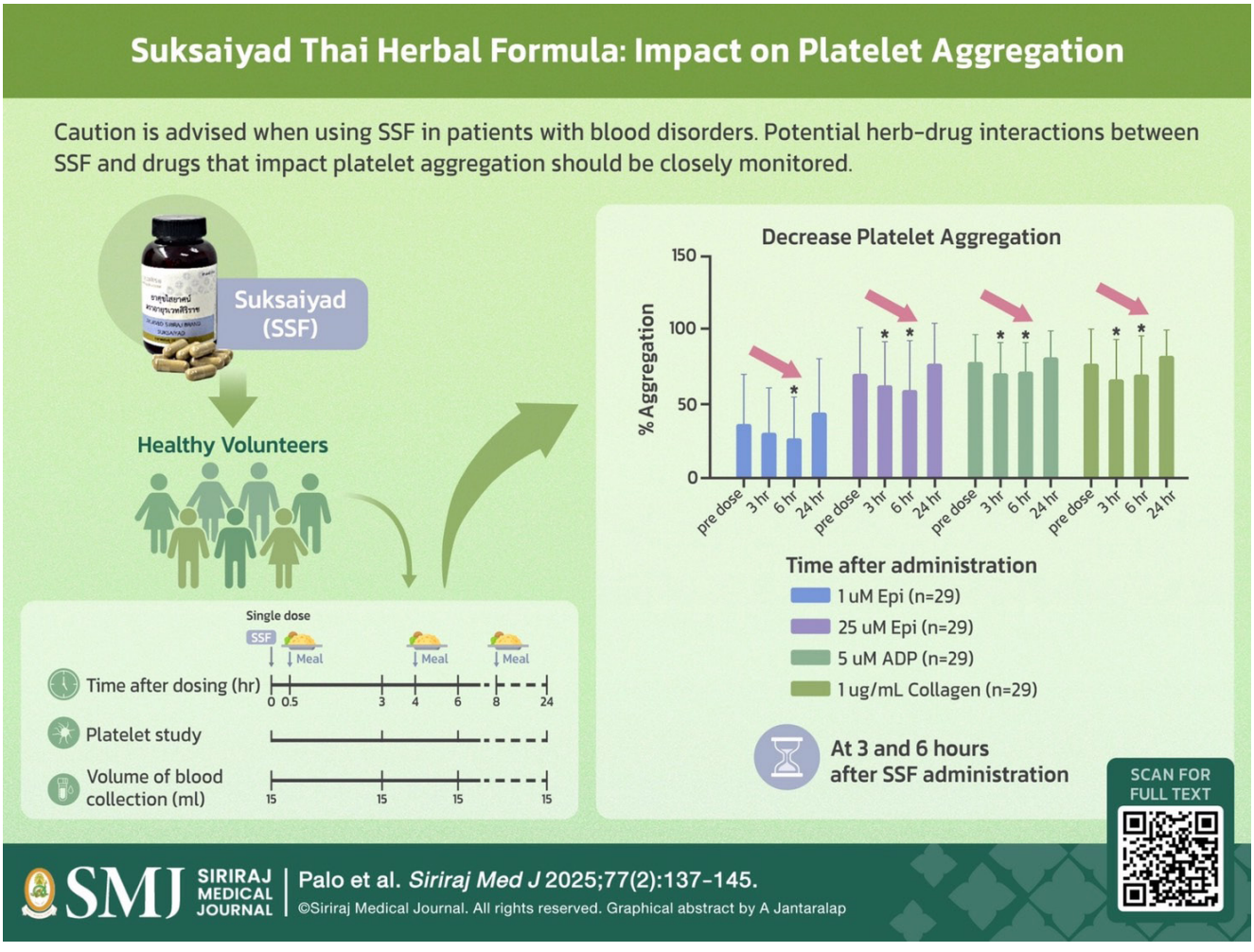
The Effect of the Thai Herbal Suksaiyad Formula on Platelet Aggregation in Healthy Volunteers: A Quasi-experimental, Single-dose Study

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Received 31 October 2024 Revised 25 November 2024 Accepted 25 November 2024
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https://doi.org/10.33192/smj.v77i2.271976

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ABSTRACT

Objective: To investigate the effects of the Thai Herbal Suksaiyad formula (SSF) on platelet aggregation in healthy volunteers.

Material and Methods: In a quasi-experimental study, thirty healthy volunteers received a single dose of 2,000 mg SSF. Blood samples were taken at 0, 3, 6, and 24 hours after SSF administration for platelet aggregation analysis using aggregometry. Platelets were induced with epinephrine, adenosine diphosphate, and collagen.

Results: SSF significantly decreased platelet aggregation at 3 and 6 hours post-administration. Sub-analysis revealed no significant differences between males and females. SSF significantly decreased platelet aggregation in normal and hyperaggregation groups but had no effect on the disaggregation group. The effect of SSF was short-lived, reverting to pre-dose values after 24 hours for all agonists. Adverse events included flatulence (1 participant) and diarrhea (1 participant).

Conclusion: Caution is advised when using SSF in patients with blood disorders. Potential herb-drug interactions between SSF and drugs that impact platelet aggregation, such as aspirin, should be closely monitored. These interactions could result in fluctuations that may enhance or diminish the effectiveness of concurrent antiplatelet therapies, potentially increasing the risk of bleeding or decreasing therapeutic outcomes.

Keywords: Thai Herbal Suksaiyad formula; herbal medicine; platelet aggregation; Thai traditional medicine (Siriraj Med J 2025; 77: 137-145)

INTRODUCTION

The re-legalization of marijuana in 2019 has reignited interest in its potential therapeutic applications in Thai medicine.[1,2] To effectively integrate cannabis-based treatments into clinical practice, further research is essential to provide empirical evidence supporting its use in medicinal formulations.

The Suksaiyad formula (SSF) is one of 16 Thai medicinal formulas that contain marijuana (*Cannabis sativa* L.). It has been approved by the Department of Thai Traditional and Alternative Medicine, Ministry of Public Health, in powdered and capsule form for treating diseases or conducting research studies.[3] This formula was first recorded in *Thart Phra Narai Scripture*[4], a palm-leaf (bai-lahn) manuscript composed of various drug formulas. The published version, known as *Tamra Phra Osot Phra Narai* was revised by Prince Damrong Rajanupab in 2466 B.E. (1923) during the Rattanakosin period.[5]

SSF consists of 12 components, including *Cannabis sativa* L. (Leaf), *Piper retrofractum* Vahl. (Flower), *Zingiber officinale* Roscoe (Rhizome), *Piper nigrum* L. (Seed), *Mesua ferrea* L. (Flower), *Myristica fragrans* Houtt. (Nutmeg), *Aucklandia lappa* DC. (Root), *Nigella sativa* L. (Seed), *Cinamomum bejolghota* (Buch. -Ham.) Sweet (Bark), *Micromelum minutum* Wight & Arn. (Stem), *Azadirachta indica* A.Juss. (Leave), and camphor. The SSF has traditionally been used for treating various illnesses, including insomnia and anorexia.[3,6] According to the National List of Essential Medicines, the recommended dosage for treating insomnia is 0.5-2 grams, taken once daily before bedtime. For improving appetite, 0.5-2 grams can be taken once or twice before meals.[7]

Cannabis sativa L. contains key active compounds such as Delta-9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD). Previous studies have shown that these compounds can inhibit human and rabbit platelet aggregation, and chronic THC administration via edibles has been found to desensitize platelet activity and function.[8-10] Previous studies also demonstrate that other components, including *Zingiber officinale* Roscoe[11-13], *Piper nigrum* L.[14], *Myristica fragrans* Houtt.[15], and *Nigella sativa* L.[16,17], exhibit antiplatelet effects through different mechanisms. This suggests that the SSF may influence platelet function. However, balancing its anti-thrombotic potential with the risk of bleeding remains a concern, as evidenced by previous studies on the effects of the traditional herbal formula "Wattana" on platelet aggregation.[18] Accordingly, this study aims to investigate the effect of the Thai Herbal Suksaiyad Formula on platelet aggregation and report any adverse events in healthy volunteers. The findings will provide empirical evidence to support the clinical use of SSF and enhance its safety.

MATERIALS AND METHODS

Study drugs

SSF capsules (500 mg) were manufactured according to GMP PIC/S (Good Manufacturing Practices) by the Manufacturing Unit of Herbal Medicines and Products, Center of Applied Thai Traditional Medicine (CATTM),

Faculty of Medicine, Siriraj Hospital, Mahidol University. All SSF capsules used in the study came from the same batch and underwent quality control testing, including FTIR, UPLC methods, physical properties analysis, and microbial contamination checks. Capsules were stored at room temperature in dry conditions until use.

Patients

Thirty healthy volunteers were recruited for this pilot study. Inclusion criteria were: 1) Thai male or female, 18-45 years old; 2) body mass index (BMI) between 18-29 kg/m^2; 3) good health confirmed by normal or clinically insignificant vital signs, physical examination, and blood chemistry, per the research physician's assessment. Exclusion criteria included: 1) use of drugs affecting platelet function such as aspirin, clopidogrel, and ticlopidine; 2) history of psychiatric disorders such as psychosis or anxiety disorder; 3) use of central nervous system depressants (eg; anti-seizure medications); 4) fever, peptic ulcers, or and gastroesophageal reflux disease; 5) history of major abnormal bleeding within the past 6 months; 6) blood donation or transfusion in the past 2 months; 7) known allergic reactions to herbal medicine; 8) history of impaired kidney and liver function; 9) pregnancy and breastfeeding. Volunteers experiencing adverse events due to SSF or believed to have had such events were withdrawn with physician agreement. All participants were advised to avoid caffeine, alcohol, vitamins, dietary supplements, and foods containing any of the 12 SSF components for at least two weeks prior to and throughout the study.

Study design

A pre-post study was conducted at the Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand. The protocol received approval from the Siriraj Institutional Review Board (COA: Si 269/2020) and registered with the Thai Clinical Trials Registry (TCTR20210405001). All participants provided written informed consent and retained the right to withdraw from the study at any time. Participants were required to fast for 10 hours before taking the SSF. On the day of the experiment, participants underwent a physical examination by a doctor and had blood drawn at pre-dose (baseline) and at 3, 6, and 24 hours after administration single-dose of SSF (2,000 mg), which is the recommended maximum daily dosage. However, since there is no prior research indicating the duration of the drug's effects, the dosage was set as a single dose, with follow-up evaluations conducted at 3, 6, and 24 hours after administration to cover potential effects of SSF that may occur. Blood samples were kept in sodium citrate vacutainers (Greiner Bio-one GmbH, Austria). All participants received standardized food provided by the researchers and were not allowed to eat anything else until the final blood sample was taken. The study physicians evaluated and recorded vital signs, and adverse events were assessed by questioning the participants. (Fig 1).

Platelet aggregation assay

Platelet aggregation was assessed using light transmission aggregometry (LTA) following Born's technique.[19] Platelet aggregation was measured with an aggregometer (AggRAM, Helena, USA) within three hours of blood collection. The platelet agonists used were epinephrine (Epi), adenosine diphosphate (ADP), and collagen (Col), which is crucial because each targets different receptors and mechanisms, providing a comprehensive assessment of platelet function.[20] Platelet-rich plasma (PRP) was prepared by centrifuging citrated whole blood at 250 g for 10 minutes at room temperature. A portion of PRP was further centrifuged at 4500 g for 2 minutes at room temperature to create platelet-free plasma (PFP) as a blank control. PRP was stirred at 600 rpm and incubated at 37°C for about 3 minutes before induction. The reaction

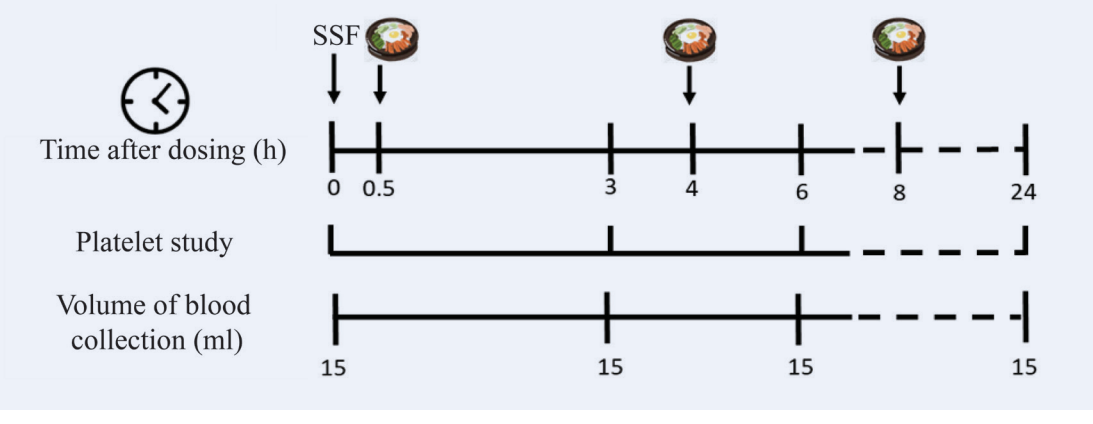


Fig 1. Intervention and outcome measurement screen.

lasted for 5 minutes. The maximal amplitude of platelet aggregation, expressed as a percentage, was determined by computing light transmission between aggregated PRP and PFP. Additionally, platelet count was assessed using a non-metallic hemocytometer (Helena USA).

Platelet status classification

There is no officially accepted standard for evaluating platelet function. A previous method categorized platelet function into three groups based on platelet responses to different epinephrine concentrations.[21,22] The primary phase of platelet aggregation, induced by 25μM epinephrine, is referred to as the "disaggregation pattern". Platelet aggregation triggered by 1μM epinephrine, representing the secondary phase, is referred to as the "hyperaggregation pattern". Consequently, the concentration-dependent response of platelets to both 1μM and 25μM epinephrine is considered the "normal aggregation pattern".[21,22]

Statistical analyses

Data are presented as mean ± standard deviations (SD). Statistical analyses were performed using GraphPad Prism version 10.0.2 (GraphPad Software Inc., San Diego, CA, USA). The normality of platelet aggregation data was assessed using the Kolmogorov–Smirnov and Shapiro-Wilk tests. Time-dependent changes in platelet aggregation data after SSF administration within groups after SSF administration were evaluated using nonparametric Friedman test, followed by Dunn's pairwise post hoc tests. Categorical variables were evaluated using the chi-square test. Statistical significance was defined as a p-value below 0.05.

RESULTS

Demographic characteristics

This study included 30 healthy volunteers, with one participant withdrawing due to difficulty collecting blood at 6 hours after SSF administration. Data from 29 healthy volunteers were analyzed. The average age of the male and female groups was 29.3±5.7 and 30.21±4.6 years, respectively. All participants had normal baseline characteristics (Table 1).

TABLE 1. Demographic data and reference range for laboratory values.

Topic	Mean ± SD		Reference range	
	Male (n=10)	Female (n=19)	Male	Female
Age (years)	29.3±5.7	30.21±4.6	≥18	
Body weight (kg)	64.83±7.4	55.96±7.5	-	
Height (cm)	170±10	161±4.5	-	
Body mass index (kg/m^2)	22.47±2.7	21.56±2.5	18-29	
hemoglobin (g/dL)	14.46±1.2	12.2±1	12.70-16.90	12.0-14.90
hematocrit (%)	44.38±2.5	38.8±2.2	40.30-51.90	37.0-45.70
WBC (x 10^3/uL)	6.03±1	6±1.2	4.50-11.30	4.40-10.30
Platelet count (x 10^3/uL)	264.2±28.3	294.5±54.8	160-356	179-435
MCV (fl)	84.65±7.6	84.53±5.9	80.4-95.9	
MCHC (g/dL)	32.57±1.2	31.37±1.1	30.2-34.2	
MCH (pg)	27.56±2.5	26.55±2.4	25.0-31.2	
FBS (mg/dL)	85.7±8.2	83±7	74-99	
BUN (mg/dL)	13.05±2.9	10.4±1.5	6-20	
Creatinine (mg/dL)	0.90±0.1	0.72±0.1	0.67-1.17	0.51-0.95
AST (U/L)	19.8±4	17.5±5.1	0-40	0-32
ALT (U/L)	18.4±5.1	14.4±12.3	0-41	0-33

Platelet status pattern before dosing

Before SSF treatment, 35% of the 29 subjects exhibited a hyperaggregation pattern, while 41% had a normal pattern, and 24% showed a disaggregation pattern, respectively (Fig 2a). The Chi-square test results showed no significant association between gender and platelet status pattern before SSF dosing (Fig 2b).

Effect of SSF on platelet aggregation

Among the 19 female participants, 24 hours after SSF administration, 26% experienced an increase in platelet aggregation, 68% showed no change, and 5% a decrease in platelet aggregation (Fig 3). Among the 10 male participants, 30% showed an increase in platelet aggregation, 60% showed no change, and 10% experienced a decrease in platelet aggregation (Fig 3). Figs 3 and 4 demonstrate the individual response variations observed in the study.

The results indicated a significant decrease in the percentage of maximum aggregation for all agonists. Platelet aggregation induced by 1μM epinephrine significantly decreased at 6 hours after SSF administration. Aggregation induced by other agonists significantly decreased at 3 and 6 hours post-administration. By 24 hours, there was no significant difference in aggregation compared to pre-dose levels for all agonists (Fig 5a).

Both male and female groups showed a significant decrease in the percentage of maximum platelet aggregation at 3 and 6 hours after SSF administration. By 24 hours, there were no significant differences compared to pre-dose levels for any agonists in either group (Fig 5b, 5c).

In the normal aggregation group, a significant decrease in maximum aggregation was observed after induction with 25μM Epi at 6 hours and with 5μM ADP at 3 and 6 hours post-SSF administration. The hyperaggregation group also showed a significant decrease in maximum aggregation with all agonists at 3 and 6 hours post-SSF administration. By 24 hours, no significant differences were noted compared to pre-dose levels in either the normal or hyperaggregation groups. However, the

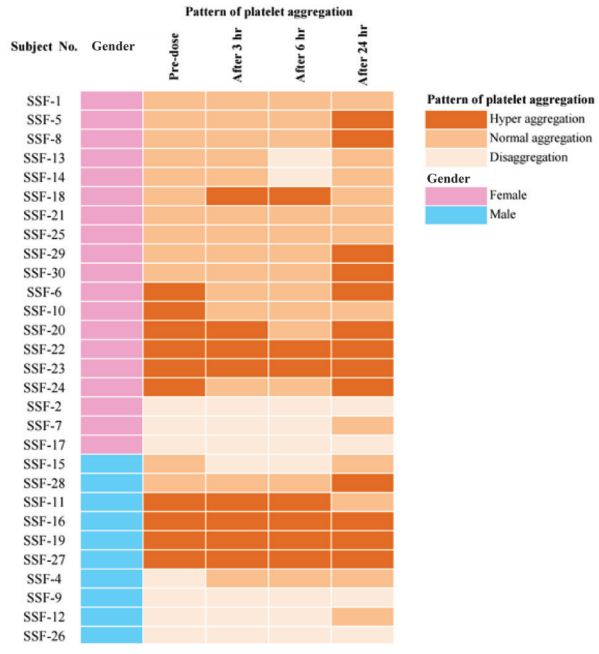


Fig 3. Effect of SSF on platelet aggregation by gender and platelet aggregation characteristics at pre-dose and at 3, 6, and 24 hours after administration of SSF.

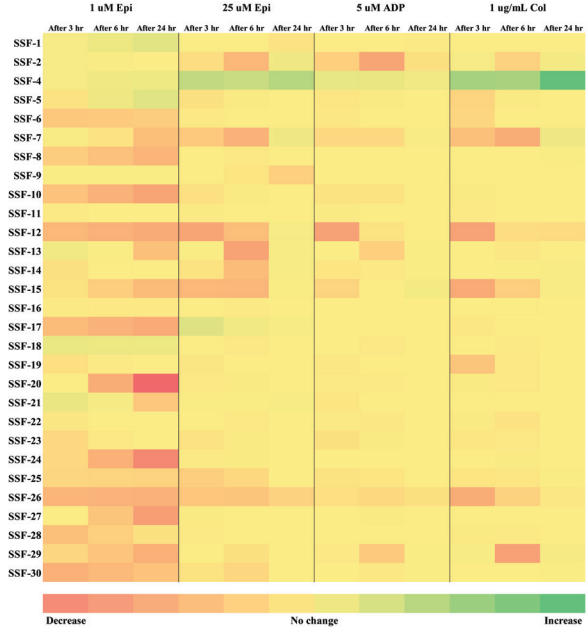


Fig 4. Heatmap illustrating the percentage of platelet aggregation in each participant for each agonist after 3, 6, and 24 hours of SSF administration.

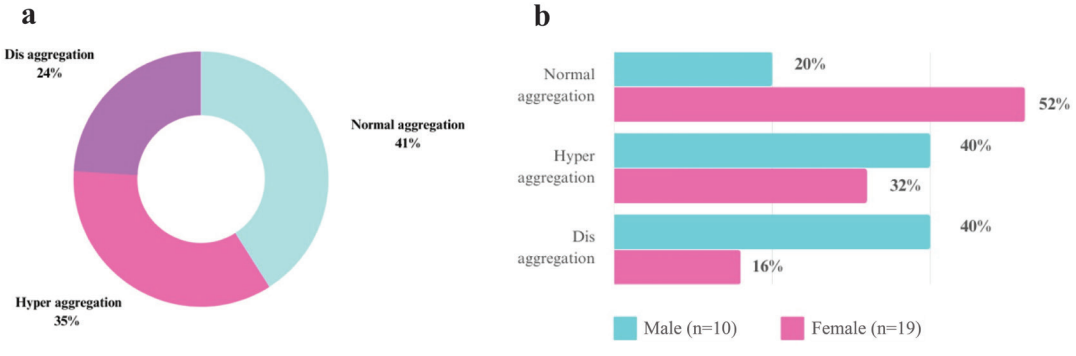


Fig 2. Percent platelet status pattern before SSF dosing: a) all 29 participants b) 10 males and 19 females.

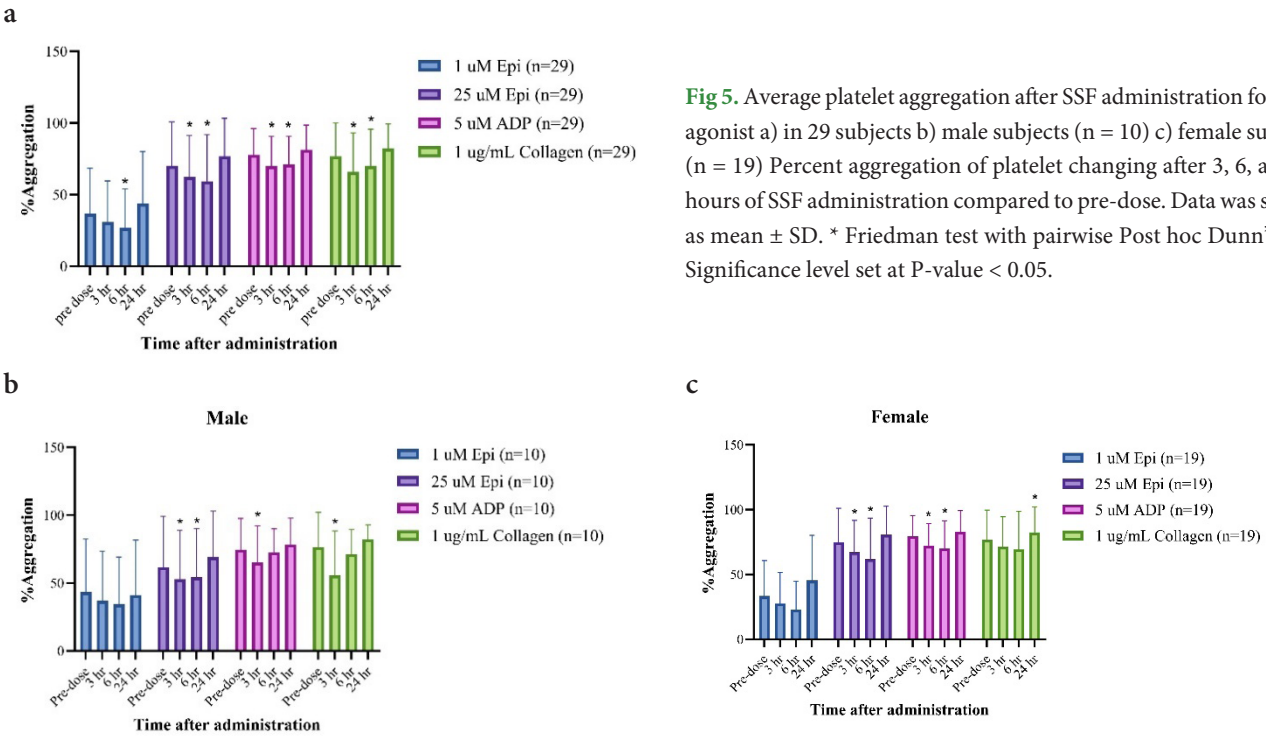


Fig 5. Average platelet aggregation after SSF administration for each agonist a) in 29 subjects b) male subjects (n = 10) c) female subjects (n = 19) Percent aggregation of platelet changing after 3, 6, and 24 hours of SSF administration compared to pre-dose. Data was shown as mean ± SD. * Friedman test with pairwise Post hoc Dunn's test; Significance level set at P-value < 0.05.

disaggregation group showed no significant changes in maximum aggregation after induction with any agonists following SSF administration (Fig 6). Adverse events reported by the 30 participants included flatulence (3.33%, n=1) and diarrhea (3.33%, n=1).

DISCUSSION

The novel findings of this study reveal changes in platelet aggregation after a single administration of 2000 mg of SSF. This herbal formula can reduce platelet aggregation induced by ADP, collagen, and epinephrine. However, this suppressive effect is short-lived, typically resolving within 24 hours post-SSF ingestion. The process of platelet aggregation is intricate, involving numerous receptors and signaling pathways. Collagen-induced platelet aggregation plays a key role in platelet adhesion and activation at sites of vascular injury, serving as one of the initial triggers for clotting.[23] ADP-induced platelet aggregation is vital for the early stages of clot formation, initiating platelet recruitment and activation.[24] Epinephrine-induced aggregation, less specific to vascular injury, responds primarily to circulating catecholamines like

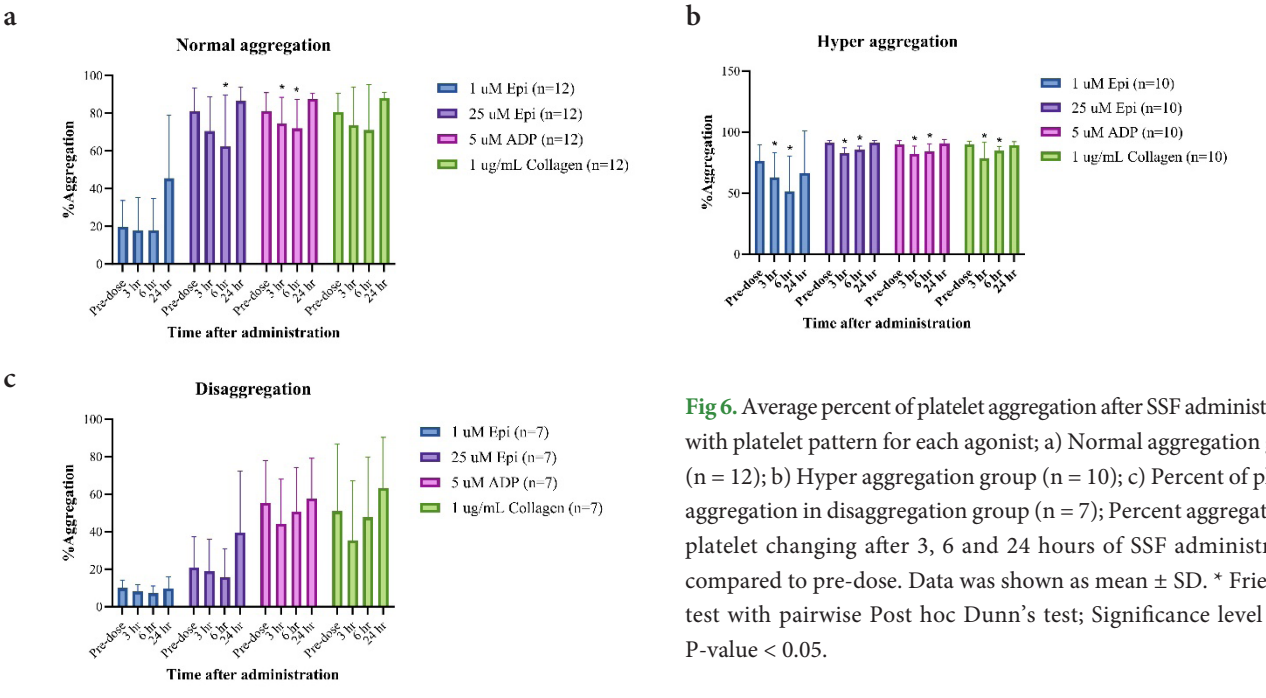


Fig 6. Average percent of platelet aggregation after SSF administration with platelet pattern for each agonist; a) Normal aggregation group (n = 12); b) Hyper aggregation group (n = 10); c) Percent of platelet aggregation in disaggregation group (n = 7); Percent aggregation of platelet changing after 3, 6 and 24 hours of SSF administration compared to pre-dose. Data was shown as mean ± SD. * Friedman test with pairwise Post hoc Dunn's test; Significance level set at P-value < 0.05.

adrenaline and is part of the body's overall hemostatic response but is not as site-specific as collagen or ADP-induced aggregation.[25-27]

The mechanisms of platelet aggregation induced by ADP, collagen, and epinephrine involve distinct pathways. The results indicate that SSF broadly inhibits platelet aggregation, likely due to its multiple components affecting these pathways. Previous studies have demonstrated that many SSF components inhibit platelet aggregation. For example, cannabinoids from *Cannabis sativa* L. inhibited epinephrine-induced human platelet aggregation in a dose-dependent manner, partially inhibiting primary aggregation and completely inhibiting secondary aggregation.[10] *Zingiber officinale* Roscoe extracts suppressed platelet aggregation induced by ADP, epinephrine, collagen, and arachidonate in a dose-dependent manner.[11-13] *Piper nigrum* L. extract displayed moderate antiplatelet effects induced by thrombin and collagen.[14] A neolignan extracted from *Myristica fragrans* Houtt. demonstrated inhibition of thrombin- and platelet-activating factor (PAF)-induced platelet aggregation in a concentration-dependent manner, without causing any damage to the platelets.[15] *Nigella sativa* L. extract also showed inhibitory effects on arachidonic acid (AA) and ADP-induced platelet aggregation.[16,17]

The individual variation in response to SSF's inhibitory effects on platelet aggregation, as shown in the heatmap, may be influenced by several factors. While the study protocol aimed to control for lifestyle and environmental factors such as age, diet, exercise, smoking habits, and overall health status, which can influence response to drug administration, platelet function and overall response to treatments[28], other physiological parameters, such as differences in baseline platelet activity, platelet count can affect the degree of platelet aggregation inhibition.[29,30] Additionally, genetic polymorphisms among individuals can influence the expression and function of platelet receptors and enzymes involved in aggregation, leading to diverse treatment responses.[31] Metabolic variability, such as variations in drug metabolism and clearance rates, can also impact the bioavailability and effective concentration of the drug. Factors like liver function, enzyme activity, and other metabolic processes can influence how the drug is processed and eliminated, affecting the degree and duration of platelet aggregation inhibition.[32]

The potential interaction of SSF with antiplatelet drugs could increase bleeding risks when co-administered. For patients already on such therapies, the use of SSF may require close monitoring or dosage adjustments. Recognizing and accounting for these individual variations is essential in assessing and managing SSF's effects on platelet aggregation. A personalized medicine approach, considering individual variability, can lead to more effective, tailored treatments that optimize therapeutic outcomes while minimizing potential adverse effects.

This study's small sample size may limit the generalizability of the results to broader populations and reduce the ability to detect individual response variations. Furthermore, the use of a single dose and the brief observation period may not adequately capture the prolonged or cumulative effects of repeated SSF administration. Future research should aim to increase the number of participants, utilize a randomized controlled trial design, and explore the long-term effects of repeated dosing to enhance the robustness and applicability of the findings.

CONCLUSIONS

A single administration of 2,000 mg of SSF can inhibit platelet aggregation induced by ADP, collagen, and epinephrine, but this effect is short-lived, with recovery occurring within 24 hours. SSF use may pose certain contraindications, particularly for individuals with health conditions such as bleeding disorders or a history of hemorrhagic stroke. Its use should be approached with caution, especially among individuals taking antiplatelet medications, as SSF may amplify their effects and increase the risk of bleeding complications. Patients on such therapies or with clotting disorders are advised to consult a healthcare provider before using SSF.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article.

ACKNOWLEDGEMENTS

The authors would like to thank Natchaya Ziangchin and the research team for their collaboration during data collection. Furthermore, the authors would like to thank the Manufacturing Unit of Herbal Medicines and Products, the Center of Applied Thai Traditional Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, for authenticating the plant material and providing the study facilities.

DECLARATION

Grants and Funding Information

The study was financially supported by the Siriraj Routine to Research (R2R) (No. 21TT00023/032/21) Management Fund.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Author Contributions

T.P., P.A., and S.B. conceived and designed the experiments. T.P., N.N., and S.B. conducted the experiments. T.P. and S.B. contributed to data interpretation. S.B. led the manuscript writing. All authors provided critical feedback and contributed to refining the research, analysis, and manuscript.

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