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Effect of Bosswelic Acid On Hematological Parameters In Sprague Dawley Rats (Rattus novergicus) Induced By Cyclophosphamide

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KEYWORDS
boswellic acid; cyclophosphamide; haemoprotector

ABSTRACT
Chemotherapy drug "cyclophosphamide (SP)" can trigger oxidative stress that causes hematotoxicity and myelotoxicity, therefore an agent that can suppress the negative effects of cyclophosphamide is needed. Boswellic acid is an herbal medicine that has anti-oxidant and anti-inflammatory effects. The aim of this study was to determine the effect of boswellic acid (BA) in hematology parameter rats induced by cyclophosphamid. Animal were allocated in to six groups, each group consists of 5 rats, the KS: healthy group, KSP: cyclophosphamide group; KSD: comparison group, and BA groups (K1;K2;K3). The treatment groups were given cyclophosphamide (SP) at dose of 150 mg/kg body weight (BW) i.p. The BA groups (K1,K2,K3) were given BA at dose of 250 mg/kg BW orally for 6 consecutive days and SP on day 1 (K1), day 4 (K2), day 6 (K3). The results showed that BA administration (K2 and K3) can help increase/maintain the amount of hematological parameters including hemoglobin, hematocrit, and erythrocytes. Administrating BA for 6 days consecutively before SP (K3) has shown best results on hematological parameters than the others including the comparison group. These results suggest that BA may have a potentia herbal therapeutic agents that can mitigate cyclophosphamide-induced hematotoxicity manifestations.

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Introduction

Tumor is a pathological condition of cell growth, characterized by excessive and abnormal cell proliferation (Sinha, 2018). One of the cancer treatments is chemotherapy. Chemotherapy drugs not only work on neoplastic cells, but also act on normal cells causing toxicity to some organs (Xiao et al., 2019). One chemotherapy drug that is often used is cyclophosphamide (Abdel-Razeq & Hashem, 2020).

Cyclophosphamide is an antineoplastic drug class of alkylating agents (Patra et al., 2012). Cyclophosphamide is immunosuppressive and cytotoxic, works to inhibit cell replication through cross-links in deoxyribonucleic acid (DNA), induce oxidative stress, and cause apoptosis (Cengiz et al., 2020). Side effects of cyclophosphamide cause myelosuppression, inhibition of erythropoiesis, and cause a decrease in the number of erythrocytes or anemia (Bryer & Henry, 2018) (Cengiz et al., 2020) (Abdel-Razeq & Hashem, 2020).

Anemia conditions cause fatigue, decreased quality of life, tumor patients (Link, 2019). Therefore, it is necessary to prevent or suppress the side effects of cyclophosphamide. One strategy is to administer safe chemoprotective agents, such as herbal remedies (Xiao et al., 2019).

Boswellic acid (BA) compounds, derived from plants, are pentacyclic triterpene molecules, have hydroxyl, acetyl, and keto-acetyl groups (Iram et al., 2017) BA compounds are reported to have anti-oxidant, anti-inflammatory and immunomodulatory activities (Sami et al., 2019) (Vo et al., 2019) (Chahal & Jha, 2020) (Rashan et al., 2019). This study is an early exploratory study that aims to determine the effect of boswellic acid administration on sprague dawley rats (Rattus novergicus) given cyclophosphamide.

Previous research aligned with the "Effect of Bosswelic Acid On Hematological Parameters In Sprague Dawley Rats Induced By Cyclophosphamide" may encompass investigations into various compounds or interventions aimed at mitigating hematological toxicity induced by chemotherapy agents in animal models or human subjects. Studies in this domain might have explored the protective effects of herbal compounds, such as curcumin, resveratrol, or other plant extracts, against cyclophosphamide-induced hematological toxicity in preclinical models or cancer patients. Additionally, research investigating the potential of nutritional supplements, such as vitamin E, vitamin C, or folic acid, to alleviate chemotherapy-induced hematological toxicity could be relevant. Furthermore, investigations into alternative hematoprotective agents, like amifostine, and their ability to attenuate blood cell damage and hematopoietic tissue injury caused by cancer treatment could contribute to the broader understanding of mitigating chemotherapy side effects. Studies examining combination therapies, such as the co-administration of Bosswelic Acid with other hematoprotective agents or compounds, to enhance the effectiveness of cancer treatment while reducing associated toxicity may also offer valuable insights. Through a comprehensive review of the existing literature, previous research can provide context and expand understanding regarding the potential of Bosswelic Acid in protecting against cyclophosphamide-induced hematological toxicity in experimental animals or cancer patients.

This research represents a significant breakthrough in understanding the potential of Bosswelic Acid as a protective agent against hematological toxicity induced by cyclophosphamide in Sprague Dawley rats. Through this exploration, researchers expand the scope of knowledge regarding potential new therapies to mitigate the negative impacts of cancer treatment, which often include decreased blood cell counts and disruptions in hematopoietic function. By selecting cyclophosphamide as the inducing agent for toxicity, this study also underscores its clinical relevance, considering it is one of the primary choices in chemotherapy. The findings of this research not only provide valuable insights into the potential of Bosswelic Acid as a hematological protector but also may pave the way for the development of more effective treatment strategies focused on patient well-being in the context of cancer care. The aim of this study was to determine

the effect of Boswellic Acid (BA) in hematology parameter rats induced by cyclophosphamid.

Research Methods

Time and Place of Research

This research was conducted from August to October 2022. Maintenance and testing of experimental animals, blood analysis, and data collection were carried out at the Saraswati Indo Genectech (SIG) Toxicity Laboratory, Jakarta.

Tools and Materials

The tools used in this study include experimental animal rearing equipment (cages, feed bins, and drinking places), 1 mL syringes, markers, vacutainer containing tripotassium ethylene diamine tetraacetic acid (K3EDTA), hematology analyzer. The ingredients used in this study were boswellic acid (BA) powder, cyclophosphamide (SP) chemotherapy drugs, commercial blood enhancer (SD) supplements, 70% alcohol, normal saline (NS) NaCl 0.9%, aquades, ketamine 10%, xylazine 2%.

Code of Ethics

This research has been approved by the Ethics Commission of PT. Saraswati Indo Genectech (GIS). The protocol number is 082-2022/KEH/SIG.

Research Procedure

Test Sample Preparation (Boswellic acid solution)

Boswellica extract used is produced by the company Hunan Nutramax Inc. Boswellica extract contains 65% boswellic acid (BA) derived from Boswellia serrata L. resin, BA as much as 250 mg mixed with 1 mL of corn oil.

Experimental Animal Treatment

The experimental animals used in this study were 30 male white sprague dawley rats, aged 6-7 weeks with a weight ranging from 170-200 grams provided by PT. Saraswati Indo Genectech (GIS). The rats were acclimatized for 7 days before testing. The rats were placed indoors in a controlled environment and got a 12-hour cycle of light and dark. Rats are facilitated with cages, bedding, feed bins, and clean drinking places. Rats were given standard feed and drinking water ad libitum.

In Vivo Test of Hemoprotective Activity of Boswellic acid

The design of this study is a modification of the research method of Cengiz et al. (2020). This test was conducted for 7 days. A total of 30 rats were randomly divided into 6 groups, each group consisting of 5 mice. The division of treatment groups can be seen in Table 1.

Table 1 Design of in vivo testing of hemoprotective activity of Boswellic acid

Group Treatment	Day						
	H1	H2	H3	H4	H5	H6	H7
KS	-	-	-	NS	-	-	eutanasia
KSP	-	-	-	SP	-	-	eutanasia
KSD	-	-	-	SD+SP	-	-	eutanasia
K1	BA+SP	BA	BA	BA	BA	BA	eutanasia
K2	BA	BA	BA	BA+SP	BA	BA	eutanasia
K3	BA	BA	BA	BA	BA	BA+SP	eutanasia

Information:
Normal saline (NS) 0.5 mL ; cyclophosphamide (SP) 150 mg/kg; blood enhancer supplement (SD) 32 mg/kg body weight; Boswellic acid (BA) 250 mg/kg body weight; Healthy control (KS); SP control (KSP); comparator control (KSD); BA treatment group (K1; K2; K3).

Hematology Profile Examination Using Hematology Analyzer

Blood samples that have been inserted into the K3EDTA vacutainer are then analyzed using a hematology analyzer. Hematological data of each sample recorded include hemoglobin (Hb) level, hematocrit value (HCT), erythrocyte count (RBC), and erythrocyte index [(mean corpuscular volume (MCV); mean corpuscular hemoglobin (MCH); mean corpuscular hemoglobin concentration (MCHC)].

Data Analysis

Hemogram data (Hb level, hematocrit value, erythrocyte count, erythrocyte count and index (MCV, MCH, MCHC) were analyzed using one-way analysis of variance (ANOVA). After that, continue with the duncan post hock test to see the differences between treatment groups.

Results and Discussions

Results of Rat's Hematological Value

Results of hematological examination before treatment (H0) in Table 2. showed that there was no significant difference ($p>0.05$) in all blood parameters between all treatment groups (KS; KSP; KSD; K1; K2; and K3). The value of hematological parameters is still within the range of normal values according to the standards of (Giknis & Clifford, 2006).

Table 2 Average values of rat hematological parameters before treatment (H0)

PARAMETER	GROUP						REFERENCE*
	KS	KSP	KSD	K1	K2	K3	
Hb (g/dL)	13.84±11.99[a]	14.76±13.28[a]	14.54±7.92[a]	15.34±20.61[a]	14.72±5.45[a]	14.14±8.44[a]	14.40 – 16.00
HCT (%)	40.14±3.23[a]	41.72±3.53[a]	41.24±1.66[a]	43.78±5.34[a]	42.06±1.53[a]	40.48±2.15[a]	41.20 - 47.30
RBC (10^6/µL)	7.212±0.79[a]	7.468±0.67[a]	7.374±0.34[a]	8.036±0.96[a]	7.576±0.32[a]	7.316±0.59[a]	7.77 - 8.19
MCV (fL)	55.86±2.69[a]	55.92±0.99[a]	56.02±1.83[a]	54.56±1.51[a]	55.62±1.88[a]	55.48±1.79[a]	53.00 - 59.50
MCH (pg)	19.16±0.8[a]	19.72±0.57[a]	19.7±1.1[a]	19±0.49[a]	19.4±0.7[a]	19.3±0.55[a]	18.30 - 20.00
MCHC (g/dL)	34.42±2.59[a]	35.3±4.7[a]	35.18±8.14[a]	34.94±6.19[a]	34.8±4.53[a]	35.02±7.23[a]	32.70 - 35.70

Description: different letters in the same line showed a marked difference between treatment groups, a 95% confidence interval; *Giknis and Clifford (2006)

Hematological examination of KSP rats (Cyclophosphamide treatment group) was carried out on day 0 (H-0) before treatment and day 7 (H-7) after treatment as an indicator of success of cyclophosphamide (SP) induction. Hb levels, HCT values, RBC counts, between KSP-H0 and KSP-H7 differ markedly ($p<0.05$). The MCV, MCH, and MCHC values between KSP-H0 and KSP-H7 did not differ markedly ($p>0.05$).

SP induction in the KSP group caused a decrease in all hematological parameters (Table 3), in accordance with the results of previous studies (Patra et al., 2012) (Alqahtani & Mahmoud, 2016). The results of hematological analysis after cyclophosphamide treatment are listed in Table 4.

Table 3 Comparison of cyclophosphamide (KSP) groups on day 0 and day 7

PARAMETER	TIME	
	KSP H-0	KSP H-7
Hb (g/dL)	147.6±13.28[a]	95.2±26.89[b]
HCT (%)	41.72±3.53[a]	27.96±7.5[b]
RBC (10^6/µL)	7.468±0.67[a]	5.224±1.33[b]
MCV (fL)	55.92±0.99[a]	53.52±1.43[a,b]
MCH (pg)	19.72±0.57[a]	18.04±0.73[ab]
MCHC (g/dL)	35.30±4.7[a]	33.86±6.47[ab]

Based on Table 4, Hb levels in all treated groups (H7) tended to decrease when compared to before treatment (H0). The results of the analysis showed that Hb levels between the K3 and KSP groups were significantly different ($p<0.05$). Hb levels between KSP and K1 and K2 did not differ markedly ($p>0.05$). The K2 group showed higher Hb values than K1 and KSP, while the K1 group had the lowest Hb levels. Hemoglobin in K3 has a higher value of 47% compared to Hb levels in the KSP group. The K3 group showed the best results in maintaining Hb levels compared to the other groups. Hb levels in the K3 group have the highest values and are closest to the normal range. The results of the study of Ismail et al. 2019 showed that BA administration was able to increase Hb levels in rabbits given BA supplementation.

Table 4 Average values of hematological parameters in rats after treatment

Parameter	Treatment Group						Reference *
	KS	KSP	KSD	K1	K2	K3	
Hb (g/dL)	11.6±16.47 ^{a,b}	9.52±26.89 ^{a,b}	12.12±4.15 ^{b,c}	8.68±17.08 ^{a}	11.78±4.55 ^{b}	13.96±34.77 ^{c}	14.40 – 16.00
HTC (%)	33.78±4.37 ^{a,b}	27.96±7.5 ^{a,b}	34.9±1.02 ^{b}	25.5±4.88 ^{a}	33.54±1.61 ^{a,b}	39.6±9.23 ^{c}	41.20 - 47.30
RBC (10^6/µL)	6.264±0.68 ^{a,b}	5.224±1.33 ^{a}	6.372±0.17 ^{a,b}	4.958±0.88 ^{a}	6.322±0.46 ^{a,b}	7.316±1.74 ^{b}	7.77 - 8.19
MCV (fL)	54.02±3.72 ^{a,b}	53.52±1.43 ^{a,b}	54.88±1.79 ^{a}	51.42±1.82 ^{b}	53.22±2.03 ^{a,b}	54.3±2.35 ^{a,b}	53.00 - 59.50
MHC (pg)	18.44±1.43 ^{a,b}	18.04±0.73 ^{a,b}	18.98±0.72 ^{a}	17.42±0.82 ^{b}	18.62±0.98 ^{a,b}	19±0.95 ^{a}	18.30 - 20.00
MCHC (g/dL)	34.24±6.43 ^{a,b}	33.86±6.47 ^{a}	34.68±2.59 ^{a,b}	33.94±7.34 ^{a}	35.08±7.7 ^{b}	35.12±8.9 ^{b}	32.70 - 35.70

Description: different letters on the same line showed a marked difference between treatment groups, 95% confidence interval; * Giknis and Clifford (2006)

Hematocrit is the ratio of erythrocytes to blood volume (Giknis & Clifford, 2006). The results of the analysis showed that the highest HCT values were found in the K3 group, followed by the KSD, K2, KSP, K1 groups (Table 4). HCT scores in the K3 group were significantly different compared to other groups ($p<0.05$). HCT values in the K3 group were 42% higher than in the KSP group. According to (Ismail et al., 2019) BA was able to increase HCT values in rabbits given BA supplementation.

Rat erythrocytes are biconcave spherical, do not have a nucleus with a diameter ranging from 5.7–7.0 µm. Erythrocytes have the main function as transporters of hemoglobin, carrying oxygen from the lungs to tissues (Rosidah et al., 2020). The results of hematological parameter analysis in Table 4 showed that the number of erythrocytes of the KSP group was not significantly different ($p>0.05$) compared to the K1, K2, KSD groups, but was significantly different ($p<0.05$) from the K3 group. The K3 group has the highest number of erythrocytes. The erythrocyte count of the K3 group was 40% higher than that of the KSP group, and the erythrocyte count of the K2 group was 21% higher than that of the KSP. Previous research mentioned that BA supplementation in rabbits increased the number of erythrocytes.

The erythrocyte index includes MCV, MCH and MCHC values (Giknis & Clifford, 2006). The results showed that almost all MCV, MCH and MCHC values in the treatment group were still within the normal range (Table 4). The results of erythrocyte index analysis between all treatment groups were not significant ($p>0.05$). The erythrocyte index in the K3 group showed the best results compared to other groups. The provision of BA is able to maintain / increase the value of MCH and MCHC in accordance with the results of Ismail et al's research in rabbits.

Discussion of the Value of Rats Hematology

Metabolism of cyclophosphamide occurs in the liver with the help of cytochrome P450 enzymes. Cyclophosphamide (SP) has two active metabolites, namely phosphorus

mustard (MF) and acrolein (Iqubal et al., 2019). Phosphorus mustard is an anticancer metabolite, while acrolein is a toxic metabolite.

SP metabolites are thought to cause hemolytic anemia due to impaired erythrocyte osmolarity although not significant. Phosphorus mustard and acrolein can affect circulating erythrocytes, triggering erythrocyte intracellular antioxidant depletion causing a decrease in glutathione (GSH) levels and interfering with the activity of some enzymes such as glutathione-S-transferase, catalase, glutathionie peroxidase, and glutathione reductase, further causing oxidative stress. As a result, changes in erythrocyte morphology and erythrocyte conformation - protein crosslinking, lipid peroxidation, hemolysis, and culminate in cell death (Akamo et al., 2021) (Skverchinskaya et al., 2023).

SP metabolites in cells are reported to initiate the formation (reactive oxygen species) of ROS, including H2O2, HOCl, O2, and OH. High levels of ROS cause disruption of intracellular oxidant/antioxidant balance resulting in a decrease in intracellular GSH and causing lipid peroxidation. Oxidative stress is further suspected of triggering toxicity, causing myelotoxic causes including anemia, thrombocytopenia, and leukopenia (Liu et al., 2014) (Raj & Gothandam, 2015) (El-Naggar et al., 2018) (Iqubal et al., 2019).

Cyclophosphamide triggers inflammation that is closely related to oxidative stress. Cyclophosphamide induces the production of cytokines such as tumor necrosis factor (TNF)-a, interleukin (IL)-6, and IL-1b triggering inflammatory processes in tissues or organs, causing direct damage to the liver, kidneys, bone marrow cells and hematopoietic stem cells thereby inhibiting hematopoiesis (Alqahtani & Mahmoud, 2016). Further damage to hematopoietic organs results in leukopenia, thrombocytopenia and anemia (Alqahtani & Mahmoud, 2016).

The evaluation of Boswellic acid (BA) administration is divided based on the time of administration. According to (Glassman & Muzykantov, 2019), several factors that affect drug effectiveness include individual physiological, genetic, age, weight, drug interactions, drug tolerance, gender, drug administration and dosage, pharmaceutical preparations, time/interval. Drug interactions can affect drug effectiveness. Drug interactions can occur in the process of absorption, distribution, metabolism, and excretion of drugs. Drug interactions can be used as a treatment strategy aimed at reducing side effects or toxicity caused by one of the drugs (Jarada et al., 2020).

Administration of BA extract in the K1 group simultaneously with SP showed the results of a decrease in hemoglobin, hematocrit, erythrocyte parameters. The treatment group given BA first before being given SP (K2 and K3) showed a good response in maintaining hemoglobin levels, hematocrit count, and erythrocyte count. BA administration for 6 days before cyclophosphamide administration (K3 group) showed the best value including when compared to the comparison control group (KSD).

The results of this study showed that BA administration was able to increase values on hematological parameters (Hb, HCT, and erythrocytes) in mice. The results of this research are almost the same as the results of Ismail et al's research 2019. Research results of (Ismail et al., 2019) showed that supplementation of Boswellia serrata resin in rabbit feed can increase hematological values in general although it is not significant and does not show symptoms of toxicity. The study used a BA level of 30% with a dose of 0.5; 0,75; 1.0 grams / Kg body weight as a feed supplement in rabbits

Boswellic acid has anti-oxidant and anti-inflammatory activity. Boswellic acid has anti-oxidant activity through ROS inhibition (Majeed et al., 2021). In addition, active

metabolites of BA can inhibit pro-inflammatory cytokines, 5-lipoxygenase, TNF-α, IL-6, and COX-2 secretion responsible for inflammatory processes (Rashan et al., 2019).

The decrease in SP side effects on hematological parameters is thought to be related to BA's ability as an anti-inflammatory and anti-oxidant agent. The possibility of oxidative stress due to SP can be prevented by the active metabolite BA, either directly or indirectly. Metabolic BA is thought to be able to prevent oxidative stress due to SP through the prevention of ROS and inhibition of lipid peroxidase so as to prevent DNA damage. It is suspected that the mechanism of action and interaction of BA and SP is similar to BA and Doxorubicin. Research (Barakat et al., 2018) showed that BA was able to prevent ROS formation, inhibit lipid peroxidase and DNA damage in mice induced Doxorubicin. BA metabolites are also thought to be able to inhibit the inflammatory process due to SP administration through inhibition of pro-inflammatory cytokines, TNF-α, and or IL-6. BA's anti-inflammatory and anti-oxidant activities are thought to be able to reduce / prevent myelotoxicity, which in turn reduces / inhibits the occurrence of hematopenia. This research suggests BA is a potential component for the development of hemoprotective agents.

Conclusion

The administration of boswellic acid (BA) affects the value of hematological parameters of hemoglobin levels, hematocrit values, and erythrocyte count. In general, BA administration for 6 days (K3) before SP administration gave the highest hematological parameter value compared to other masked groups when compared to the comparison group. Further studies need to be carried out on the histopathological features of hematopoietic organs, the mechanism of action and interaction of BA in the blood and hematopoietic organs to provide a more complete explanation of the effect of BA administration on cyclophosphamide-induced mice.

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