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Effect of Boswellic Acid Administration on Blood Biochemical Profile of Sprague Dawley Rats in Cyclophosphamide-Induced Cardiotoxicity Conditions

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Abstract:

Cyclophosphamide (CP) is a chemotherapeutic agent that belongs to the alkylating agent group that is widely used in the treatment of cancer. Cardiotoxicity is often a side effect of using CP in medical therapy. In this study, 24 Sprague Dawley rats were randomly divided into 4 groups. Group 1 (K1) was given injection with aqua pro injection intraperitoneally (IP) once a week for 21 days. Group 2 (K2) was given IP CP with a dose of 50 mg/kg BW, once a week for 21 days. Group 3 (K3) was given boswellic acid extract at a dose of 250 mg/kg BW orally, every day for 21 days. Group 4 (K4) was given boswellic acid nanoparticles at a dose of 250 mg/kg BW orally, every day for 21 days. During the treatment the body weight of the rats was weighed every day. At the end of the treatment, the rats were euthanized and blood samples were taken for blood biochemical evaluation, namely CPK, LDH, AST, and ALT. The results showed that the levels of CPK, LDH, AST, and ALT in K2 were significantly higher ($p<0.05$) than K1, K3 and K4. Statistically, the results of CPK, LDH, AST and ALT in K3 and K4 were not significantly different ($p<0.05$) compared to K1. The two groups (K3 and K4) were not significantly different ($p<0.05$) but on average the CPK, LDH, AST, and ALT results in K4 had lower scores than K3. This can indicate the protective effect of boswellic acid and boswellic acid nanoparticles on the heart against cyclophosphamide-induced cardiotoxicity.

Keywords:
boswellic acid; cyclophosphamide; nanoparticles; rats; cardiotoxicity

I. Introduction

Cancer treatment in the last decade has made progress to improve patient survival. One of the chemotherapy that is widely used for cancer treatment is cyclophosphamide. This drug belongs to the alkylating agent class (Ghobadi et al. 2017). Cyclophosphamide has various side effects including cardiotoxic which often causes myocardial dysfunction and even heart failure (Atalay et al. 2014, Kim et al. 2017). Cardiotoxicity due to cancer drugs poses a serious risk to human health, and is a concern for cardiooncologists today. This cardiotoxicity is associated with an imbalance of free radicals and antioxidants or oxidative stress. According to Angsutararux et al. (2015) oxidative stress can activate a series of pathways that can damage cardiomyocyte membranes, proteins, and deoxyribonucleic acid (DNA). The total dose of anticancer agent received by the patient, rate of drug administration, previous history of heart disease, and elevated blood pressure are risk factors for cardiotoxicity (Remesh 2012). Cardiotoxicity of cyclophosphamide can be reduced by consuming compounds that act as antioxidants such as flavonoids, triterpenoids and polyphenols found in various natural products (Gabriella et al. 2005).

Boswellic acid is a pentacyclic triterpenoid compound known as the most important component of Boswellia resin (Zhang et al. 2014). Besides having strong antioxidant activity, this compound also exhibits a number of other biological activities including hepatoprotective, antidiabetic, antibacterial, and anticancer (Rahila et al. 2013; Cai et al. 2019). Several studies have shown that boswellic acid has antioxidant properties that can protect the heart from the cardiotoxic effects of doxorubicin in mice carrying Ehrlich carcinoma (Shimaa et al. 2015). Research conducted by Sami et al. (2019) demonstrated the existence of an antioxidant effect that acts as a nephroprotective in doxorubicin-induced nephrotoxicity. Research conducted by Sterk et al. (2004) regarding the pharmacokinetics of boswellic acid revealed that the concentration of boswellic acid in plasma after administration of Boswellia serrate extract was very low. The results of further studies revealed that about 80% of the initial concentration of boswellic acid is metabolized after 15 minutes and less than 1% of the initial concentration remains in plasma after 120 minutes (Kruger et al. 2008). In terms of overcoming these limitations, many approaches have been investigated such as synthetic analogues, combination with other foodstuffs and the use of nanoscale drugs (nanoparticles). Among these methods, nanoparticles have become the main alternative for many researchers as a potential area to develop new formulations of bioactive components (Mehta et al. 2014). To the best of the researcher's knowledge, The cardioprotective efficacy of boswellic acid nanoparticles against cyclophosphamide-induced cardiotoxicity has not been studied previously. Therefore, this study was conducted to determine the effect of boswellic acid on the biochemical profile of rat blood on cardiotoxicity induced by cyclophosphamide.

II. Research Methods

2.1 Sample and Drug

The sample consisted of Boswellia gum resin extract containing 65% boswellic acid obtained from Hunan Nutramax Inc, China.

2.2 Manufacture of Nanoparticles

The manufacture of boswellic acid nanoparticles using the ultrasonication method with an amplitude of 40%. The boswelic acid powder was dissolved in a combination of Tween 80 in aquadest. The ultrasonication process uses an ultrasonic bath at a temperature of 65℃ with a variation of the ultrasonication time for 180 minutes (Bairwa et al. 2016).

2.3 Code of Conduct

This research has been approved by the Health Research Ethics Commission, Health Research and Development Agency (KEPK-BPPK) with protocol number LB.02.01/2/KE.229/2021.

2.4 Experimental Animal Treatment

Mice were acclimatized for 5 days. After the acclimatization period was completed, it was continued with the treatment stage, namely the administration of cyclophosphamide (CP) intraperitoneally (IP) and boswellic acid (BA) orally (PO) which lasted for 21 days and was a modification of the previous research method (Komolafe et al. 2020 ; Regards et al. 2016). During the treatment period, the body weight of the rats was weighed every day. In Table 1, it can be seen the division of experimental and treatment groups of animals.

Table 1. The distribution of experimental and treatment groups of animals

	Group	Treatment
K1	(Normal Control)	Mice were given aqua pro injection IP
K2	(CP Control)	Rats were injected with CP at a dose of 50 mg/kg BW IP on days 1,13, and 21 to induce cardiotoxicity.
K3	(CP+BA)	Rats were given BA 250 mg/kg + PO olive oil for 21 days and CP by IP on days 3, 10 and 17.
K4	(CP+nanoBA)	Rats were given BA 250 mg+ PO olive oil nanoparticles for 21 days and CP 50 mg/kg BW on days 3,10 and 17.

2.5 Blood Sample Collection

Mice were euthanized by injection of anesthetic ketamine and xylazine and then exsanguination was performed. Blood samples were collected from each animal through cardiac puncture into a capillary tube sample vial without coagulant. Blood samples were centrifuged at 2000 rpm. Serum was used for the biochemical determination of creatinine phosphokinase (CPK), lactate dehydrogenase (LDH), aspartate transaminase (AST), and alanine aminotransferase (ALT).

2.6 Biochemical Measurement of Blood

Biochemical measurement of blood using blood serum. Blood serum taken as much as 400 and reacted with reagents. The increase in the sample-reagent reaction will be read at an absorbance of 340 nm. Blood biochemical samples were processed by automatic chemistry analyzer.

2.7 Statistical Analysis

All quantitative data were analyzed using the one-way ANOVA analysis of variance and presented in the form of mean and standard deviation. Subsequently, a post hoc test using Tukey's test (significance at $p<0.05$) was used to make comparisons between groups.

III. Discussion

3.1 Results

a. Weight Change

Data on the average response to changes in body weight (BB) for 21 days of treatment are presented in Table 2.

Table 2. Average weight gain for 21 days of treatment

Treatment	BB (grams)		
	Day 1	Day 21	BB difference
K1	183.42±10.84a	208.02±12.94a	24.60±a
K2	181.57±5.10a	164.10±4.76c	-17.47±c
K3	194.32±16.37a	186.80±17.15ab	-7.52±b
K4	184.85±19.17a	176.60±15.92bc	-8.25±bc

Different letters in the same column indicate significantly different test results ($P<0.05$). K1 (normal, aqua pro injection), K2 (CP), K3 (CP+BA extract 250 mg/kg BW), K4 (CP+BA nanoparticles 250 mg/kg BW).

b. Heart Weight and Heart Weight/Body Weight Ratio

The data on the average heart weight (BJ) and the ratio of heart weight to body weight are presented in Table 3.

Table 3. Average BJ and BJ/BW ratio after 21 days of treatment

Group	BJ (mg)	BJ/BB x10-3 (mg/gram)
K1	650.00±88.38b	3.14±0.51b
K2	811.50±101.99a	4.95±0.69a
K3	642.83±50.65b	3.48±0.49b
K4	673.67±69.84b	3.82±0.34b

Different letters in the same column indicate significantly different test results (P<0.05). K1 (normal, aqua pro injection), K2 (CP), K3 (CP+BA extract 250 mg/kg BW), K4 (CP+BA nanoparticles 250 mg/kg BW).

c. Blood Biochemistry

The average blood biochemical results data after 21 days of treatment are presented in Table 4.

Table 4. Average blood biochemical results after 21 days of treatment

Group	Blood serum level (U/L)			
	ALT	AST	LDH	CPK
K1	39.50±3.73b	124.33±6.15b	215.50±51.85c	233.33±76.75c
K2	76.83±14.50a	150.67±14.75a	686.83±62.15a	760.67±68.39a
K3	63.83±12.53a	139.83±9.64ab	424.17±94.29b	615.33±59.22b
K4	61.33±11.59a	134.67±21.48ab	379.50±87.81b	584.33±86.39b

All data are mean ± standard deviation.. n=6. Different letters in the same column indicate significantly different test results (P<0.05). K1 (normal, aqua pro injection), K2 (CP), K3 (CP+BA extract 250 mg/kg BW), K4 (CP+BA nanoparticles 250 mg/kg BW). ALT (Alanine Transaminase), AST (Aspartate Aminotransferase), CPK (Creatinine Phosphokinase), LDH (Lactate Dehydrogenase)

3.2 Discussion

Cyclophosphamide (CP) is a drug that is widely used in the treatment of tumors and autoimmune diseases. This drug has side effects on the heart that are dose dependent (Kamel et al. 2020). Acrolein is a metabolite of CP and is the main metabolite that causes toxic effects produced during oxidative stress. Acrolein causes inhibition of DNA replication and apoptosis in cancer cells but can also cause damage to cardiac mitochondrial membranes and reduce oxygen radical detoxification capacity of cardiac mitochondria (Jeelani et al. 2017). Toxicity induced by oxidative stress can be reduced by substances having antioxidant activity. These antioxidants are found in many plants and herbs. Flavonoids, flavones, isoflavones, anthocyanins, catechins, and isocatechins are antioxidants that are often found in plants and herbs (Shindi et al. 2013). Boswellia serrata is a species of Boswellia plant that is widely used in traditional medicine. Boswellia serrata extract has an active substance called boswellic acid (Zhang et al. 2014). The literature states that boswellic acid has shown potential as anti-inflammatory, anti-asthmatic, antitussive, anti-tumor, anti-microbial (Iram et al. 2017; Vuddanda et al. 2016), hepatoprotective and antidiabetic (Rahila et al. 2013; Cai et al. 2016). al. 2019).

Based on the one-way Anova test and continued with the Tukey Test (Table 2) difference test, rat body weight on day 1 for treatment K1 (normal control), treatment K2 (negative control), K3 treatment (CP+BA), and K4 treatment (CP). +BA nanoparticles) were not significantly different (p>0.05). However, the body weight of rats on day 21 for treatment K4 (CP+nano BA) with treatment K3 (CP+BA) and treatment K2 was not significantly different (p>0.05) but significantly different (p<0.05) with treatment K1 (control normal).

Observation of the difference in body weight in K3 (CP+BA) and K4 (CP+nano BA) treatments were not significantly different ($p>0.05$), but significantly different ($p<0.05$) with K1 treatment (normal control). When compared with treatment K2 (negative control) it was significantly different ($p<0.05$) with treatment K3 (CP+BA) and not significantly different ($p>0.05$) with treatment K4 (CP+nano BA).

Treatment K2 (negative control) given cyclophosphamide experienced significant weight loss compared to treatment K1 (normal control) and other treatment groups. This is in accordance with the results of previous studies (Tarek et al. 2010; Komolafe et al. 2020) where the general condition of the rats decreased which is an indication of cyclophosphamide toxicity. In the K3 (CP+BA) treatment and K4 (CP+BA nanoparticles) treatment there was also a decrease in body weight compared to day 1 weight. However, based on the average difference in weight loss, the two treatment groups had a lower difference in reduction compared to K2 treatment (negative control). This indicates a reduction in the toxicity of cyclophosphamide by boswellic acid. The difference in weight loss between the two treatment groups was almost the same, meaning that boswellic acid given in the form of nano and powder can increase weight loss improvements.

The results of this study indicate that the administration of CP resulted in a significant increase in heart weight. In this study, it was found that there was an increase in heart weight and ratio to body weight in the rat group when compared to the normal group. The results of this study are supported by Baky et al. (2009) which states that an increase in heart weight can be caused by an increase in edema, hemorrhage, necrosis, infiltration of inflammatory cells by inflammatory cells.

Based on the one-way Anova test and continued with Tukey's follow-up test (Table 4, Appendix), at the end of the period, ALT levels in blood serum were treated with K2 (negative control), K3 treatment (CP+BA) and K4 treatment (CP+BA nanoparticles).) was not significantly different ($p>0.05$), but significantly different ($p<0.05$) with treatment K1 (positive control). AST levels in the K3 (CP+BA) treatment and K4 (CP+BA nanoparticles) treatment were not significantly different between the two but significantly different from K2 (negative control).

Blood serum CPK levels in K3 treatment (CP+BA) and K4 treatment were not significantly different ($p>0.05$), but significantly different ($p<0.05$) with treatment K1 (normal control) and treatment K2 (negative control). Blood serum CPK level in K1 treatment was significantly different ($p<0.05$) with K2 treatment (negative control). Based on the one-way Anova test and continued with the Tukey difference test at the end of the treatment period, blood serum LDH levels in K3 (CP+BA) treatment and K4 treatment were not significantly different ($p>0.05$), but significantly different ($p<0.05$) with treatment K1 (normal control) and treatment K2 (negative control). Blood serum LDH levels in treatment K1 (normal control) were significantly different ($p<0.05$) with treatment K2 (negative control).

Side effects of cyclophosphamide are related to oxidative stress. Oxidative stress causes myocardial cell damage. Enzymes such as CPK, LDH, AST and ALT enter the bloodstream and can be used as diagnostic tools for tissue damage. The enzyme can be used as a marker of organ and cellular damage because the enzyme is secreted into the blood and can be measured by taking a blood sample. Lactate dehydrogenase (LDH) is a cytoplasmic enzyme that is present in almost all tissues but at high concentrations in muscle, liver, and kidneys. In tissues, cells release the enzyme LDH into the blood. Increased LDH in blood serum due to organ damage occurs due to significant cell death. Causes of tissue damage can

be in the form of diseases such as acute myocardial infarction, anemia, pulmonary embolism, hepatitis and acute renal failure (Yamaguchi et al. 2020). In this study, the highest average was found in K2 (negative control). In the K3 and K4 groups there was no significant difference but on average, K4 (CP+BA nanoparticles) had a lower average value than K3 (CP+BA).

Creatine phosphokinase or creatine kinase (CPK) is an enzyme that catalyzes the reaction of creatine and adenosine triphosphate (ATP) to phosphocreatine and adenosine diphosphate (ADP). Phosphocreatine made from this reaction is used to supply ATP to tissues and cells that require large amounts of ATP, such as the brain, skeletal muscle, and heart (Chanson et al. 2018). In this study, the highest average was found in K2 (negative control). In the K3 and K4 groups there was no significant difference but on average, K4 (CP+BA nanoparticles) had a lower average value than K3 (CP+BA). From these results, it can be seen that boswellic acid has the potential to reduce heart damage caused by cyclophosphamide toxicity. Alanine Transaminase (ALT) is found in many body tissues. This enzyme catalyzes the transfer of an amino group from alanine to alpha-ketoglutarate, resulting in the formation of pyruvate and glutamate. ALT is found in the cytoplasm of liver, kidney cells, cardiac cells and skeletal muscle (Mirdayanti et al. 2018). In this study, the highest average was found in K2 (negative control). In the K3 and K4 groups there was no significant difference but on average, K4 (CP+BA nanoparticles) had a lower average value than K3 (CP+BA). It can be interpreted that nanoparticles have better efficacy. In addition to LDH and CPK, aspartate aminotransferase (AST) is one of the cardiac metabolic enzymes that is released into the serum in response to cardiac damage (Yan et al. 2012). In this study, the highest AST level was in K2 (negative control) and the lowest was in K1 (normal control).

IV. Conclusion

From the results of the study, it was found that the improvement in rat body weight and the administration of boswellic acid in the form of powder and nanoparticles gave an effect that was not significantly different but on average the boswellic acid nanoparticle treatment group gave better results than the boswellic acid group. It can showhas the potential to reduce heart damage caused by cyclophosphamide toxicity seen from the biochemical profile of blood, body weight and heart weight of rats.

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