulation factor expression) were not performed. Future studies should incorporate advanced molecular and translational approaches, including clinical trials, to clarify the therapeutic potential of these micronutrients in managing age-related thrombotic disorders.

Conclusion

This study demonstrates that aging is associated with platelet hyperactivity and coagulation dysfunction, likely mediated by oxidative stress. Supplementation with Vitamin E and Zinc attenuated these alterations, with the combined treatment showing greater efficacy than either agent alone. These findings suggest that targeted antioxidant strategies may hold promise in mitigating age-related thrombotic risk. While further molecular and clinical studies are warranted, the present results provide experimental evidence supporting the role of nutritional antioxidants in preserving vascular health during aging.

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