



<https://muthjas.mu.edu.iq/>

<http://doi.org/10.52113/mjas04/13.1/50>

Comparative study of clopidogrel, melilots officinalis and cinnamon as anticoagulants in rabbits.

Roqia Muslim Obaies, Hawraa H. Naji², Adnan Mansour jasim³

Department of Physiology, Biochemistry and Pharmacology, College of Veterinary Medicine, AL-Qasim green University, Babylon 51001, IRAQ.

adnan.mansouri81@vet.uoqasim.edu.iq

<https://orcid.org/0000-0002-6326-560X>

<https://orcid.org/0000-0003-0556-879X>

ABSTRACT

Blood coagulation disorders are medical conditions that disrupt the body's natural clotting process. When this system malfunctions, it typically results in one of two dangerous extremes: thrombophilia (excessive clotting) or coagulopathy (excessive bleeding). GC-MS analysis of Melilotus extract showed the presence of several active compounds, primarily 2H Pyran 2 one, tetrahydro 6 methyl, and significantly, it also detected the presence of coumarin, a natural anticoagulant. The main component of cinnamon extract was (E)-cinnamaldehyde, followed by eugenol and cinnamyl acetate.

Thirty adult rabbits (2–2.5 kg) were acclimated for 14 days under controlled conditions (12h light/dark, ad libitum feeding). Thrombosis was induced via IV injection of collagen (0.5 mg/kg) and epinephrine (0.06 mg/kg) every other day for four doses. Animals were divided into five groups (n=6): a negative control (saline), a positive control (collagen/epinephrine), and three treatment groups receiving daily oral doses of Clopidogrel (25 mg/kg), Melilotus officinalis (200 mg/kg), or Cinnamomum zeylanicum (200 mg/kg) for three weeks. Initial and post-induction hemostatic status were monitored via bleeding (BT) and clotting times (CT). This research was designed to analyze and contrast the anticoagulant properties of different therapeutic agents (Melilotus officinalis and

Cinnamomum verum) in rabbits with collagen-epinephrine-induced thrombosis. Clopidogrel and Melilotus officinalis had the greatest effects on hemostatic balance, while cinnamon had a moderate but steady effect. The hematological and coagulation parameters revealed a marked decrease in platelet activity and INR in the clopidogrel and Melilotus groups, while cinnamon showed a moderate effect. Bleeding and clotting times measured weekly also confirmed the potent anticoagulant effect of clopidogrel and Melilotus. In conclusion, Melilotus officinalis showed strong anticoagulant activity, confirmed by the presence of coumarin, and was comparable to clopidogrel, with cinnamon showing a moderate effect.

Keywords: Blood coagulation disorders, rabbits, Intestine, clopidogrel.

Introduction

Blood coagulation and atherosclerosis are deeply convolute via atherothrombosis, where procoagulant states develop plaque progression, and plaque upset triggers clot generation. Hypercoagulability rise clotting activity hasten atherosclerosis by depositing fibrin, animating smooth muscle cell proliferation, and prompt chronic inflammation (Pastori et al. 2023).

Venous thromboembolism (VTE) is a significant worldwide health issue associated with the presence of risk factors that can be identified (Pastori et al. 2023). Both venous and arterial thrombosis have common mechanisms which are largely mediated by endothelial dysfunction, which facilitates platelet activation and a pro coagulant state. (Donadini et al. 2025; Ambrosino et al. 2022).

Platelets stick to vascular damage and promote the production of thrombin, whereas natural anticoagulants ensure the balance to prevent excessive clotting. (Vilahur & Fuster, 2025; Pezeshkpoor et al. 2025).

Clopidogrel is a commonly used antiplatelet drug that prevents thrombotic events by irreversibly inhibiting the platelet P2Y₁₂ receptor, thereby reducing ADP mediated platelet activation and aggregation. Being a prodrug, it needs hepatic bioactivation, which is mainly through CYP2C19, and genetic variations in this enzyme can affect therapeutic response. Its antiplatelet effect lasts as long as the circulating platelets, which is usually 710 days (Nappi, 2024).

Interest has grown in natural compounds with potential anticoagulant effects; sweet clover and cinnamon contain bioactive molecules such as coumarins and flavonoids that may modulate platelet activity and coagulation pathways (Hou et al. 2025; Sowa-Borowiec et al. 2025). This study compares the anticoagulant effects of clopidogrel, Melilotus officinalis, and Cinnamomum verum in rabbits using hematological, coagulation, platelet function, and vascular histological assessments.

Material and methods

The experimental animals.

The experiment was employed on Thirty Healthy adult rabbits (weight 2–2.5 kg), randomized into 5 groups and 5 to 6 months of life were used in the experiment. The rabbits were housed in the College of Veterinary Medicine/Al-Qassim Green's University animal house, which has a 12-hour light and 12-hour dark cycle and a moderate temperature. With the department's ethics committee's agreement, the animals were housed in sawdust-filled, mesh plastic cages, fed fresh vegetables (carrot, lettuce, and cucumber), with free access to tap water throughout the experimental period. The animals were left to adapt for 14 days before starting the experiment for the period from November 2025 to December 2025.

Induction of thrombosis:

Thrombosis was induced by intravenous administration of a mixture containing collagen (0.5 mg/kg) and epinephrine (0.06 mg/kg), following the protocol of (Kucheryavenko et al. 2016). Animals received four doses; each administered every two days. Bleeding time (BT) and clotting time (CT) were measured prior to induction to establish baseline hemostatic values, and reassessed afterward to confirm the disturbance of hemostatic balance.

Dividing of experimental animals:

Thirty healthy adult rabbits (2–2.5 kg) were randomized into five groups (n = 6 per group). Animals received their respective treatments orally by gastric gavage for three weeks, except the positive control group, which received thrombosis-inducing injections. The groups were organized as follows:

- Group NC (negative control): received physiological saline only.
- Group T1 (positive control): injected intraperitoneally with collagen (400 µg/kg) and epinephrine (60 µg/kg) to induce thrombosis.
- Group T2 (clopidogrel): received clopidogrel 25 mg/kg orally once daily.
- Group T3 (*Melilotus officinalis*): received *Melilotus officinalis* extract 200 mg/kg orally once daily.
- Group T4 (cinnamon): received *Cinnamomum zeylanicum* extract 200 mg/kg orally once daily.

Determination of Bleeding Time and Clotting Time:

Bleeding time (BT) and clotting time (CT) were measured according to standard procedures described by (Mirdha & Jena 2016) and (Baishya et al. 2017).

Measurements were taken before thrombosis induction, after induction, and at the end of

the first, second, and third weeks following treatment with Clopidogrel, *Melilotus officinalis*, and Cinnamon. **Hematological studies:** Complete blood count (CBC) was performed using an automated veterinary hematology analyzer **Coagulation studies (PT and APTT):** Prothrombin time (PT) and activated partial thromboplastin time (APTT) were determined using a semi-automated coagulation analyzer following standard laboratory procedures.

The Results

GC–MS Analysis

GC-MS analysis for *Melilotus* extract:

Analysis of *Melilotus* extract in table (1) by GC-MS produced a TIC showing distinct peaks according to compound abundance and retention time. The major constituent was

2H-Pyran-2-one, tetrahydro-6-methyl (42.87%, RT 8.955 min), representing the predominant component of the extract. Early eluting, low molecular weight compounds such as 1,4 Dioxane 2,6 dione (3.18%, RT 2.041 min), Cyanamide (4.86%, RT 2.149 min), and Methanesulfonylacetonitrile (3.97%, RT 3.376 min) were also detected, representing small volatile intermediates. Mid retention peaks included Hexanoic acid, 2 ethyl (1.02%, RT 17.766 min), two peaks of 1,6,11 Trioxacyclopentadecane (4.39% and 3.36% at RT 19.041 and 19.483 min), and N, N Dimethyl 1,3 dioxan 2 amine (11.21%, RT 19.559 min). Notably, the presence of Coumarin, a major bioactive compound linked to *Melilotus* pharmacological activity, was detected at RT 15.24 min with an area of 8.40%.

Table 1. GC–MS Profile of *Melilotus* Extract

NO	Compounds	RT (min)	Chemical formula	MW	Area%	BA
1	1,4-Dioxane-2,6-dione	2.041	C ₄ H ₄ O ₄	116	3.18	Antibacterial
2	Cyanamide	2.149	CH ₂ N ₂	42	4.86	Antifungal
3	Methanesulfonylacetonitrile	3.376	C ₃ H ₅ NO ₂ S	119	3.97	Antimicrobial
4	2H-Pyran-2-one, tetrahydro-6-methyl-	8.955	C ₆ H ₁₀ O ₂	114	42.87	Antimicrobial, flavoring
5	Coumarin	15.24	C ₉ H ₆ O ₂	146.15	8.40	Anticoagulant,

6	Hexanoic acid, 2-ethyl-	17.766	C8H16O2	144	1.02	Antifungal
7	1,6,11- Trioxacyclopentadecane	19.041	C12H24O3	216	4.39	Bioactive agent
8	1,6,11- Trioxacyclopentadecane	19.483	C12H24O3	216	3.36	Bioactive agent
9	N, N-Dimethyl-1,3- dioxan-2-amine	19.559	C6H13N02	131	11.21	Chemical intermediate
10	D-Fructose, 3-O-methyl-	19.788	C7H14O6	194	12.63	Nutritive agent
11	α -D- Methylglucofuranoside derivative	19.893	C7H12O6	192	12.43	Antioxidant

Cinnamon extract (Cinnamomum) GC-MS analysis.

GC Ms analysis of Cinnamon (Cinnamomum) extract in table (2) revealed a TIC with clear peaks based on the abundance of the compounds and their retention time. The results indicated that (E)-Cinnamaldehyde was the dominant compound, representing 78.12% at RT 16.480 min. It was followed by Eugenol (6.35%, RT 18.254 min). Other detected compounds included Cinnamyl acetate (4.10%, RT

20.125 min), Linalool (2.80%, RT 12.352 min), Beta Caryophyllene (2.15%, RT 22.051 min), and Benzyl benzoate (1.45%, RT 25.405 min). The presence of Coumarin at 0.45% was also confirmed by the analysis.

The high concentration of Cinnamaldehyde, as well as the other identified constituents, are indicative of the strong biological activities of Cinnamon extract, including antioxidant, antimicrobial, and anti-inflammatory effects.

Table 2. GC-MS of Cinnamomum verum extract.

NO	Compounds	RT (min)	Chemical formula	MW	Area%	BA
1	(E)-Cinnamaldehyde	16.48	C9H8O	132	78.12	Antioxidant, Anti-inflammatory
2	Eugenol	18.25	C10H12O2	164	6.35	Antimicrobial, Analgesic

3	Cinnamyl acetate	20.12	C11H12O2	164	6.35	Antifungal, Flavoring
4	Linalool	12.35	C10H18O	154	2.80	Sedative, Antibacterial
5	Beta-Caryophyllene	22.05	C15H24	204	2.15	Anti- inflammatory, Anticancer
6	Benzyl benzoate	25.40	C14H12O2	212	1.45	Antimicrobial
7	Coumarin	24.50	C9H6O2	146	0.45	Antioxidant

Hematological Parameters

The complete blood count was illustrated in table (3) showed that value of WBC Cinnamon (5.56 ± 0.28^a) and Melilotus (5.37 ± 0.88^a) groups recorded the highest WBC counts, showing significantly ($p \leq 0.05$) increased values compared with the negative control (3.37 ± 0.15^b). Clopidogrel (3.96 ± 0.53^b) remained comparable to the negative group, while the positive control (5.46 ± 1.92^a) exhibited a significantly elevated response. on the other aspect . RBC data in negative (6.91 ± 0.41^a) and positive control (6.65 ± 0.08^a) groups recorded the highest RBC values. Cinnamon (5.97 ± 0.09^b) showed a significantly ($p \leq 0.05$) reduced level, while Clopidogrel (5.05 ± 0.54^c) and Melilotus (4.48 ± 0.29^d) exhibited the lowest and significantly decreased values.

PLT in rats received Clopidogrel (704.8 ± 94.1^a) produced the highest and significantly ($p \leq 0.05$) increased platelet count, followed by Cinnamon (581.6 ± 16.6^b). In contrast, the negative (393.7 ± 37.4^c), positive (374.3 ± 111.7^c), and Melilotus (393.7 ± 56.6^c) groups showed significantly lower values. The values of MPV in negative (5.95 ± 0.13^a) and Cinnamon (5.92 ± 0.12^a) groups recorded the highest MPV values. Clopidogrel (5.12 ± 0.08^b) and Melilotus

(5.05 ± 0.12^b) showed significantly ($p \leq 0.05$) reduced MPV, indicating smaller platelet size.

The negative (15.0 ± 0.24^a) and positive control (15.15 ± 0.30^a) groups recorded the highest PDW values. Cinnamon (6.18 ± 0.08^b) showed a significantly ($p \leq 0.05$) reduced value, while Clopidogrel (4.68 ± 0.08^c) and Melilotus (3.45 ± 0.15^d) exhibited the lowest and significantly decreased PDW. On the other hand negative control (2.29 ± 0.21^a) recorded the highest PCT. The positive control (1.72 ± 0.35^b) showed a significantly ($p \leq 0.05$) reduced value, while Cinnamon (0.34 ± 0.01^c), Clopidogrel (0.41 ± 0.07^c), and Melilotus (0.19 ± 0.02^d) demonstrated markedly and significantly decreased platelet mass.

The negative control (13.72 ± 0.93^a) exhibited the highest PLCR. All treated groups showed significantly ($p \leq 0.05$) reduced values, with Clopidogrel (1.93 ± 0.10^c) recording the lowest, while Cinnamon (3.20 ± 0.16^b) and Melilotus (3.48 ± 0.35^b) remained moderately decreased. PLCC was highest in the negative control (36.0 ± 4.47^a). The positive control (17.33 ± 1.03^b) and Cinnamon (18.8 ± 1.48^b) showed significantly ($p \leq 0.05$) reduced values, whereas Clopidogrel (15.5 ± 3.15^{bc}) and Melilotus (14.0 ± 2.76^c) recorded the lowest levels.

Table 3. Effect of clopidogrel, melilotofficials and cinnamon on blood profile

Group Parameter	WBC	RBC	PLT	MPV	PDW	PCT	PLCR	PLCC
Negative	3.37 ± 0.15 ^b	6.91 ± 0.41 ^a	393.7 ± 37.4 ^c	5.95 ± 0.13 ^a	15.0 ± 0.24 ^a	2.29 ± 0.21 ^a	13.72 ± 0.93 ^a	36.0 ± 4.47 ^a
Positive	5.46 ± 1.92 ^a	6.65 ± 0.08 ^a	374.3 ± 111.7 ^c	5.90 ± 0.30 ^a	15.15 ± 0.30 ^a	1.72 ± 0.35 ^b	3.18 ± 0.11 ^b	17.33 ± 1.03 ^b
Clopidogrel	3.96 ± 0.53 ^b	5.05 ± 0.54 ^c	704.8 ± 94.1 ^a	5.12 ± 0.08 ^b	4.68 ± 0.08 ^c	0.41 ± 0.07 ^c	1.93 ± 0.10 ^c	15.5 ± 3.15 ^{bc}
Melilotus	5.37 ± 0.88 ^a	4.48 ± 0.29 ^d	393.7 ± 56.6 ^c	5.05 ± 0.12 ^b	3.45 ± 0.15 ^d	0.19 ± 0.02 ^d	3.48 ± 0.35 ^b	14.0 ± 2.76 ^c
Cinnamon	5.56 ± 0.28 ^a	5.97 ± 0.09 ^b	581.6 ± 16.6 ^b	5.92 ± 0.12 ^a	6.18 ± 0.08 ^b	0.34 ± 0.01 ^c	3.20 ± 0.16 ^b	18.8 ± 1.48 ^b

□ The value represent mean ± S E

□ N=6 for each group

□ Different small letters indicated significant (P < 0.05) among groups.

Weekly Assessment of Bleeding Time and clotting time Under Different Treatments:

Bleeding Time (BT) was indicated in table (4) that negative control group recorded fairly constant bleeding times during the experiment, where no significant changes occurred as compared to breathing in recent times.

Conversely, the positive control group showed a significantly lower bleeding time beginning at Week 1(1.07 0.02) onwards recording the lowest value in all the time points (p=0.05) and thereby confirming the successful induction of

thrombosis. The Clopidogrel group, demonstrated strong and sustained anticoagulant effect, and significantly (p=3.67-0.15) increased bleed times, starting at Week 2 (3.67-0.15) and rising steadily through Week 3 (3.86-0.17) and Week 4 (4.70-0.17), above baseline. Similarly, the Melilotus group showed a significant (p≤0.05) increase from Week 2 (2.65 ± 0.11) onward, with progressive elevation at Week 3 (3.05 ± 0.16) and Week 4 (3.35 ± 0.05). The Cinnamon group displayed moderate but significant (p≤0.05) increases, starting at Week 2 (2.49 ± 0.02), rising at Week 3 (2.89 ± 0.11), and reaching

near Clopidogrel-like levels by Week 4 (3.29 ± 0.05). These findings highlight the potent effect of Clopidogrel, the intermediate

efficacy of Melilotus, and the moderate activity of Cinnamon in prolonging bleeding time compared to controls.

Table 4. The influence of clopidogrel, melilotus officinalis and cinnamon on Bleeding Time (min)

Group	Baseline	Week 1	Week 2	Week 3	Week 4
Negative control	2.232±0.040 Aa	2.390±0.130 Ba	2.588±0.189 Ba	2.328±0.054 Ba	2.258±0.032 Ba
Positive control	2.322±0.025 Ab	1.070±0.022 Aa	1.080±0.126 Aa	1.130±0.027 Aa	1.225±0.049 Aa
Clopidogrel	2.363±0.155 Ab	1.080±0.126 Aa	3.665±0.151 Cc	3.858±0.173 Dc	4.700±0.173 Dd
Melilotus	2.340±0.054 Ab	1.135±0.047 Aa	2.655±0.113 Bbc	3.050±0.167 Ccd	3.352±0.058 Cd
Cinnamon	2.447±0.179 Ab	1.225±0.049 Aa	2.490±0.021 Bbc	2.893±0.119 Ccd	3.290±0.053 Cd

* Uppercase letters = between-group comparison at same time point; Lowercase letters = within-group comparison across time points. Different letters indicate significant difference ($p < 0.05$, Tukey HSD).

Findings of Clotting Time (CT) in table (5) revealed that the negative control group (3.59 ± 0.14) had the highest clotting time at baseline, and the values had no significant changes over the course of the study. Conversely, the positive control group showed a significantly lower clotting time since Week 1 (1.17 ± 0.02) onwards and always registered the lowest values across the time span ($p < 0.05$). The Clopidogrel group showed a strong anticoagulant activity, with significantly ($p \leq 0.05$) lower clotting times at Week 1 (1.51 ± 0.07) then recovery to baseline at Week 2 (3.28 ± 0.07) then recovery to baseline in Week 3 (3.42 ± 0.07). Similarly, the Melilotus group showed a pronounced

reduction at Week 1 (1.29 ± 0.04), partial recovery at Week 2 (1.81 ± 0.12), and progressive increase through Week 3 (2.07 ± 0.02), stabilizing at Week 4 (2.32 ± 0.03). The Cinnamon group displayed moderate anticoagulant activity, with significantly ($p \leq 0.05$) reduced values at Week 1 (1.45 ± 0.12), gradual increase at Week 2 (2.36 ± 0.02) and Week 3 (2.46 ± 0.03), and near-baseline levels by Week 4 (3.10 ± 0.04). These findings highlight the potent and sustained effect of Clopidogrel, the intermediate efficacy of Melilotus, and the moderate but measurable activity of Cinnamon in modulating clotting time compared to controls.

Table 5. The effect of clopidogrel, melilots officinalis and cinnamon Clotting Time (min)

Group	Baseline	Week 1	Week 2	Week 3	Week 4
Negative control	3.592±0.148 Aa	3.455±0.128 Ba	3.460±0.131 Ca	3.487±0.114 Ca	3.582±0.155 Da
Positive control	3.477±0.117 Ab	1.172±0.029 Aa	1.512±0.170 Aa	1.525±0.166 Aa	1.453±0.120 Aa
Clopidogrel	3.473±0.122 Ab	1.512±0.170 Aa	3.285±0.086 Cb	3.427±0.191 Cb	4.248±0.082 Ec
Melilotus	3.517±0.111 Ad	1.293±0.043 Aa	1.812±0.128 Ab	2.078±0.028 Bbc	2.323±0.036 Bc
Cinnamon	3.638±0.145 Ad	1.453±0.120 Aa	2.365±0.023 Bb	2.460±0.039 Bb	3.100±0.045 Cc

* Uppercase letters = between-group comparison at same time point; Lowercase letters = within-group comparison across time points. Different letters indicate a significant difference ($p < 0.05$, Tukey HSD).

DISCUSSION

Numerous studies have demonstrated that administration of adrenaline leads to an increase in peripheral white blood cell counts (lymphocytosis). In animal models, injection of adrenaline has been observed to rapidly elevate the number of these cells as a result of their mobilization from the bone marrow, spleen, and lymphatic system into the circulation (Ince, Weber, & Scheiermann, 2019). In this study, which utilized clopidogrel therapy, a reduction in leukocyte count was observed. This decrease is attributed to the indirect anti-inflammatory

effect of clopidogrel through inhibition of the P2Y₁₂ receptor on platelets, leading to diminished release of inflammatory mediators and reduced leukocyte adhesion to the endothelium (Endarwati et al. 2025). Clopidogrel inhibits ADP-mediated platelet aggregation and thereby reduces inflammatory processes linked to platelet-leukocyte interactions. It lowers P-selectin expression and circulating platelet-leukocyte aggregates, while its active metabolite further decreases aggregate formation and tissue factor exposure on platelet and leukocyte surfaces (Franks et al. 2010). Dietary

supplementation with 250 mg cinnamon/kg of diet had a highly significant ($p \leq 0.01$) effect on differential white blood cells. Changes were observed in neutrophils, lymphocytes, the neutrophil/lymphocyte ratio, segmented neutrophils, and stab neutrophils. No significant influence was found on hemoglobin, hematocrit, red blood cells, or other hematological indices (Abdel-Azeem & El-Kader, 2022). Further examination of immune cell populations in human samples showed that T cells were more susceptible to cinnamaldehyde-induced apoptosis compared to B cells (Roth-Walter et al. 2014). *Melilotus officinalis* acts as an immune modulator by increasing the proliferation of B cells in a dose- and time- dependent manner. It also enhances IgM secretion, indicating functional activation of these cells. Rather than raising the overall leukocyte count indiscriminately, alfalfa specifically stimulates B cells, leading to their expansion and thereby improving both the total leukocyte number and the effectiveness of the immune response (Zhang et al. 2019).

Following treatment with the methanolic fractions of *Melilotus officinalis* (MFME and MFAE), these parameters showed a significant ($p < 0.01$) increase on both the 15th and 30th day of treatment, indicating recovery of the hematopoietic system impaired by iron overload (Sheikh et al. 2020) In untreated diabetic rats, RBCs were significantly reduced compared to controls. Administration

of cinnamon extract improved RBC counts to a significant level, with slight increases in Hb and PCV. These effects are attributed to the hypoglycemic action of cinnamon, which reduces hyperglycemia-induced damage in the kidney and liver and supports protein synthesis required for RBC and Hb production. Antioxidant activity, particularly glutathione, may further contribute to these improvements (Mhammad et al. 2015).

Collagen is a strong platelet activator that promotes adhesion, aggregation, and mediator release. Epinephrine alone is weak but significantly enhances platelet aggregation when combined with collagen, producing a synergistic effect that accelerates clot formation and increases thrombosis risk (Lahiri et al. 2009). Collagen stimulates platelet activation by stimulating P2 receptors and TxA_2 synthesis, whereas epinephrine acts via P2Y1 and P2Y12 pathways. A low level of ATP increases the action of both agonists. (Aslam et al. 2013).

Clopidogrel prevents platelet aggregation through the action of inhibiting P2Y12 receptors, thus inhibiting ADP-dependent platelet activation. Inhibition deficiency, such as CYP2C19 polymorphisms, makes clopidogrel less protective, although clopidogrel is more effective than aspirin at high shear rates, making it important for the prevention of stable clots (Hosokawa et al. 2013). Dicoumarol was isolated from moldy sweet clover (*Melilotus officinalis*),

demonstrating anticoagulation properties, but with limited clinical application because of the high risk of bleeding and small therapeutic window.

There was a significant reduction in platelets in diabetic rats without treatment. Cinnamon extract exhibited a significant increase in platelets, although metformin showed a more pronounced effect. Furthermore, cinnamon acts as a preventive agent for platelet aggregation in the presence of hyperlipidemia and hyperglycemia, thereby reducing the risk of cardiovascular complications and providing an alternative natural substitute to antithrombotic agents (Mhammad et al. 2015).

According to reports, administration of CE was seen to cause a significant reduction in PT and aPTT values, albeit not statistically significant. In another report, the CE injection group had a reduction in PT and aPTT values when compared to other groups. Thus, it can be seen that collagen and epinephrine have the capability to induce thrombosis via the intrinsic and extrinsic pathway (Kim et al. 2018; Kim et al. 2023).

The results showed that there were no significant alterations to PT and INR when administering dual antiplatelet therapy using aspirin and clopidogrel. However, the duration of the aPTT was reduced and the number of platelets (PLT) increased in the responder group. This implies that the effect

of the dual therapy on coagulation factors was selective, since it increased platelet activity and decreased the aPTT without affecting PT and INR.

It was discovered that certain cinnamon extracts increased PT and aPTT times by around 10%. This result is believed to be the product of the combined action of all active components in the extract, whereas there might be other substances in the mixture that have higher anticoagulant properties (Kim et al. 2010). The alfalfa extract was shown to affect coagulation factors. First, it reduced the prothrombin time (PT), which means that the alfalfa extract exhibits procoagulant activity along the extrinsic pathway. Secondly, no significant changes in the aPTT factor were observed, implying that the intrinsic pathway was unaffected by the substance (Ahmadianfar et al. 2023).

Low levels of adrenaline cause an increase in platelet adherence to collagen under high shear stress, causing less bleeding time. Furthermore, thromboelastometry displays faster clotting because of elevated thrombin creation. These mechanisms account for the shortened bleeding and clotting times associated with adrenaline and collagen combinations (Golaszewska et al. 2021). The most notable finding from this research suggests that the higher sensitivity to clopidogrel causes a higher probability of bleeding episodes, mainly significant bleeding

incidents. Patients were classified into two groups based on their sensitivity to clopidogrel than the rest; those with more sensitivity had around three times the risk of developing major bleeding instances. (Sibbing et al. 2010).

The coumarin content in cinnamon inhibits vitamin K epoxide reductase, thus preventing the activation of factor II, VII, IX, and X in the clotting process. These actions result in reduced coagulation and increase in INR because the intrinsic pathway is affected (Chase et al. 2022).

Conclusions

According to the results of the experiment, clopidogrel and *Melilotus officinalis* demonstrated the greatest ability to reduce the risk of development of thrombotic disorders after the induction of thrombosis via collagen-epinephrine-induced procedure among all examined drugs. Both medications helped achieve proper hemostasis and reduced the level of platelet activation. Moreover, both clopidogrel and *Melilotus officinalis* provided better results than cinnamon extract concerning changes in coagulation parameters. The GC-MS test showed that there were active compounds found in plant extracts. These findings provide a scientific basis for further exploration of plant-derived agents as supportive or alternative anticoagulant therapies.

REFERENCES

1. Pastori, D., Cormaci, V. M., Marucci, S., Franchino, G., Del Sole, F., Capozza, A., ... & Pignatelli, P. (2023). *A comprehensive review of risk factors for venous thromboembolism: From epidemiology to pathophysiology. International Journal of Molecular Sciences*, **24(4)**, 3169. <https://doi.org/10.3390/ijms24043169>
2. Donadini, M. P., Calcaterra, F., Romualdi, E., Ciceri, R., Cancellara, A., Lodigiani, C., ... & Mavilio, D. (2025). *The link between venous and arterial thrombosis: Is there a role for endothelial dysfunction? Cells*, **14(2)**, 144. <https://doi.org/10.3390/cells14020144>
3. Ambrosino, P., Bachetti, T., D'Anna, S. E., Galloway, B., Bianco, A., D'Agnano, V., ... & Maniscalco, M. (2022). *Mechanisms and clinical implications of endothelial dysfunction in arterial hypertension. Journal of Cardiovascular Development and Disease*, **9(5)**, 136. <https://doi.org/10.3390/jcdd9050136>
4. Vilahur, G., & Fuster, V. (2025). *Interplay between platelets and coagulation: From protective haemostasis to pathological arterial thrombosis. European Heart*

- Journal**, **46(5)**, **413–423**.
<https://doi.org/10.1093/eurheartj/ehae776>
5. Pezeshkpoor, B., Fischer, R., Preisler, B., Hartlieb, K., Rühl, H., Müller, J., ... & Oldenburg, J. (2025). *Modulation of haemostatic balance in combined von Willebrand disease and antithrombin deficiency: A comprehensive family study*. **Haemophilia**, **31(1)**, **140–147**.
<https://doi.org/10.1111/hae.15147>
 6. Nappi, F. (2024). *P2Y12 receptor inhibitor for antiaggregant therapies: From molecular pathway to clinical application*. **International Journal of Molecular Sciences**, **25(14)**, **7575**.
<https://doi.org/10.3390/ijms25147575>
 7. Hou, Y., Li, H., Zhu, L., Li, Y., Zeng, Y., Quan, T., ... & Wei, Y. (2025). *A review of natural compounds to regulate platelet aggregation: Molecular mechanism and research advance*. **Frontiers in Pharmacology**, **16**, **1537776**.
<https://doi.org/10.3389/fphar.2025.1537776>
 8. Sowa-Borowiec, P., Czernicka, M., Jarecki, W., & Dżugan, M. (2025). *Sweet Clover (*Melilotus spp.*) as a source of biologically active compounds*. **Molecules**, **30(3)**, **526**.
<https://doi.org/10.3390/molecules30030526>
 9. Kucheryavenko, A. F., Spasov, A. A., Tyan, M., & Suzdalev, K. F. (2016). *Antithrombotic activity of SBT-828 in models of arterial thrombosis*. **Journal of Clinical Pharmacology & Toxicology**, **1(2)**, **8–11**.
 Available at:
<https://nobleresearch.org/Content/PDF/20/JCPT-2016005/JCPT-2016005.pdf>
 10. Mirdha, M., & Jena, S. K. (2016). *Distribution of blood group and its relation to bleeding time and clotting time*. **International Journal of Medical Science and Public Health**, **5(12)**, **2566–2569**.
 Available at:
https://www.researchgate.net/publication/305344753_Distribution_of_blood_group_and_its_relation_to_bleeding_time_and_clotting_time
 11. Baishya, R., Sarkar, R., & Barman, B. (2017). *Blood group and its relationship with bleeding time and clotting time*. **International Journal of Research in Medical Sciences**, **5(9)**, **4147–4150**.
<https://doi.org/10.18203/2320-6012.ijrms20174000>
 12. Ince, L. M., Weber, J., & Scheiermann, C. (2019). *Control of leukocyte trafficking by stress-associated hormones*. **Frontiers in Immunology**, **9**, **3143**.
<https://doi.org/10.3389/fimmu.2018.03143>

13. Eदारwati, T., Kurniasih, K. I., Fauziah, F., Sunarti, S., & Salim, M. A. (2025). *Comparison of effectiveness of aspirin, clopidogrel and cilostazol monotherapy treatment in ischaemic stroke*. **BIO Web of Conferences**, **152**, 01001. <https://doi.org/10.1051/bioconf/202515201001>
14. Franks, Z. G., Campbell, R. A., Weyrich, A. S., & Rondina, M. T. (2010). *Platelet–leukocyte interactions link inflammatory and thromboembolic events in ischemic stroke*. **Annals of the New York Academy of Sciences**, **1207**(1), 11–17. <https://doi.org/10.1111/j.1749-6632.2010.05733.x>
15. Abdel-Azeem, A. A. S., & El-Kader, I. A. A. (2022). *Growth performance, carcass attributes, blood hematology and biochemical constituents of growing rabbits supplemented with cinnamon and clove powder*. **Animal Science Papers & Reports**, **40**(3), 351–370. Available at: <https://www.igbzpan.pl/uploaded/FSiBundleContentBlockBundleModelTranslatableBlockTranslatableFilesElement/filePath/2207/str351-370.pdf>
16. Roth-Walter, F., Moskovskich, A., Gomez-Casado, C., Diaz-Perales, A., Oida, K., Singer, J., ... & Jensen-Jarolim, E. (2014). *Immune suppressive effect of cinnamaldehyde due to inhibition of proliferation and induction of apoptosis in immune cells: Implications in cancer*. **PLOS ONE**, **9**(10), e108402. <https://doi.org/10.1371/journal.pone.0108402>
17. Zhang, C., Li, Z., Zhang, C.-Y., Li, M., Lee, Y., & Zhang, G.-G. (2019). *Extract methods, molecular characteristics, and bioactivities of polysaccharide from alfalfa (Medicago sativa L.)*. **Nutrients**, **11**(5), 1181. <https://doi.org/10.3390/nu11051181>
18. Sheikh, N. A., Kosalge, S. B., Desai, T. R., Dewani, A. P., Mohale, D. S., & Tripathi, A. S. (2020). *Evaluation of beneficial effects of Melilotus officinalis on blood profiles in iron overloaded rats*. **Journal of Hematology Research**, **7**, 23–30.
19. Mhammad, H. A., Jubrail, A. M. S., & Najeeb, M. K. (2015). *Impact of cinnamon extract on hyperlipidemic and diabetic rats*. **International Journal of Chemical and Biomolecular Science**, **1**(3), 96–106.
20. Lahiri, P., Roy, S., Sardar, P., Deb, S., Chakrabarti, P., Guha, P., ... & Dasgupta, A. K. (2009). *Platelet*

- responsiveness to yohimbine hydrochloride...* **Blood Cells, Molecules, and Diseases**, **43(1)**, 105–110.
<https://doi.org/10.1016/j.bcnd.2009.02.002> ([doi.org in Bing](#))
21. Aslam, M., Sedding, D., Koshty, A., Santoso, S., Schulz, R., Hamm, C., & Gündüz, D. (2013). *Nucleoside triphosphates inhibit ADP, collagen, and epinephrine-induced platelet aggregation.* **Thrombosis Research**, **132(5)**, 548–557.
<https://doi.org/10.1016/j.thromres.2013.08.021> ([doi.org in Bing](#))
22. Hosokawa, K., Ohnishi, T., Sameshima, H., Miura, N., Ito, T., Koide, T., & Maruyama, I. (2013). *Analysing responses to aspirin and clopidogrel...* **Thrombosis and Haemostasis**, **109(1)**, 102–111.
<https://doi.org/10.1160/TH12-06-0441> ([doi.org in Bing](#))
23. Kim, L., Lim, Y., Park, S. Y., Kim, Y. J., Kwon, O., Lee, J. H., ... & Kim, J. Y. (2018). *Antithrombotic effect of garlic powder and tomato extracts...* **Food Science and Biotechnology**, **27(5)**, 1513–1518.
<https://doi.org/10.1007/s10068-018-0469-z> ([doi.org in Bing](#))
24. Kim, J. T., Lee, S. B., Son, M. J., Zhou, Y., Qiu, S., Park, H. J., ... & Lee, H. J. (2023). *Perilla oil and α -linolenic acid ameliorated thrombosis...* **Food Science and Biotechnology**, **32(7)**, 997–1003.
<https://doi.org/10.1007/s10068-022-01241-6> ([doi.org in Bing](#))
25. Shin, J. H., & Han, H. J. (2025). *Evaluation of clopidogrel responsiveness using PFA-200 in dogs.* **Frontiers in Veterinary Science**, **12**, 1595147.
<https://doi.org/10.3389/fvets.2025.1595147> ([doi.org in Bing](#))
26. Kim, S. Y., Koo, Y. K., Koo, J. Y., Ngoc, T. M., Kang, S. S., Bae, K., ... & Yun-Choi, H. S. (2010). *Platelet anti-aggregation activities of compounds from Cinnamomum cassia.* **Journal of Medicinal Food**, **13(5)**, 1069–1074.
<https://doi.org/10.1089/jmf.2009.1365> ([doi.org in Bing](#))
27. Ahmadianfar, S., Mehrabi, N., Mohammadi, S., Sobhanizadeh, A., Moradabadi, A., & Noroozi-Aghideh, A. (2023). *Effects of Horsetail, Alfalfa, Ortie, Chêne and Aleppo oak...* **Natural Product Sciences**, **29(1)**, 42–49.
<https://doi.org/10.20307/nps.2023.29.1.42> ([doi.org in Bing](#))
28. Golaszewska, A., Misztal, T., Marcinczyk, N., Chabielska, E., & Rusak, T. (2021). *Adrenaline may contribute to prothrombotic condition...* **Frontiers in Physiology**, **12**, 657881.

- <https://doi.org/10.3389/fphys.2021.657881> ([doi.org in Bing](https://doi.org/10.3389/fphys.2021.657881))
29. Sibbing, D., Schulz, S., Braun, S., Morath, T., Stegherr, J., Mehilli, J., ... & Kastrati, A. (2010). *Antiplatelet effects of clopidogrel...* **Journal of Thrombosis and Haemostasis**, **8(2)**, 250–256.
<https://doi.org/10.1111/j.1538-7836.2009.03709.x> ([doi.org in Bing](https://doi.org/10.1111/j.1538-7836.2009.03709.x))
30. Chase, C., Doyle, A., St John, S., Laurent, T., & Griffith, S. (2022). *Post-operative haemorrhage secondary to cinnamon use.* **International Journal of Surgery Case Reports**, **95**, 107179.
<https://doi.org/10.1016/j.ijscr.2022.107179> ([doi.org in Bing](https://doi.org/10.1016/j.ijscr.2022.107179))