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Original Article

Ex vivo anticoagulant effect of *Zingiber officinale* in whole blood samples

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ABSTRACT

Background and Aims: *In vitro* and *in vivo* studies have shown that *Zingiber officinale* (*Z. officinale*, Ginger) may have an anticoagulant effect. Although there are studies on the anticoagulant effect, the results are inconclusive. Our study investigated the anticoagulant effect of *Z. officinale* on the whole blood sample *ex vivo*.

Methods: The inner and shell parts of *Z. officinale* were extracted with methanol, ethanol, and water. 0.1 mg/mL of different volumes (100, 150 and 200 µL) of *Z. officinale* extracts were added to the blood of a healthy volunteer *ex vivo*. Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were measured in the coagulation analyser. Measurements were performed twice, before and after the ginger treatment. International Normalised Ratio (INR) values were calculated using the following mathematical formula: INR = Patient PT/Control PT. The IBM SPSS 25.0 software was used for statistical analyses.

Results: A notable prolongation in PT, aPTT, and INR was detected after the addition of *Z. officinale* extract to blood samples ($p<0.001$). As the volume of *Z. officinale* extract added to the blood sample increased, coagulation parameters were observed to display a corresponding increase ($p<0.001$).

Conclusion: *Z. officinale* was associated with prolonged PT, aPTT, and INR *ex vivo*. *In vivo* studies are needed to demonstrate the mechanism of the anticoagulant effect.

Keywords: Activated partial thromboplastin time, Anticoagulant herbs, Ginger, Prothrombin time, *Zingiber officinale*

INTRODUCTION

Blood vessels, platelets, coagulation factors, and the fibrinolytic system make up the haemostasis system, which helps control bleeding. The vascular constriction phase followed by platelet adhesion. The extracellular matrix facilitates platelet adhesion and aggregation through the secretion of cytokines and inflammatory markers. This process ensures the formation of the platelet plug. Platelets release cytoplasmic granules after adhesion. The cytoplasmic granules contain platelet-activating factors such as adenosine diphosphate (ADP), thromboxane A2 (TXA2), and serotonin. There are two pathways in the coagulation process: extrinsic and intrinsic. Coagulation factors participate in these pathways. Prothrombin is degraded to during preoperative examinations, and in patients with bleeding (Winter, Flax, & Harris, 2017).

Thrombosis frequently is the main cause of cardiovascular illnesses, such as myocardial infarction, atrial fibrillation, and associated mortality (McEwen, 2015). Despite advances in the identification and treatment of cardiovascular diseases, approximately half of all deaths are due to cardiovascular diseases (Wong et al., 2019). Many cardiovascular disorders are characterised by increased clotting activity; therefore, treatments include antithrombotic and anticoagulant drugs to prevent blood clotting (Lowe & Rumley, 2014). These drugs include antithrombotic agents, anticoagulants that stop the coagulation system and prevent clot expansion, antiplatelet agents that reduce platelet aggregation and prevent thrombus forma-

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tion, and fibrinolytic enzymes that directly dissolve thrombus. Anticoagulant drugs can have side effects, such as bleeding and thrombocytopenia (Harter, Levine, & Henderson, 2015). Given these potential side effects, studies investigating the use of herbal medicines against cardiovascular diseases are coming to the fore. Patients with cardiovascular diseases such as atherosclerosis and systolic hypertension tend to use herbal medicines (McEwen, 2015).

Zingiber officinale (Z. officinale, Ginger) is an herb that has been used as a spice and herbal medicine since ancient times. It contains a wide variety of active ingredients. The main types of gingerols are shogaol, paradol, quercetin, zingerone, and zingerone (Mao et al., 2019). There have been studies that demonstrate it possesses anti-oxidant (Abolaji et al., 2017), anti inflammatory (Teschke & Xuan, 2018), anti-microbial (Nassan & Mohamed, 2014), anti-cancer (El-Ashmawy, Khedr, El-Bahrawy, & Abo Mansour, 2018), and antiemetic (Bossi et al., 2017) properties. In addition to these functions, *in vitro* and *in vivo* studies have shown that *Z. officinale* may have an anticoagulant effect (Flynn, Rafferty, & Boctor, 1986; Koo, Ammit, Tran, Duke, & Roufogalis, 2001; Liao, Leu, Chan, Kuo, & Wu, 2012; Shih et al., 2014). Although there are studies on the anticoagulant effect, the results are inconclusive. This study aimed to determine the anticoagulant effect of *Z. officinale* in human blood. The effects of extracting *Z. officinale* in different solvents, such as methanol, ethanol, and water, on PT, aPTT, and INR in blood samples from healthy volunteers were investigated.

MATERIALS AND METHODS

Participants

The University of Health Sciences Turkey Hamidiye Scientific Research Ethics Committee (registration number: 21/563) approved the study. Fifty healthy volunteers from the Haydarpasa Numune Hospital were included in the study. Written consent to participate in the study was obtained from the participants. The study size was determined to be at least 30 people for the study group, with a G-power analysis of the effect size=80% at the α=0.05 significance level. Our study excluded individuals with diabetes, kidney dysfunction, liver dysfunction, hypertension, cardiovascular disorders, acute or chronic diseases, coagulation problems, or those taking medication.

Z. officinale extract preparation

Z. officinale samples were obtained from a grocery store (Istanbul, Türkiye). They were extracted using solvents. The inner and shell parts of 10 g of fresh *Z. officinale* were grinded and treated with 100 mL of 80% ethanol (Sigma, Darmstadt, Germany), 80% methanol (Isolab, Eschau, Germany), and 100% distilled water solutions, respectively, and mixed at room temperature for 24 h. Then, it was filtered using Whatman filter paper (0.45 µm). Solvents and water in the extract were removed using an evaporator and lyophilizer (Buchi Rotavapor R100, New Castle, USA). The extracts were stored in a refrigerator at -80°C until the study.

Blood Collection

Human blood was collected from fifty healthy volunteers. Approximately 5 mL of blood was taken from each volunteer in a sodium citrate tube (0.109 M Na_3Citrate).

Coagulation Analysis

Plasma coagulation analysis was performed using the STA Compact Max® automatic coagulation analyser (Asnières-sur-Seine, France). The aPTT and PT were measured in adherence to the protocols outlined by the manufacturer. The anticoagulant activity was quantified as the clotting time in seconds, with heparin serving as the reference.

Anticoagulant Activity

After blood was collected from each volunteer in a sodium citrate tube, the tube was turned upside down. Then, 0.1 mg/mL inner and shell parts of *Z. officinale* extract were added to whole blood samples in 3 different volumes as 100 µL, 150 µL, and 200 µL. After 15 min of incubation at room temperature, blood samples were collected separately and centrifuged at 3000 rpm for 10 min in a NUVE, NF 1200R centrifuge machine (Ankara, Türkiye), and plasmas were separated. Measurements were performed twice, before and after the *Z. officinale* treatment. PT and aPTT measurements were performed using the STA Compact Max® automatic coagulation analyser (Asnières-sur-Seine, France). International Normalised Ratio (INR) values were calculated using the formula INR = Patient PT/Control PT (Shikdar, Vashisht, & Bhattacharya, 2022).

Statistical Analysis

The IBM SPSS 25.0 software was used for statistical analyses. The data distribution was determined using the Kolmogorov-Smirnov test. Mean ± standard deviation values were used to express continuous variables. One-way analysis of variance (ANOVA) was used to determine differences between the means of two or more independent groups. Two-way ANOVA was used to examine differences in coagulation parameters before and after the *Z. officinale* extraction treatment. The 95% confidence intervals are used to show differences between groups. Statistical significance was defined as $p<0.05$.

RESULTS

Z. officinale extraction was performed on whole blood samples of the participants. Table 1-2 and Figure 1 compare the

PT, aPTT, and INR before and after the *Z. officinale* treatment. A statistically significant increase in PT values was observed after adding 100 µL IG (Inner of ginger)-Ethanol (3.0%), IG-Methanol (3.78%), IG-Water (2.3%), SG (Shell of ginger)-Ethanol (5.48%), SG-Methanol (2.07%), and SG-Water (0.74%) to the samples (p<0.001). As more *Z. officinale* extract was administered to the blood, increase in parameters was seen (p<0.001, For 200 µL extract: IG-Ethanol: 8.67%, IG-Methanol: 8.44%, IG-Water: 6.9%, SG-Ethanol: 10%, SG-Methanol: 5.9%, SG-Water: 2.37%). The greatest increase was observed after adding 200 µL of SG-ethanol (Pre-treatment: 13.50±1.02 second, post-treatment 14.90±1.02 second) (Figure 1.).

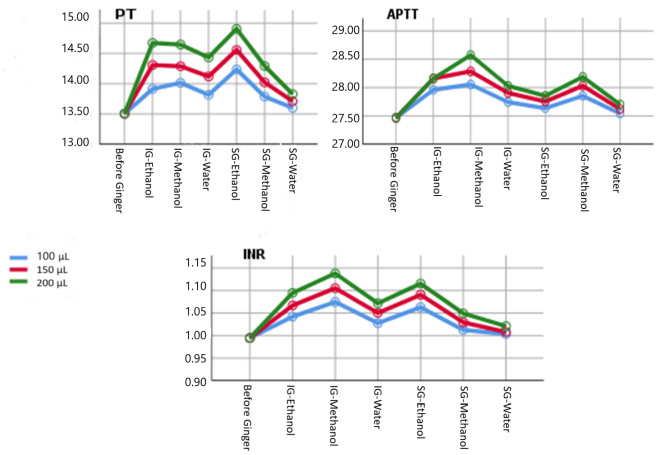

Figure 1. *Coagulation parameters before and after ginger supplementation PT: Prothrombin time, aPTT: Activated partial thromboplastin time, INR: International Normalised Ratio, IG: Inner of ginger, SG: Shell of Ginger*

Considering the difference in aPTT, a statistically significant increase was observed in all *Z. officinale* forms, except IG-Ethanol, compared with the pre-treatment (p<0.001). As the amount of *Z. officinale* extract added to the blood increased, aPTT values increased significantly (p<0.001). The most significant increase was observed after adding 200 µL of IG-Methanol (Pre-treatment: 27.46±3.28 second, post-treatment 28.57±3.36 second) (Figure 1.)

Similar to the other parameters, a statistically significant increase in INR was observed in all *Z. officinale* forms compared with the pre-treatment (Table 2, Figure 1) (p<0.001). As more *Z. officinale* extract was infused into the blood, INR levels increased significantly (p<0.001). Adding 200 µL of IG-methanol, similar to aPTT, resulted in the most significant rise (Pre-treatment: 0.99±1.06 second, post-treatment 1.13±0.09 second) (Figure 1.).

DISCUSSION

Coagulation, which is a part of the body's haemostasis mechanism, becomes a potentially fatal occurrence in pathological situations. Anticoagulant medications are commonly used to reduce blood clotting in various conditions, such as cardiovascular disease. Because anticoagulant medications may have adverse effects, researchers are looking for novel anticoagulants with fewer negative side effects (Ayodele, Onajobi, & Osoniyi, 2019). *Z. officinale* has been used in traditional medicine for centuries, and its potential medical properties are still being studied (Chrubasik, Pittler, & Roufogalis, 2005). This study found that *Z. officinale* extracts prepared in different solvents had anticoagulant effects by prolonging the PT, aPTT, and INR values in whole blood samples. The parameters were prolonged as the concentration of the *Z. officinale* extract increased. To the author's knowledge, this is the first study in the literature to show the effect of *Z. officinale's* inner and shell parts prepared in different solvents (water, ethanol, and methanol) and in different volumes (100, 150, 200 µL) on the coagulation parameters.

PT and aPTT are coagulation parameters used to determine the coagulation mechanism. The extrinsic coagulation cascade was assessed using PT, whereas intrinsic and common pathways were assessed using aPTT. In clinical evaluation, prolonged aPTT and/or PT indicates coagulation impairment. Prolonged PT and aPTT suggests that common pathway factors may be inhibited (V, X, and prothrombin) (Yang & Moosavi, 2022). In our study, *Z. officinale* showed anticoagulant effects by prolonging PT, aPTT, and INR. This effect may be caused by common pathway factors V, X, and prothrombin. More research is needed to understand the mechanism by which this mechanism is affected.

There have been studies showing that *Z. officinale* has an anticoagulant effect *in vitro*. In a study similar to our findings, researchers explored the impact of an aqueous extract from *Z. official* roots on blood PT *in vitro* and found a dose-dependent prolongation of PT (Eldin, Elmutalib, & Hamedelniel, 2016). In a study assessing the *in vitro* anticoagulant effect of ethanol extracts from *Z. officinale* roots, researchers observed prolonged PT, with no significant difference noted in aPTT (Ahmad, Mohammed, Mohamed Eltayeb, Mohammed Elmosaad, & Waggiallah, 2022). In an *in vitro* investigation, rat basophilic leukaemia 2H3 cells, which accurately reflect arachidonic acid metabolism, were used to demonstrate the antithrombotic efficacy of synthetically produced Gingerols. The effects of gingerols on arachidonic acid-induced platelet serotonin release and platelet aggregation were compared with aspirin, which has potent antiplatelet activity. According to these findings, gingerols can decrease the release and aggregation of platelets produced by arachidonic acid in human platelet-rich plasma. These changes were 2–4 times less effective than aspirin. Furthermore, in the same study, Prostaglandin D2 (PGD2), a result of arachi-

Table 1. Differences between before and after ginger treatmentfor PT and aPTT

Variable			Mean±SD	F	*p**	Difference
PT (sec)	Baseline		13.50±1.02	1496.633	**0.001**	4>3>2>1
	IG-Ethanol	100 µL	13.91±1.02			
		150 µL	14.30±1.02			
		200 µL	14.67±1.03			
	Baseline		13.50±1.02	591.528	**0.001**	4>3>2>1
	IG-Methanol	100 µL	14.01±1.01			
		150 µL	14.28±1.03			
		200 µL	14.64±1.04			
	Baseline		13.50±1.02	1056.928	**0.001**	4>3>2>1
	IG-Water	100 µL	13.81±1.02			
		150 µL	14.12±1.01			
		200 µL	14.43±1.00			
	Baseline		13.50±1.02	1084.970	**0.001**	4>3>2>1
	SG-Ethanol	100 µL	14.23±1.02			
		150 µL	14.55±1.03			
		200 µL	14.90±1.02			
	Baseline		13.50±1.02	787.703	**0.001**	4>3>2>1
	SG-Methanol	100 µL	13.78±1.02			
		150 µL	14.02±0.99			
		200 µL	14.29±0.99			
	Baseline		13.50±1.02	193.679	**0.001**	4>3>2>1
	SG-Water	100 µL	13.60±1.01			
		150 µL	13.71±1.01			
		200 µL	13.82±1.01			
aPTT (sec)	Baseline		27.46±3.29	10.187	0.338	3>4>2>1
	IG-Ethanol	100 µL	27.96±3.34			
		150 µL	28.16±3.34			
		200 µL	28.15±3.26			
	Baseline		27.46±3.29	397.998	**0.001**	4>3>2>1
	IG-Methanol	100 µL	28.05±3.38			
		150 µL	28.28±3.39			
		200 µL	28.57±3.36			
	Baseline		27.46±3.29	435.233	**0.001**	4>3>2>1
	IG-Water	100 µL	27.74±3.32			
		150 µL	27.90±3.34			
		200 µL	28.03±3.32			
	Baseline		27.46±3.29	236.510	**0.001**	4>3>2>1
	SG-Ethanol	100 µL	27.63±3.30			
		150 µL	27.75±3.29			
		200 µL	27.85±3.28			
	Baseline		27.46±3.29	532.898	**0.001**	4>3>2>1
	SG-Methanol	100 µL	27.85±3.34			
		150 µL	28.03±3.32			
		200 µL	28.18±3.32			
	Baseline		27.46±3.29	70.582	**0.001**	4>3>2>1
	SG-Water	100 µL	27.54±3.30			
		150 µL	27.62±3.27			
		200 µL	27.70±3.28			

1=Pre-treatment; 2=100 µL; 3=150 µL; 4=200 µL PT: Prothrombin time, aPTT: Activated partial thromboplastin time, INR: International Normalised Ratio, IG: Inner of ginger, SG: Shell of Ginger, *: Two-way analysis of variance (two-way ANOVA).

Table 2. Differences between before and after ginger treatmenton INR

Variable			Mean±SD	F	*p**	Difference
INR	Baseline		0.99±0.10			
	IG-Ethanol	100 µL	1.04±0.10	373.943	**0.001**	4>3>2>1
		150 µL	1.06±0.10			
		200 µL	1.09±0.10			
	Baseline		0.99±0.10			
	IG-Methanol	100 µL	1.07±0.10	711.178	**0.001**	4>3>2>1
		150 µL	1.10±0.10			
		200 µL	1,13±0,09			
	Baseline		0.99±0.10			
	IG-Water	100 µL	1.02±0.10	423.455	**0.001**	4>3>2>1
		150 µL	1.05±0.10			
		200 µL	1.07±0.10			
	Baseline		0.99±0.10			
	SG-Ethanol	100 µL	1.06±0.10	606.383	**0.001**	4>3>2>1
		150 µL	1.09±0.10			
		200 µL	1.11±0.10			
	Baseline		0.99±0.10			
	SG-Methanol	100 µL	1.01±0.10	252.143	**0.001**	4>3>2>1
		150 µL	1.02±0.10			
		200 µL	1.04±0.10			
	Baseline		0.99±0.10			
	SG-Water	100 µL	1.00±0.10	74.761	**0.001**	4>3>2>1
		150 µL	1.00±0.10			
		200 µL	1.02±0.10			

1=Pre-treatment; 2=100 µL; 3=150 µL; 4=200 µL

INR: International Normalised Ratio, IG: Inner of ginger, SG: Shell of Ginger, *: Two-way analysis of variance (two-way ANOVA).

donic acid metabolism, was measured in RBL-2H3 cells, and gingerols were found to suppress COX (cyclooxygenase) activity (Koo et al., 2001). The COX enzyme converts arachidonic acid, an omega-6 fatty acid, into prostaglandins (PGD2, PGE2, PGF2, PGI2) and thromboxanes (TXA2, TXB2). These lipid mediators, synthesised and released from endothelial cells and platelets, are associated with platelet aggregation and inflammation (Wang et al., 2021). In another study, gingerdione, a component of ginger, was found to suppress the synthesis of 5-hydroxyeicosatetraenoic acid (5-HETE) and PGE2 from arachidonic acid in human neutrophil cells. Furthermore, shogaol in ginger inhibits 5-HETE and gingerol and dehydroparadol inhibit COX (Flynn et al., 1986; Thomson et al., 2002). *In vitro* inhibition of arachidonic acid-induced platelet activation in whole human blood examined by Effie et al. using 20 active components of *Z. officinale*. It has been observed that the components of *Z. officinale* have much greater antiplatelet activity than do aspirin. Additionally, [8]-Paradol was shown to be the substance that inhibits COX most (Nurtjahja-Tjendraputra, Ammit, Roufogalis, Tran, & Duke, 2003).

Z. officinale antithrombotic properties have been studied in animals. Thomson et al. administered 500 mg/kg aqueous extract of *Z. officinale* to rats for 4 weeks in an *ex vivo* study. A 50% reduction in TXB2 levels was observed (Thomson et al., 2002). In rabbits, [6]-Paradol prevented arachidonic acid-induced platelet aggregation (Shih et al., 2014). Similarly, Liao et al. (2012) reported that [6]-Gingerol and [6]-Shogaol exhibit antiplatelet activity in rabbits (Liao et al., 2012). A reduction in platelet adenosine deaminase activity and an increase in adenosine levels were observed in a hypertensive rat study following the administration of *Z. officinale* root according to these find-

ings, *Z. officinale* may help reduce hypertension-related problems induced by platelet activity (Akinyemi et al., 2016).

While *in vitro* research on *Z. officinale*'s anti-coagulant activity is promising, human studies are conflicting. In a placebo-controlled study, 30 patients with myocardial infarction were administered *Z. officinale* capsules for 3 months, and fibrinogen, fibrinolytic activity, and platelet aggregation were measured. Significant reductions in adenosine diphosphate (ADP) and adrenaline-induced platelet aggregation were observed 4 h after the administration of 4 g of *Z. officinale* (Bordia, Verma, & Srivastava, 1997). ADP, adrenaline, and TXA2 stimulate platelet activation (McEwen, 2015). Contrary to these findings, Janssen et al. administered raw and cooked *Z. officinale* to healthy volunteers for 2 weeks in a placebo-controlled study. TXA2 levels were measured on days 12 and 14, and there was no significant reduction compared with placebo (Janssen, Meyboom, van Staveren, de Vegt, & Katan, 1996).

Studies conducted both *in vivo* and *in vitro* revealed that reduced TXA2 or PG endoperoxide synthesis causes antiplatelet activity. It has been reported that this may be caused by the inhibition of platelet COX enzymes and/or the antioxidants found in *Z. officinale* (Bordia et al., 1997). It is thought that the carbonyl functional group in 3.C of the paradol and diarylheptanoid series in the content of *Z. officinale* may exert antithrombotic effects by inhibiting COX-1 (Nurtjahja-Tjendraputra et al., 2003). In the structure-activity relationship (SAR) analysis, it was revealed that the phenolic compounds in *Z. officinale* have an inhibitory effect on the COX-2 enzyme due to the lipophilic feature of the alkyl side chain, the position of the hydroxy and carbonic groups in the side chain, and the hydroxy and methoxy groups in the aromatic side chain (Tjendraputra, Tran, Liu-Brennan, Roufogalis, & Duke, 2001).

As a result, in our study, extracts of fresh *Z. officinale* obtained with water, ethanol, and methanol solvents prolonged the coagulation parameters in human whole blood samples. PT, aPTT, and INR continued to be prolonged as the concentration of *Z. officinale* extracts added to the samples increased. Based on these findings, *Z. officinale* appears to influence coagulation. Its potential therapeutic and pharmacological effects, along with the underlying mechanisms, require further investigation through various study designs.

Study Limitations: *Z. officinale* employed in this investigation lacks comprehensive characterisation. Consequently, due to the absence of standardised characteristics, it is not suitable to assess its effects using only this study. Furthermore, the active constituents of the used plant have not been isolated or subjected to analysis. Identification of the specific molecule within its composition that is responsible for the primary effect remains uncertain based on the present study. Hence, we propose that future studies should aim to determine the active ingredients of *Z. officinale* and evaluate its anticoagulant activity.

Ethics Committee Approval: The University of Health Sciences Hamidiye Scientific Research Ethics Committee (registration number: 21/563) approved the study.

Informed Consent: Written consent to participate in the study was obtained from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study: E.M.G., M.M.Y., M.S.K., E.Ş.Ö., S.K.; Data Acquisition: E.Ş.Ö., S.K., D.Ö., F.G.; Data Analysis/Interpretation: S.A., E.P.H., E.M.G.., S.K; Drafting Manuscript: E.Ş.Ö., S.K., D.Ö., E.M.G.; Critical Revision of Manuscript: E.M.G., S.A., M.M.Y., E.P.H., M.S.K., F.G.; Final Approval and Accountability: E.M.G., S.A., M.M.Y., E.P.H., M.S.K., F.G., E.Ş.Ö., S.K., D.Ö.

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