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Inhibitory Effects of Crocin and Crocetin on Platelet Aggregation and Adhesion in Healthy Volunteers

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ABSTRACT

Medicinal plants have shown potential in preventing cardiovascular diseases due to their bioactive compounds. This study evaluated the inhibitory effects of saffron-derived crocin and crocetin on platelet aggregation induced by various agonists and also their impact on platelet adhesion. This experimental laboratory study included 10 healthy individuals. Hemostasis was assessed using prothrombin time (PT) and partial thromboplastin time (PTT) tests, while complete blood count (CBC) analysis was performed with a Sysmex hematology analyzer. Platelet aggregation was evaluated in the presence of crocin and crocetin using a Chronolog dual-channel aggregometer with agonists including collagen, ADP, epinephrine, and calcium ionophore A23187. Platelet adhesion was also assessed using the Bellavite method and ELISA. Statistical analyses were performed with SPSS version 24 and GraphPad Prism version 8. A p-value < 0.05 indicated statistical significance. The participants had an average age of 27.3 ± 3.4 years. PT, PTT, and CBC indices were within normal ranges. Both crocin and crocetin significantly inhibited platelet aggregation in a dose-dependent manner compared to the untreated group ($p< 0.001$). Platelet adhesion also decreased considerably at higher concentrations of crocin and crocetin (100 and 200 µg/ml) compared to the control group ($p< 0.01$). Crocin and crocetin, key bioactive compounds in saffron, demonstrated potent antiplatelet effects by inhibiting platelet aggregation and adhesion. These findings suggest that these compounds could prevent and potentially treat thrombotic disorders.

Keywords: Crocin, Crocetin, Platelet Aggregation, Platelet Adhesion

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INTRODUCTION

Platelets play a critical role in hemostasis and thrombosis. Upon vascular injury, platelets adhere to exposed subendothelial structures via interactions with von Willebrand factor (vWF) and collagen, forming a hemostatic plug [1]. This process is further amplified by activation through agonists such as ADP, collagen, ristocetin, and calcium. ADP binds to P2Y receptors, enhancing platelet aggregation, while collagen strengthens adhesion through glycoprotein and integrin pathways [2]. Ristocetin simulates high-shear conditions, promoting vWF-mediated platelet adhesion crucial for thrombosis. Calcium ions facilitate granule secretion and cytoskeletal rearrangements, stabilizing platelet aggregates [3]. While these mechanisms are vital for hemostasis, uncontrolled platelet activity can lead to the formation of harmful thrombi, leading to thromboembolic issues.

Regulating platelet function is crucial for preventing thrombotic disorders. Antiplatelet drugs like aspirin reduce aggregation by targeting COX-1, lowering arterial thrombosis risk [4]. New strategies focus on inhibiting vWF-mediated adhesion to prevent thrombosis with minimal bleeding [5]. Additionally, platelet-immune cell interactions exacerbate thromboinflammatory conditions, such as in COVID-19, highlighting the need for targeted therapies [6]. Understanding platelet aggregation and adhesion is vital for treating thrombotic and inflammatory vascular diseases. Natural products, like flavonoids, polyphenols, and terpenoids, offer safer alternatives to synthetic antiplatelet drugs. They inhibit platelet aggregation via mechanisms such as blocking arachidonic acid metabolism, ADP pathways, and thromboxane production [7]. Similarly, bioactive peptides and proteins derived from natural sources, such as snake venom and plants, show promise as next-generation antiplatelet agents with fewer side effects [8]. These findings highlight the growing interest in natural antiplatelet agents as safer and more effective options for thrombotic disorder management.

Saffron (*Crocus sativus* L.) is a medicinal plant known for its antioxidant, anti-inflammatory, and neuroprotective properties. Its carotenoids, crocin and crocetin, aid in managing cardiovascular diseases, neurodegenerative disorders, and oxidative stress [9-11]. Crocin and crocetin exhibit significant antiplatelet activity by modulating platelet aggregation and adhesion mechanisms. Crocin inhibits oxidative stress-induced platelet apoptosis by reducing reactive oxygen species (ROS) and stabilizing mitochondrial function, particularly in response to collagen and calcium ionophore stimuli [12]. Crocetin, on the other hand, attenuates ADP- and collagen-induced platelet activation by reducing dense granule release and intracellular calcium mobilization, which are pivotal steps in platelet aggregation and thrombus formation [13]. Crocin and crocetin show promise in reducing platelet hyperactivity and oxidative stress, but require further study to assess their impact on platelet aggregation and adhesion. This study aims to evaluate the antiplatelet properties of crocin and crocetin in

healthy volunteers by comparing their effects on platelet aggregation and adhesion.

MATERIAL AND METHODS

Study Design

This experimental laboratory trial was conducted to investigate the effects of crocin and crocetin on platelet aggregation and adhesion using blood samples from healthy individuals. The study was performed in a controlled laboratory setting to ensure accuracy and reliability. Ethical approval for the study was obtained from the Ethics Committee of Jahrom University of Medical Sciences (Code: IR.JUMS.REC.1399.023). All participants provided informed consent before sample collection, and the study adhered to the ethical guidelines of the Declaration of Helsinki to ensure the confidentiality and safety of participants.

Sample Size and Selection

This study included 10 healthy male participants who were selected from among available healthy individuals using convenience sampling. Participants were required to meet the following inclusion criteria: no use of antiplatelet or anticoagulant medications (e.g., aspirin, clopidogrel, warfarin), nonsteroidal anti-inflammatory drugs (NSAIDs), immunosuppressants, or other drugs affecting platelet and coagulation factors; absence of platelet or coagulation disorders; no underlying conditions such as cardiovascular diseases, or liver disorders; platelet count above 100,000/µL; hemoglobin level of at least 10 g/dL; and non-smoker status. Participants were excluded if they did not cooperate during the study, failed to adhere to study protocols, or consumed medications affecting platelet or coagulation function. After obtaining written consent and conducting the coagulation screening tests as well as full blood counts, the volunteer participants entered the study.

Blood Collection

After obtaining informed consent, 10 ml of peripheral blood samples were collected from the antecubital vein through a 21-gauge needle (BD Vacutainer needles). Blood samples were collected in ethylene diamine tetra-acetic acid anticoagulant (EDTA, 1.5 mg/ml) for CBC analysis. For evaluation of coagulation screening tests, and also platelet aggregation and adhesion, blood samples were collected in sodium citrate (3.8 %) vials in a ratio of nine volumes of blood to one volume of anticoagulant.

Laboratory Analysis

CBC was performed using EDTA-treated blood samples. The measured CBC indices included erythrocytes, hemoglobin, hematocrit, platelets, and leukocytes. A Sysmex XT-2000i hematology analyzer (Diamond Diagnostics, USA) was used for this purpose. In addition, screening tests such as PT, APTT, and BT were performed to evaluate primary and secondary hemostasis. BT was measured based on the Template method, as previously reported [14]. PT and PTT were measured through plasma clotting time.

Platelet Aggregation

Platelet aggregation was assessed using a dual-channel Chrono-log aggregometer. Platelet-rich plasma (PRP) was prepared by mixing venous blood with acid citrate dextrose in a 6:1 ratio, followed by centrifugation at 90g for 15 minutes. The PRP supernatant was collected, and platelet counts were adjusted to 250,000–300,000/µL. Aggregation tests involved incubating 240 µL of PRP at 37°C with varying concentrations of crocin (Cat no: BP0406, Chengdu Biopurify Phytochemical, China; purify 98%), and crocetin (Cat no: BP0405, Chengdu Biopurify Phytochemical, China; purify 98%)(0, 2, 10, and 20 µg/ml) in HEPES-buffered saline for 3 minutes. Aggregation was initiated using agonists such as collagen (10 µg/ml), ADP (10 µM), calcium ionophore A23187 (6 µM), and ristocetin (1.25 µM), and changes in plasma turbidity were then recorded.

Platelet Adhesion

Platelet adhesion was evaluated using collagen-coated polystyrene 96-well plates. Collagen was fixed by incubating 20 µL of type I collagen and 200 µL PBS overnight at 4°C, followed by blocking with 200 µL of 1% BSA in PBS for 1 hour at 37°C. Following washing wells with PBS, the pre-treated PRP with different concentrations of crocin or crocetin (0, 10, 25, 50, 100, and 200 µg/ml) for 10 minutes was added. The mixture was incubated for 90 minutes at 37°C, followed by washing and platelet lysis with 150 µL of 0.1 M citrate buffer (pH 5.4) for 90 minutes at 37°C. The reaction was terminated with 100 µL of 2N NaOH, and absorbance at 405 nm was measured. Platelets treated with PBS were considered to exhibit 100% adhesion.

Statistical Analysis

Statistical analyses were conducted using SPSS software, version 24 (IBM SPSS Statistics version 24, USA). Graphs and figures were created using GraphPad Prism (version 8.0) software. The Kolmogorov-Smirnov test was used to assess the normality of data distribution. Descriptive data were expressed as the mean ± standard deviation, while analytical data were evaluated using one-way analysis of variance (ANCOVA). A *p*-value of less than 0.05 was considered statistically significant for all statistical analyses.

RESULTS

The hematological parameters of 10 healthy male volunteers are represented in Table 1. The participants had an average age of 27.3 ± 3.4 years (range, 21-32). These results confirm that the cohort represents a healthy population, providing a robust baseline for evaluating the antiplatelet effects of crocin and crocetin in subsequent experiments (Table 1).

Table 1 Characteristics of the study participants

Participant	Age (year)	RBC (× 10^6/µl)	Hb (g/dl)	HCT (%)	Platelets (× 10^3/µl)	Leukocyte (× 10^3/µl)	PT (sec)	PTT (sec)	BT (sec)
1	25	5.3	16.4	49	330	5.8	12.5	42	250
2	28	4.8	14.3	43	447	7.5	11	32	180
3	21	4.3	13.9	41	187	6.3	12	37	280
4	24	4.9	15.1	46	326	8.8	13.2	32	215
5	27	5.5	16.5	51	277	6.5	13	34	310
6	29	5.6	17	52	385	5.5	12	33	290
7	31	4.9	15.6	47	195	7.2	13	37	340
8	26	5.9	16.7	58	268	8.0	12	33	210
9	30	5.0	15.1	47	313	9.4	12.8	41	300
10	32	4.8	14.6	45	235	6.1	12	36	220
Mean ± sd	27.3 ± 3.4	5.1 ± 1.2	17.0 ± 0.35	47.9 ± 4.8	296 ± 81.6	7.0 ± 1.3	12.3 ± 0.6	35.7 ± 3.5	259.5 ± 52.0

Platelet Aggregation

Results demonstrated a significant, dose-dependent inhibition of platelet aggregation across all agonists (p = 0.000) in treatment with crocin. For collagen-induced aggregation, platelet aggregation decreased from 95 ± 4.3% in the untreated group to 18 ± 2.1% at 20 µg/ml. Similarly, ADP-induced aggregation was reduced from 97 ± 5.4% to 9 ± 0.9%, while epinephrine-induced aggregation showed the strongest inhibition, decreasing from 98 ± 4.8% to 6 ± 0.7%. Aggregation triggered by calcium ionophore A23187 also declined significantly, from 94 ± 4.2% to 21 ± 1.1% (Table 2 and Fig. 1).

Table 2 Platelet aggregation in the group treated with different concentrations of crocin in response to agonists

	Crocin (µg/ml)				
	0	2	10	20	p value
Collagen	95 ± 4.3	82 ± 5.1	55 ± 5.4	18 ± 2.1	<0.001
ADP	97 ± 5.4	72 ± 4.7	35 ± 3.9	9 ± 0.9	<0.001
Epinepherin	98 ± 4.8	74 ± 3.9	44 ± 2.8	6 ± 0.7	<0.001
A 23187	94 ± 4.2	79 ± 4	60 ± 3.2	21 ± 1.1	<0.001

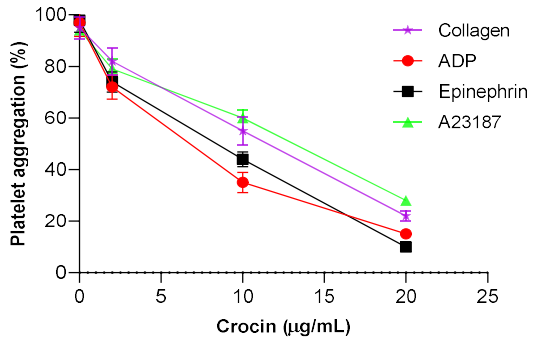

Fig. 1 Dose-dependent inhibition of platelet aggregation by crocin in response to different agonists. The figure illustrates the percentage of platelet aggregation induced by collagen, ADP, epinephrine, and calcium ionophore A23187 at varying concentrations of crocin (0, 2, 10, and 20 µg/ml). Crocin exhibits a significant, dose-dependent reduction in aggregation across all agonists, with the strongest inhibition observed at 20 µg/ml. Error bars represent standard deviations.

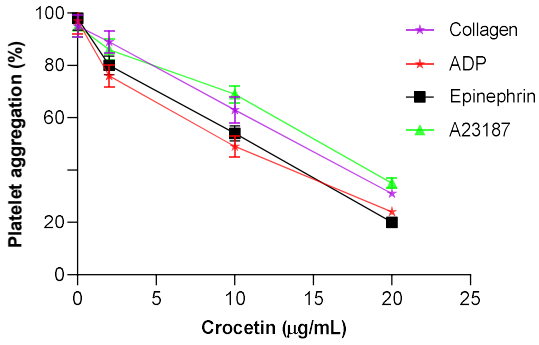

Fig. 2 Dose-dependent inhibition of platelet aggregation by crocetin in response to different agonists**.** The figure shows the percentage of platelet aggregation induced by collagen, ADP, epinephrine, and calcium ionophore A23187 at varying concentrations of crocetin (0, 2, 10, and 20 µg/ml). Crocetin significantly reduces platelet aggregation in a dose-dependent manner across all agonists, with the greatest inhibition observed at 20 µg/ml. Error bars represent standard deviations.

The effects of crocetin on platelet aggregation were also evaluated. The results demonstrated a significant, dose-dependent reduction in platelet aggregation across all agonists (p = 0.000). Collagen-induced aggregation decreased from 96 ± 4.0% in the untreated group to 31 ± 1.7% at 20 µg/ml crocetin. Similarly, ADP-induced aggregation was reduced from 97 ± 5.1% to 24 ± 0.9%, while epinephrine-induced aggregation declined from 98 ± 4.5% to 20 ± 1.1%. Aggregation triggered by calcium ionophore A23187 decreased from 95 ± 3.8% to 35 ± 2.0% at the highest crocetin concentration. These findings indicate that crocetin significantly inhibits platelet aggregation in a dose-dependent manner, with the most substantial effects observed at 20 µg/ml, further supporting its potential as an antiplatelet agent (Table 3 and Fig. 2).

Table 3 Platelet aggregation in the group treated with different concentrations of crocetin

	Crocetin (µg/ml)				p value
	0	2	10	20	
Collagen	96 ± 4.0	89 ± 4.3	63 ± 5.0	31 ± 1.7	<0.001
ADP	97 ± 5.1	76 ± 4.2	49 ± 4.0	24 ± 0.9	<0.001
Epinepherin	98 ± 4.5	80 ± 3.6	54 ± 2.9	20 ± 1.1	<0.001
A 23187	95 ± 3.8	86 ± 3.9	69 ± 3.3	35 ± 2.0	<0.001

Platelet Adhesion

The effects of crocin and crocetin on platelet adhesion were evaluated. Both compounds demonstrated a dose-dependent reduction in platelet adhesion. At 0 µg/ml, platelet adhesion was set at 100% for both crocin and crocetin. As the concentrations increased, adhesion decreased significantly (p < 0.01). At 200 µg/ml, crocin reduced platelet adhesion to approximately 20%, while crocetin exhibited a similar effect, reducing adhesion to around 25%. The observed inhibitory effects highlight the potential of both compounds to interfere with platelet adhesion, with comparable efficacy at higher concentrations (Fig. 3).

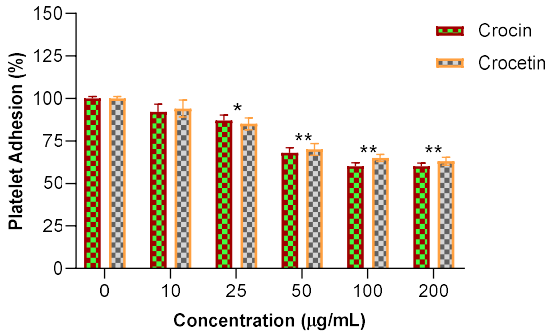

Fig. 3 Dose-dependent inhibition of platelet adhesion by crocin and crocetin. The figure illustrates the percentage of platelet adhesion at varying concentrations of crocin and crocetin (0, 10, 25, 50, 100, and 200 µg/ml). Both compounds significantly inhibited platelet adhesion in a dose-dependent manner, with comparable effects observed at higher concentrations. Statistical significance is indicated as **; p < 0.001, *; p < 0.01. Error bars represent standard deviations.

DISCUSSION

Platelet aggregation and adhesion are two critical processes involved in thrombosis and hemostasis. The inhibition of these processes by natural compounds or therapeutic agents can thus be a potential strategy for preventing thrombotic diseases.

Our study's findings that crocin and crocetin inhibit platelet aggregation and adhesion significantly contribute to the current understanding of these compounds, extending their known therapeutic effects beyond traditional applications. The observed reduction in platelet function indicates a promising strategy for preventing thrombotic events, offering potential applications in the management of cardiovascular diseases. Our study's findings on

crocin and crocetin strongly corroborate earlier research highlighting their inhibitory effects on platelet aggregation. Our study revealed a significant, dose-dependent decrease in platelet aggregation induced by various agonists, including collagen, ADP, epinephrine, and calcium ionophore A23187, with crocin exhibiting the strongest inhibitory effect on epinephrine-induced aggregation. These findings are consistent with those from Thushara *et al.* [15], who reported that crocin inhibited collagen- and A23187-induced platelet aggregation, and its effects were partially attributed to its antioxidant properties that reduce reactive oxygen species (ROS) and prevent apoptotic events in platelets. Crocetin, the aglycone form of crocin, similarly exhibited an inhibitory effect on platelet aggregation, aligning with its broader pharmacological properties as outlined by Guo *et al.* [16]. Crocetin demonstrated a weaker yet still significant reduction in platelet aggregation compared to crocin, likely attributed to structural differences and distinct bioactivity profiles, with crocin's stronger antioxidative properties potentially contributing to its more potent action.

Additionally, our findings align with the broader context of natural compounds inhibiting platelet aggregation, as shown in the review by Nouruzi *et al.* [17], which supports the idea that bioactive compounds like crocin and crocetin can modulate platelet aggregation through diverse mechanisms. Although variations exist, such as the findings by Yarijani *et al.* [18], demonstrating that crocin reduces inflammation and oxidative stress in renal ischemia/reperfusion injury, these anti-inflammatory properties may shed light on how crocin influences platelet function by regulating pathways involved in platelet adhesion and aggregation. Moreover, studies on crocin's general pharmacological effects further support its role in modulating platelet function. For instance, Mohamadpour *et al*. [19] reported that crocin exhibited a safe profile in healthy volunteers without causing major adverse events, while Yang *et al.* [20] demonstrated crocin's anti-inflammatory effects in hemorrhagic shock models by reducing markers of inflammation and tissue injury.

Our study's findings on crocin and crocetin are also consistent with previous research highlighting the critical role of the P2Y12 receptor in platelet aggregation. Fälker *et al.* [21] showed that thrombin-induced platelet activation relies on P2Y12 receptor signaling, and Wang *et al.* [22] emphasized the importance of P2Y12 in platelet aggregation and its therapeutic targeting in cardiovascular diseases. Similar to the P2Y12 antagonist AR-C69931MX, crocin and crocetin inhibited platelet aggregation, suggesting their antiplatelet effects may involve modulation of P2Y12 signaling. These findings support the idea that crocin and crocetin inhibit platelet aggregation through P2Y12 receptor pathways.

The results from our study on crocin and crocetin, specifically their inhibitory effects on platelet aggregation, are consistent with a growing body of research highlighting the diverse therapeutic benefits of saffron and its bioactive compounds. For instance, Naimi *et al.* [23] demonstrated the effects of saffron on coagulation and fibrinolysis, noting its beneficial effects on long-term coagulation homeostasis. This is in line with our findings, where crocin and crocetin displayed significant inhibition of platelet aggregation, potentially contributing to the regulation of coagulation pathways. Moreover, Khan *et al.* [24] explored the anticoagulant properties of saffron extracts, demonstrating that saffron's stigma extract (SEE) showed strong anticoagulant activity, comparable to aspirin, which supports the notion that saffron compounds like crocin and crocetin may also play a role in preventing thrombotic events. This reinforces our hypothesis that crocin and crocetin inhibit platelet aggregation through pathways that align with the established pharmacological effects of saffron compounds in various disease contexts, further validating their potential in managing thrombotic diseases.

The study has some limitations that should be considered. Firstly, the sample size of 10 healthy volunteers may not be large enough to generalize the findings to broader populations. The study also relies on in-vitro testing of platelet aggregation and adhesion, which may not fully replicate in vivo conditions where multiple physiological factors interact. Lastly, while the study suggests that saffron compounds could inhibit platelet function, further research is needed to clarify the exact mechanisms and pathways involved, as well as to confirm the findings in clinical settings.

CONCLUSION

This study provides robust evidence that crocin and crocetin, two naturally occurring compounds derived from saffron, exhibit potent anti-platelet aggregation and anti-adhesion properties. Both compounds significantly and dose-dependently inhibited platelet aggregation across a variety of agonists and reduced platelet adhesion, demonstrating their multifaceted ability to disrupt critical steps in thrombus formation. These findings underscore the potential of crocin and crocetin as promising candidates for the development of novel antiplatelet therapies, offering a natural, effective, and potentially safer alternative to current pharmacological agents. The dual action of these compounds, targeting both aggregation and adhesion pathways, could address limitations in existing therapies, such as resistance and adverse effects, and enhance the scope of treatment for thrombotic disorders. Furthermore, their natural origin adds an additional layer of appeal for their use in populations seeking plant-based therapeutic options.

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Competing Interests

The authors declare no competing interests.

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