

The Effects of *Scurrula atropurpurea* and *Dendrophthoe pentandra* Leaves on Platelet and Leukocyte Profiles: A Phase 1 Clinical Trial

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Abstract. Tea mistletoe (*Scurrula atropurpurea*) and mango mistletoe (*Dendrophthoe pentandra*) (SADP) are parasitic plants that are widely utilized as folk medicines due to the presence of some active flavonoid compounds. However, there are no scientific reports regarding the effects of SADP on platelet and leukocyte profiles in humans. Therefore, we studied the impact of SADP on healthy human subjects. This single-blinded clinical trial involved 15 days of oral administration of SADP capsules and enrolled 28 residents of Malang. They were then divided into two groups: a placebo group (n=13) and a treatment group (n=15). The treatment group received 560 mg of *S. atropurpurea* and 187 mg of the *D. pentandra* leaves powder. After 15 days, subjects were measured for platelet, leukocyte counts, platelet distribution width (PDW), and leukocyte differential count. Our findings showed no significant differences between the placebo and treatment groups in platelet and leukocyte counts, PDW, or leukocyte differential counts. It can be concluded that SADP administered orally for 15 days was safe in healthy human subjects.

Keywords: *Scurrula atropurpurea* BI. Dans, *Dendrophthoe petandra*, platelet profile, leukocyte profile, first phase of clinical trial.

1 Introduction

In recent years, there has been a growing interest in the potential benefits of medicinal plants as complementary therapies. Mistletoe leaf (Loranthaceae) has a long history of traditional use to improve the quality of life in humans [1] due to the presence of active compounds,

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including flavonoids, tannins, alkaloids, and saponins [2]. Additionally, some research demonstrated that mistletoe flavonoids had several effects, including antioxidant activities [3]. Tea mistletoe (*Scurrula atropurpurea* (Bl.) Dans) and mango mistletoe (*Dendrophthoe petandra*), which we will refer to as SADP, consist of several plant structures, including leaves, stems, and flowers. However, the leaves of SADP were found to contain higher concentrations of flavonoids than other plant parts, and these flavonoids are efficacious [4]. Although the benefits and safety of SADP leaves have been studied in experimental animals, no studies have examined the safety of administering these two plants to humans. Therefore, it is necessary to conduct clinical trials to evaluate the safety and other effects of SADP administration in humans.

The parameters of this research were platelet and leukocyte counts, PDW, and leukocyte differential counts. The participants were selected based on prior research findings indicating a correlation between flavonoids and these variables. Previous studies have demonstrated that flavonoids decrease the expression of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), as well as certain cytokines associated with inflammation, such as TNF- α , IL-6, IL-8, IL-1 β , and IFN- γ [5]. IL-6 was found to increase megakaryocyte production, thrombopoietin (TPO) levels, and megakaryocyte differentiation [6]. This decrease led to significant compensation in platelet production, altering the platelet size ratio and thus affecting the PDW value [7]. Flavonoids, with a particular emphasis on quercetin, have been shown to exert a suppressive effect on Colony Forming Unit-Granulocyte-Macrophage (CFU-GM) [8], which serves as a progenitor cell for monoblasts and myeloblasts [9]. These cells subsequently evolve into various types of white blood cells, including monocytes and granulocytes [10]. This provided a fundamental basis for the assumption that these parameters can represent other effects and the safety of flavonoids on SADP.

This Phase I clinical investigation, which included 28 healthy subjects who received a combination of SADP over 15 days, assessed various haematological parameters, providing preliminary evidence of the herbal combination's haematological safety profile. These objectives align with Sustainable Development Goal 3 (SDG 3), which aims to promote good health and well-being. The clinical safety data collected as part of this objective serve as a foundational element, providing the necessary baseline information to enable progression to subsequent research endeavours. These include efficacy testing, long-term toxicity monitoring, and studies on the interactions between pharmaceuticals and herbs. In addition, the utilization of local raw materials, such as tea and mango mistletoe, in a standardized and sustainable manner, has the potential to contribute to SDG 8 — Decent Work and Economic Growth by generating added value within local supply chains (sustainable cultivation/harvesting, processing, quality control, and packaging). Consequently, this research is situated at the intersection of public health and local economic growth. It focuses on generating scientific evidence on safety while also exploring avenues for translating these findings into safe complementary health options and sustainable economic prospects grounded in local biodiversity.

2 Materials and Methods

2.1 Ethics Approval

This research was approved by the Health Research Ethics Committee of Rumah Sakit Islam UNISMA (approval number: 05/KEPK/RSI-U/VIII/2023).

2.2 Place and Time of Research

The research was conducted at the Faculty of Medicine, Universitas Islam Malang, East Java, Indonesia, in November - December 2023.

2.3 Research Design and Sample Size

The research design was quasi-experimental. The typical sample size for phase 1 clinical trials ranged from 20 to 80 individuals [11]. Therefore, the sample size for this research consisted of 28 healthy subjects. The subjects were randomly assigned to two groups: the placebo (wheat flour powder) (n=13) and the treatment (SADP) (n=15) by a single-blind clinical trial. The pre-test in this research was conducted before administering either the placebo or SADP. The post-test was administered following a 15-day period.

2.4 Inclusion and Exclusion Criteria

The subjects were selected based on the inclusion and exclusion criteria. The inclusion criteria included healthy male or female subjects aged 18 to 45 years, with normal vital signs (blood pressure, temperature, respiratory rate, and pulse frequency), residing in the Malang area, and willing to participate by agreeing to the informed consent. The exclusion criteria included individuals with a history of severe complications, pregnant women, or those who were using hormonal contraceptives.

2.5 Output Parameters

The outcome parameters were evaluated through laboratory examinations conducted as part of pre- and post-research assessment. These included platelet and leukocyte counts, PDW, and leukocyte differential counts.

The following are the reference laboratory normal values: leukocyte $5,07 - 11,10 \text{ } 10^3/\text{mm}^3$ (male) and $4,79 - 11,34 \text{ } 10^3/\text{mm}^3$ (female); platelet $185 - 398 \text{ } 10^3/\text{mm}^3$ (male) and $216 - 451 \text{ } 10^3/\text{mm}^3$ (female); PDW $9 - 13 \text{ fL}$; eosinophil absolute $0,04 - 0,43 \text{ } 10^3/\text{mm}^3$; basophil absolute $0,02 - 0,09 \text{ } 10^3/\text{mm}^3$; neutrophil absolute $2,72 - 7,53 \text{ } 10^3/\text{mm}^3$; lymphocyte absolute $1,46 - 3,73 \text{ } 10^3/\text{mm}^3$; and monocyte absolute $0,33 - 0,91 \text{ } 10^3/\text{mm}^3$.

2.6 Herbal Materials

The herbs were provided as encapsulated dry simplisia powder. The oral single daily dose consisted of 560 mg of *Scurrula atropurpureae* and 187 mg of *Dendrophtea petandra* leaves, which were packed into three capsules. The botanical identification of each specimen was performed by a professional botanist at the Materia Medica Batu Laboratory. Freshly harvested plants were sorted, chopped, dried, pulverized, and checked for quality control (QC). The simplified powder, which met the required quality standards, was encapsulated into the daily dose and packaged for administration over 15 days.

2.7 Procedures

Subjects were instructed to take the three capsules once per day, following the consumption of meals. Daily monitoring of SADP consumption, vital signs, and any reported symptoms was observed at each subject's residence in the morning.

2.8 Statistical Analysis

The data were displayed as mean ± standard deviation (±SD). Statistical tests were performed using the Wilcoxon signed-rank test, as the data were abnormally distributed. The results were significant if the p-value is less than 0.05. The data analysis was performed using the Statistical Product and Service Solution (SPSS) software.

3 Results

The research was completed with the participation of 28 healthy individuals. Several subjects were excluded for failing to meet the inclusion criteria, and others withdrew from the study, resulting in loss to follow-up (Figure 1). The administration of SADP for the monitoring of adverse effects caused no clinically significant symptoms, including nausea, vomiting, headache, fatigue, or increased intestinal motility.

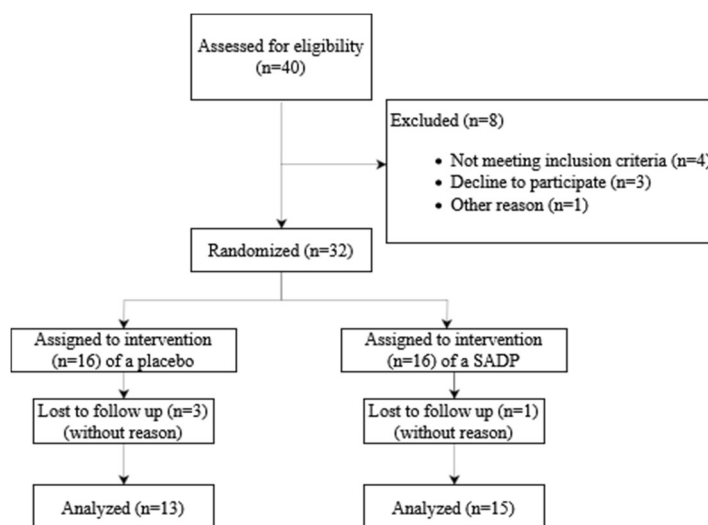


Fig. 1. Subject recruitment flow.

Table 1. Platelet and leukocyte profiles pre- and post-SADP treatment.

Parameter	SADP Group					
	Male (n=7)			Female (n=8)		
	Pre ^a	Post ^b	p value ^c	Pre ^a	Post ^b	p value ^c
Platelet (10 ³ /μL)	288.14±58.23	306.29±62.49	0.128	313.38±85.44	298.88±113.91	0.624
Platelet Distribution Width (fL)	12.64±2.08	12.89±2.75	0.933	11.39±1.87	12.28±3.35	0.482
Leukocyte (10 ³ /μL)	7.36±1.66	6.77±1.57	0.31	7.09±1.93	6.51±2.00	0.208
Leukocytes differential count (10 ³ /μL)						
Neutrophil absolute	4.37±1.31	3.66±0.95	0.176	4.35±1.54	3.94±1.75	0.233
Lymphocyte absolute	2.18±0.50	2.13±0.52	0.866	2.18±0.44	1.99±0.34	0.161
Monocyte absolute	0.55±0.18	0.53±0.18	0.553	0.37±0.14	0.40±0.10	0.362
Eosinophil absolute	0.21±0.10	0.31±0.23	0.31	0.17±0.16	0.15±0.10	0.778
Basophil absolute	0.04±0.01	0.05±0.02	0.458	0.03±0.02	0.03±0.02	0.496

^a Mean ± standard deviation (±SD) of platelet and leukocyte profiles in pre-SADP treatment

^b Mean ± standard deviation (±SD) of platelet and leukocyte profiles in post-SADP treatment

^c The p-value represents the statistical value associated with the Wilcoxon signed-rank test.

Following 15 days of SADP treatment, no notable alterations were observed in the profiles of platelets and leukocytes, as illustrated in Table 1. As in the SADP cohort, the placebo group showed no statistically significant changes in any laboratory results (Table 2). The Shapiro-Wilk normality test indicated that the distributions of platelet and leukocyte profiles were abnormal. Consequently, the Wilcoxon signed-rank test was employed as the subsequent analytical tool. The p-value for each research parameter showed that the results were statistically insignificant ($p > 0.05$). These were demonstrated by the SADP data in Table 1 and the placebo data in Table 2.

Table 2. Platelet and leukocyte profiles pre- and post-placebo treatment.

Parameter	Placebo Group					
	Male (n=6)			Female (n=7)		
	Pre ^a	Post ^b	p value ^c	Pre ^a	Post ^b	p value ^c
Platelet (10 ³ /μL)	288.00±59.94	299.00±59.02	0.08	365.71±61.17	377.00±68.64	0.176
Platelet Distribution Width (fL)	10.40±1.51	10.90±1.32	0.235	11.84±1.59	11.37±1.46	0.207
Leukocyte (10 ³ /μL)	7.18±1.06	7.47±1.48	0.866	7.15±1.05	7.26±2.16	1
Leukocytes differential count (10 ³ /μL)						
Neutrophil absolute	3.62±0.52	3.76±1.09	0.612	4.30±1.04	4.51±2.24	0.612
Lymphocyte absolute	2.74±0.68	2.74±0.47	0.6	2.27±0.52	2.16±0.43	0.612
Monocyte absolute	0.48±0.10	0.46±0.13	0.612	0.38±0.12	0.44±0.10	0.204
Eosinophil absolute	0.30±0.15	0.36±0.20	0.051	0.15±0.14	0.20±0.17	0.497
Basophil absolute	0.04±0.01	0.04±0.02	0.461	0.04±0.02	0.04±0.01	0.655

^a Mean ± standard deviation (±SD) of platelet and leukocyte profiles in pre-placebo treatment

^b Mean ± standard deviation (±SD) of platelet and leukocyte profiles in post-placebo treatment

^c The p-value represents the statistical value associated with the Wilcoxon signed-rank test.

4 Discussion

This research was conducted as part of a phase 1 clinical trial to evaluate the safety of using a combination of *S. atropurpurea* and *D. petandra* leaves. The aim was to confirm the absence of significant changes in haematological parameters, including platelet and leukocyte counts, PDW, and leukocyte differential count, among healthy individuals receiving the herbal combination. The findings of the data analysis indicated that the administration of SADP demonstrated no notable alterations in the observed parameters. Similarly, placebo administration did not yield substantial alterations in the research's findings. It suggested that both treatments were equally inconsequential in all parameters evaluated. This outcome aligned with the initial hypothesis of the research, which proposed that SADP administration is a safe and well-tolerated approach in healthy individuals, with minimal potential for adverse physiological effects.

The absence of notable alterations in hematologic parameters indicated that SADP did not affect hematopoiesis, hemostasis, or the inflammatory response in healthy subjects. This finding was consistent with previous preclinical studies, which demonstrated that the flavonoids present in SADP, including quercetin and rutin, had no toxic effects in experimental animals [12, 13]. Several studies have shown that administering SADP to female Wistar rats for 28 days at treatment doses of 250 mg/kg, 500 mg/kg, and 1,000 mg/kg resulted in no significant alterations to the rats' physiological functions, including kidney function [12] and liver function [13].

Nevertheless, a few minor details were observable, in addition to the non-significant alterations in each research parameter. The leukocyte counts of subjects who received SADP declined slightly, though this difference was not statistically significant (Figure 2). This

finding correlates with previous studies indicating that flavonoids can impede the differentiation of CFU-GM into monoblasts and myeloblasts [8-9], thereby reducing the number and differential count of leukocytes. In addition, a slight decline in platelet count was observed in female subjects who consumed the SADP (Figure 3), which aligns with prior research demonstrating that flavonoids inhibit the production of several cytokines, particularly IL-6 [5]. It has been shown that IL-6 stimulates megakaryocyte production, thrombopoietin (TPO) production, and megakaryocyte differentiation [6]. This finding provides a scientific rationale for the administration of flavonoids, which have been shown to inhibit IL-6 production, thereby preventing megakaryocyte formation and TPO production, and consequently decreasing platelet count.

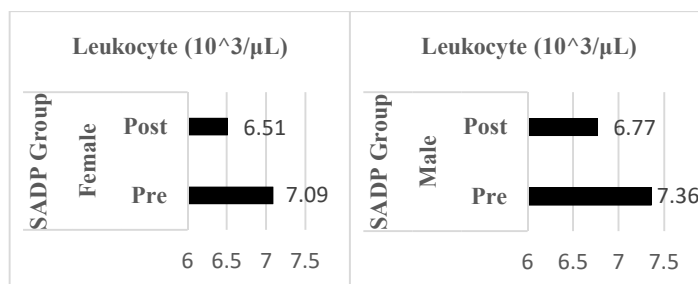


Fig. 2. Female & male leukocyte counts pre- and post-receiving SADP.

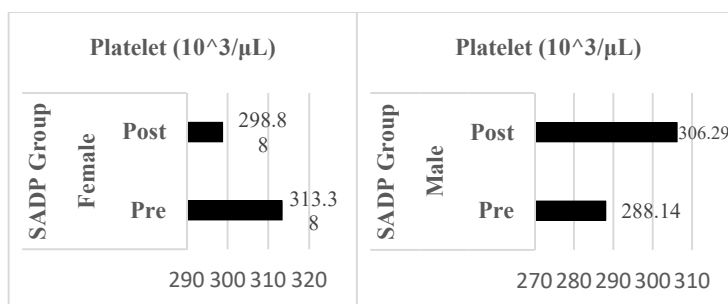


Fig. 3. Female & male platelet counts pre- and post-receiving SADP.

The effectiveness of SADP in treating hypertension was demonstrated in several studies [4,14], providing support for its use in clinical settings. Pre-clinical in vitro studies showed that SADP induced vasodilation in endothelial cells of rat tail arteries [14]. In vivo research on DOCA-salt hypertensive rats revealed that the administration of SADP at treatment doses of 50 mg/kg, 100 mg/kg, and 200 mg/kg led to an increase in nitric oxide (NO) and endothelial progenitor cells (EPC) and a reduction in circulating endothelial cells (CEC) [4]. According to in silico research, the Prediction of Activity Spectra for Substances (PASS) analysis identified that the primary active compounds in SADP, including quercitrin/quercetin 3-rhamnoside, kaempferol, quercetin, isoquercitrin/quercetin 3-glucoside, flavonol glycoside, and casticin, exhibited six biological activities that may confer health benefits. These activities included scavenging free radicals, cardioprotection, antioxidant activity, vascular protection, vasodilation, and anti-inflammatory effects [15]. Therefore, numerous studies have been conducted to provide a scientific basis for the potential therapeutic benefits of SADP.

This research had some limitations. Primarily, the sample size was limited, with only 15 people receiving SADP. It restricted the research's capacity to generalize the full phase 1 clinical trial experience. This limitation was due to people's fear of a research process involving needles, which resulted in many people refusing to participate in the study. The second limitation concerned the lack of specificity in one of the research parameters, specifically the effect of flavonoids on platelet aggregation. Therefore, laboratory tests of blood clotting factors should also be performed.

The absence of significant changes in platelet count, leukocyte count, PDW, or leukocyte differential count after 15 days of SADP administration in healthy subjects indicates that no acute hematological alterations occur under these conditions. It thus supports progression to subsequent investigational stages addressing efficacy and comprehensive safety assessment. These results are relevant to SDG 3 and provide substantiation for the requirement of randomized, double-blind, placebo-controlled efficacy trials in specific patient populations (e.g., individuals with hypertension). These trials should be accompanied by expanded safety monitoring, including coagulation panels (such as PT/aPTT), hepatic and renal function tests, and inflammatory biomarkers (such as CRP and IL-6). Additionally, pharmacokinetic and drug–herb interaction studies—particularly with antihypertensive and antiplatelet agents—to ensure safe simultaneous use. Concurrently, in relation to SDG 8, the practical application of these measures should be supported by value-chain planning that emphasizes sustainable cultivation or managed harvesting to avoid overexploitation. Furthermore, capacity building and certification should be facilitated for small and medium-sized enterprises (SMEs) engaged in processing and quality assurance. Adherence to Good Manufacturing Practice (GMP) and international quality standards must be ensured, and equitable benefit-sharing with traditional knowledge holders must be implemented.

5 Conclusion

The administration of SADP to healthy individuals for 15 days resulted in no significant alterations in platelet and leukocyte counts, PDW, or leukocyte differential count compared with the placebo treatment group, which was also evaluated for 15 days. Those provide evidence that SADP is safe to use and has no significant side effects. Therefore, this research can be advanced to a second phase of clinical trials with samples of hypertensive patients, who are the target population of SADP.

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