

Effect of Andaliman

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Effect of Andaliman (*Zanthoxylum acanthopodium* DC) methanol extract to Rats kidney and liver histology with induced by benzopyrene

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ABSTRACT

The purpose of this study to analysis effect of extract Andaliman to rats kidney and liver histology with induced benzopyrene. The fruit andaliman contains Antioxidants high and is able to repair the damage in the cells of the body. A rat model of cancer-induced benzopyren as many as 30 at a dose of 50 mg/BW and allowed to grow cancer three months later. Then, the rats given the extract of fruit andaliman with the dosage varies according to each group. This research consists of 5 group: K⁻ without any treatment, K⁺ with administration of benzopyren, P1: mice with the extracts andaliman with dose of 100 mg/BW/day, P2: rat with the extracts andaliman with a dose of 200 mg/BW/day, and P3: rat with administration of extracts andaliman with dose of 400 mg/BW/day for 30 days administration. On the 31th day, performed surgical on the subjects. The results in this study there were significant differences ($p < 0.05$) on the value of narrowing of the renal tubules with P value= 0.000 ($P < 0.001$), necrosis of the kidneys with P value= 0.00 ($P < 0.01$), and the damage of the hepatocyte cells with P value= 0.000 ($P < 0.001$), hydrophilic degeneration with P value= 0.000 ($P < 0.001$), parenchymatous degeneration with P value= 0.002 ($P < 0.01$) and liver necrosis with P value= 0.000 ($P < 0.001$), after being given the extract andaliman between the positive control group with a negative control group. The conclusion is extract andaliman affected level of necrosis renal tubules and hepatocyte cells on cancer rats.

Keywords: Zanthoxylum, kidney, liver, benzopyrene, rats

INTRODUCTION

Andaliman is a unique spice from the province of North Sumatra, Indonesia. Andaliman extract contains alkaloids, steroids, and terpenoids having antimicrobial activity against insects, bronchitis drugs, dyspepsia, antiviral, anticonvulsants, antifungals, analgesics, antibiotics, hepatoprotective agents, cancer and preeclampsia (Satria, et al., 2017; Moneim et al., 2017; Janette et al., 2015; Situmorang et al., 2019a, 2019b, 2019c). The composition of andaliman is also used as an antioxidant can be presumed as a barrier to the growth of cancer cells (Simanullang, 2018 and Simanullang 2020). Andaliman can also have anti-inflammatory and antioxidant activity. The essential oil of *Zanthoxylum* showed there is a strong inhibition of the The essential oil of *Zanthoxylum* showed there is a strong inhibition of the fungus growth and antitumor activity (Rosidah et al., 2018; Fauzi, 2015; Kristanti and Suriawati, 2015). The fruit Andaliman (*Zanthoxylum acanthopodium* DC.), is a spice in the Batak community, which can eliminate the fishy smell of raw meat and fish (Moektiwardoyo et al., 2014; Asbur and Khariunnisyah, 2018).

The utilization of traditional medicine in the treatment in humans has become the culture of society because it is proven to cure the disease. Therefore, traditional drugs of plant origin Indonesia still need to be explored, researched, developed, and inventoried. Research needs to be done about the plant that has potential as medicine and knowledge about the active ingredients contained in plants as well as the function and process in the body. In addition to easily obtained, traditional medicine derived from plants generally has no side effects and the price is relatively more easily when compared with synthetic drugs. The local potential that is beneficial to health there is still many who have not been assessed. Many herbs have been studied that have health benefits and one of them is plants Andaliman (*Zanthoxylum acanthopodium* DC.) both fruit and leaves (Suryanto et al., 2014; Negi et al., 2011; Katzer, 2012; Batubara et al., 2017).

The use of herbal medicine has been more developed and advanced rapidly, mainly due to the content of bioactive substances Andaliman recommended as a treatment for cancer and other diseases (Rosidah et al., 2019; Fauzi, 2015). For it is necessary to study whether the use of Andaliman is safe for the kidney and liver then how the standard recommended dose.

MATERIAL AND METHODS

Andaliman extract methanol

The Andaliman extract methanol. The fruit Andaliman used comes from the Bukit Gibeon Sibisa Parapat, District of North Sumatra. Andaliman is washed, then andaliman dries in room temperature for 3 days, and blended until smooth. After that, the manufacture of the extract of andaliman with three steps as follows below:

1. Drying of the crude drug: the fruit of andaliman cleaned, and drained dry, then mashed with the blender.
2. The manufacture of andaliman extract: powder, fruit of andaliman macerated with methanol 96% for one night. The results of maceration and percolation botanicals to achieve a clear liquid. The results of the percolation concentrated with the evaporator until obtained the extracts are concentrated.
3. The manufacture of pharmaceutical suspension: given the extract of andaliman is used partly do not dissolve in water, to obtain a homogeneous mixture used a suspending agent CMC 1,5 % as much as 1.0% or 1 ml in 150 ml of distilled water. The dregs are washed with solvent methanol 96%, and then transferred in a closed container and left into a cool place protected from light for 2 days (Batubara et al, 2017)

Animal

This research used 30 *Rattus norvegicus*, rats were taken and maintained in the Animal House Laboratory, University of Sumatera Utara. The rat made with the animal model of cancer by inducing benzopyrene 50 mg/BW and let growing cancer until three months later (Sikdar et al., 2013). The rats were divided into five groups. Group A was a control group, Group B was treated a dose of 100 mg/BW, group C was the treatment a dose of 200 mg/BW, group D was the treatment a dose of 300 mg/BW and group E was treated a dose of 400 mg/BW of andaliman extract during 30 days administration (Ranawat, Bhatt and Patel, 2010; Fauzi, 2015). Rats dissected on day 30 after administration of andaliman extract, for blood, kidney, and liver were taken, and then the kidneys and livers were prepared for paraffin blocks and Haematoxylin Eosin (HE) staining.

Data analysis

Data calculated with the average change of the histopathological in the kidney and liver from five of the field view with the Manja Roenigk Histopathology Scoring model. Data analysed with used Anova test and non-parametric data with Kruskal Wallis test by using SPSS 22 program.

RESULTS

Table 1. Narrowing Tubules

Groups	Values
K ⁻	32 ± 7.59
K ⁺	80 ± 9.36***
P1	75 ± 3.55
P2	73 ± 7.5
P3	68 ± 5.71

***= P<0.001

Based on table 1 and fig 1, the histology of the kidney is seen there was a significant difference in the narrowing of the renal tubules between the positive control group with a negative control group with P value= 0.000 (P< 0.001). However, there was no difference significantly with the treatment of the extract of andaliman dose of P1, P2, and P3 of the treatment induction benzopyrene (K⁺) with P-value= 0.79; P= 0.53 and P= 0.09 (P>0.05). Based on the following table it was known that the dose of each treatment does not correct the narrowing of the renal tubules due to the induction of benzopyrene.

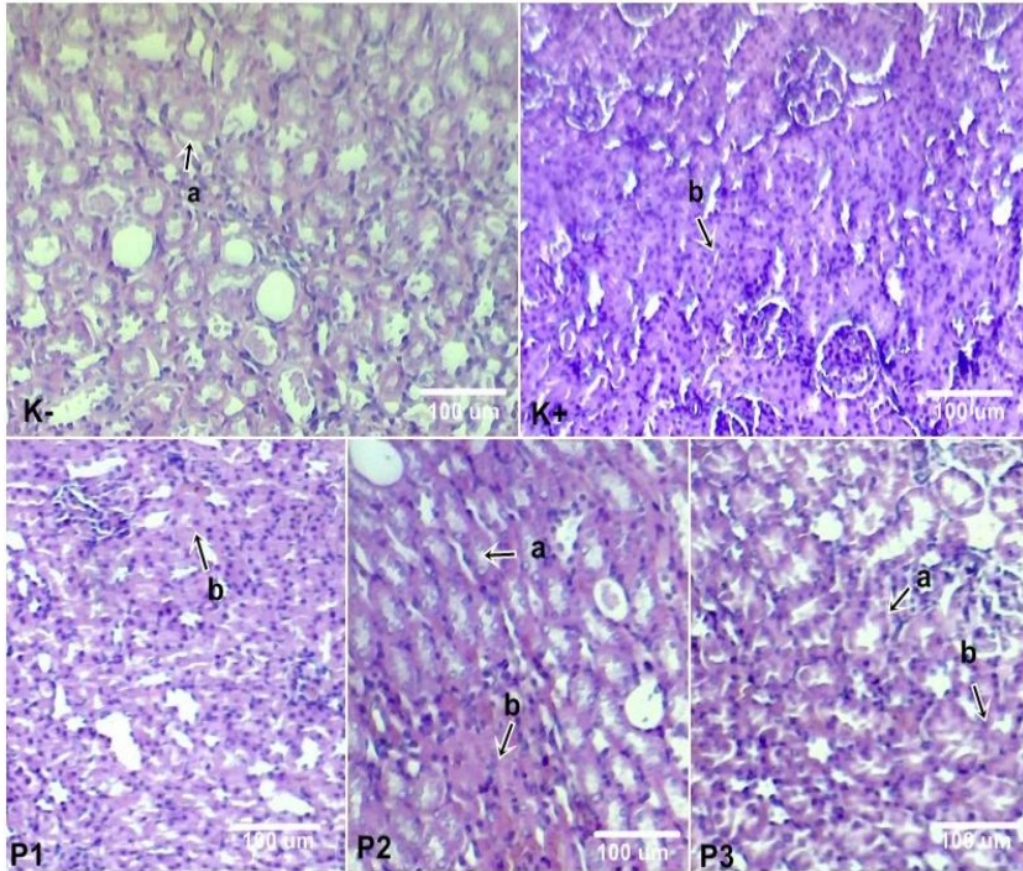


Figure 1. Histology of kidneys, a. Normal tubules b. Narrowing tubules (40x).

Table 2. Kidney's Necrosis

Groups	Values
K ⁻	71 ± 6.51
K ⁺	96 ± 8.94**
P1	88 ± 12.52
P2	86 ± 15.57*
P3	85 ± 20.61*

** = P<0.01

* = P<0.05

Based on table 2, on the histology renal parameters, necrosis of the kidneys is seen that there was a significant difference in the tubulous renal narrowing, between the positive control group with a negative control group with P value= 0.00 (P<0.01). However, there was no difference significantly with the treatment of andaliman extract of dose P1 to the treatment induction benzopyrene (K⁺) with P value= 0.99 (P>0.05). While the Value of a statistical dose of P2 and P3 P=0.02 (P<0.05). Based on the following table it is known that a dose of P1 does not fix the necrosis of the kidneys due to the induction of benzopyrene. The dose of P2 and P3 significantly looks different from the group induction benzopyrene (K⁺).

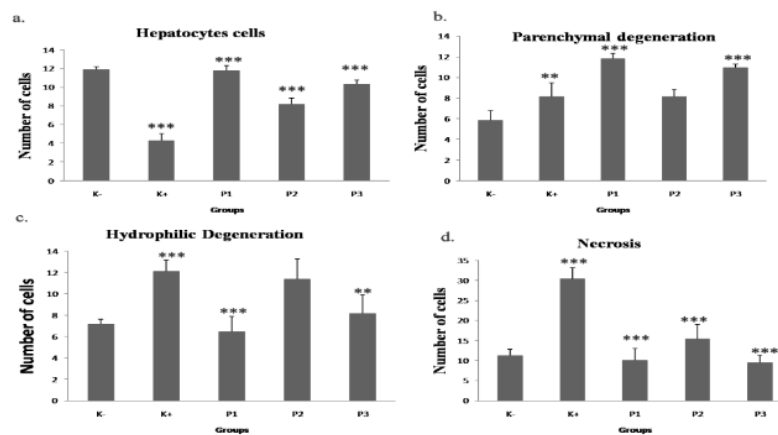


Figure 2 a. Hepatocytes cells, b. Parenchymal degeneration, c. Hydrophilic Degeneration, d. Necrosis (* = P<0.05; ** = P<0.01; *** = P<0.001).

Based on the chart in 2a and figure 3 on the histology of the liver is seen there was a difference significant in the hepatocyte cells of the liver between the positive control group with the entire dose with P value= 0.000 (P< 0.001). Cell hepatocyte looks normal between treatment group. So it is known that the group does significantly, there were value equations hepatocytes normal with the group K⁻ and different from the group, there is an induction of benzopyrene (K⁺).

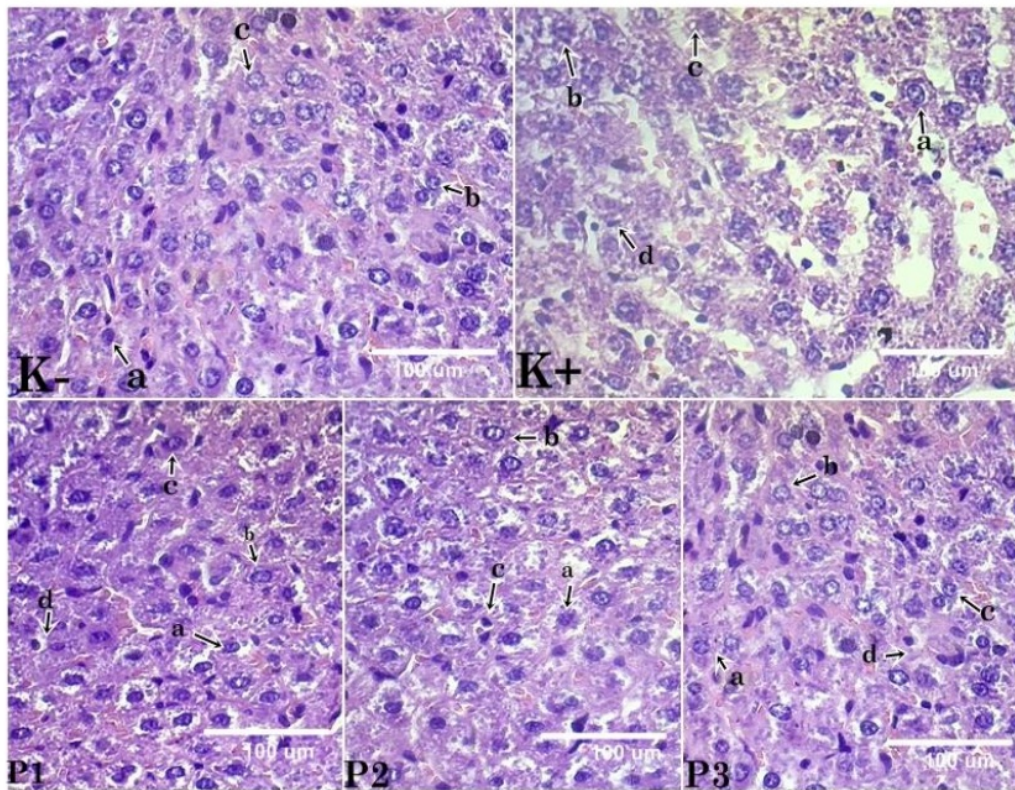


Figure 3. Histology of rat's liver a. Hepatocytes cells, b. Parenchymal degeneration, c. Hydrophilic Degeneration, d. Necrosis (40x)

Chart 3b **figure 3** on the histology of the liver shows the value of the degeneration of the parenchymatous on the histology of the liver, it is seen that there was a significant difference in the hepatocyte cells of the liver that was experiencing degeneration parenchymatous between the positive control group with a negative control with P value= 0.002 ($P < 0.01$). At a dose of P1 and P3, there was also a difference significantly in the treatment of the extract of andaliman dose P1 to the treatment injection benzopyrene (K^+) with P-value= 0.000 ($P < 0.000$). But the value of statistics at P3 = 1.00 ($P < 0.05$). It is known that the dose of P1 and P3 significantly there were value equations degeneration parenchymatous with the group K^- and dose P2 was not proven significantly affect the shape of the cells are hepatocytes.

Chart 3c shows the value of the hydrophilic degeneration on the histology of the liver, it seems there was a significant difference in the cells of the hepatocyte of the liver that is experiencing degeneration of the hydrophilic between the positive control group with a negative control with P value= 0.000 ($P < 0.001$). At a dose of P1 and P3, there was also a difference significantly in the treatment of the extract of andaliman against treatment induction benzopyrene

(K⁺) with P-value= 0.000 (P<0.000) and P= 0.002 (P<0.01). But the value of statistical on P2 = 0.92 (P<0.05). The dose of P1 and P3 significantly there was equality the value of the degeneration of the hydrophilic groups (K⁻).

Chart 3d on the histology of the liver shows values necrosis on the histology of the liver, it seems there was a significant difference in the cells of the hepatocyte of the liver that was experiencing necrosis between the positive control group with a negative control with P value= 0.000 (P< 0.001). It occurs at any dosage, there are also differences significantly with treatment extract of andaliman against treatment induction benzoapyrene (K⁺) with P-value= 0.000 (P<0.001). It is know that the dose of the extract andaliman can significantly improve the value of liver necrosis to the treatment group induction benzoapyrene.

DISCUSSIONS

Cancer patients is increasing from year to year, from the data obtained from the WHO, 2018 that new cases cancer patients is rise up to 18.1 million and in 2018 9.6 million deaths caused by cancer. Cancer patients increased a₁₀ it is affected Cancer patients is increasing and it is influenced by many factors, including population growth and aging as well as changes in the prevalence of certain causes of cancer is associated with the development of social and economic. Rapid economic growth, where the observed shift of the cancers associated with poverty and infection in cancer related to lifestyle more typical of industrial countries (WHO, 2018).

Herbal medicine began to be developed in the treatment of diseases such as cancer in the country-developed and developing countries as in Ogun State Nigeria, the results obtained showed the composition of elements in the examples of the plants studied vary greatly. Estimation of content of concentrates to minerals and essential elements show that some plants can be used as anti-cancer but need to do further research about how the impact to the system of other organs of the body (Olujimi et al, 2014). The studies therapy anti cancer conducted by Yin et al 2013 that the herbal remedies are applied as a combination therapy with the conventional chemotherapy to enhance the therapeutic benefits and quality of life (QoL) as well as to reduce side effects or complications. Based on studies conducted by researchers wh₇ they do research on some plants that the results of the research indicate that, herbal extracts containing antioxidant compounds that can cause apoptosis and inhibit cell proliferation by mechanism that is being studied (Kooti et al, 2017).

Plants andaliman also contains many health benefits in addition to its function as a spice and food preservative. Many preveus research about this

andaliman leave and fruit. On the result of study has found that andaliman has cytotoxic activity on 4T1 cancer cells (Hasib¹²n et al., 2019). According to Situmorang et al. (2020) said that herbal nano belongs to the category of toxic light weight so it can be used as herbal medicine then. Also according to Anggraeni et al. (2014) based on the results extract andaliman has high potential to be developed as co-chemotherapeutic for breast cancer with cell cycle termination.

From some research that has been done by previous researchers that andaliman can be used as a medicine. Organs which impact the process of use of this drug is liver and kidney. It is necessary to research whether the andaliman is safe for kidney and liver. The kidney is the organ that is located under the rib part of the back, near the middle of the back on either side of the spine, and function in filtering substances in the body. While the Liver is the organ that is vital for the human body, which neutralizes toxins, regulates the circulation of the hormone, regulates the composition of blood that contains fats, sugars, proteins, and other substances. The second organ is very important in the metabolism of the body

The occurrence of damage to the tubules the possible presence of toxic substances or foreign objects that get into the body that causes the cells of the epithelium of the tubules swell and eventually resulted in the tubule is damaged, it causes the lumen of the tubules narrowing. The narrowing of the tubules because induction benzopyrene cause disruption of the work of the kidneys so that the kidney is impaired (table 1 and 2). Carcinogenic substances such as benzopyrene are agents that contribute to the acceleration of tumor development, regardless of the mechanism of action and the level of specificity of the effect. In other words, this is a substance that increases the possibility of cancer. In addition to causing cancer, these substances can affect the work of the organs in the body and tubular is a marker of renal injury (Tan et al., 2016). On the other hand, damage of the kidneys can also be affected by the independent risk factors traditionally, the inhibition of insulin, and the components of other metabolic (Targher et al., 2010), impaired transport of sodium tubular will enable feedback glomerular tubular (TGF) mechanism will cause the increase in vascular resistance and a decrease in the content in the GFR (Basille et al., 2014) and these conditions would later develop into the risk of impaired kidney failure chronic and end-stage kidney disease (Negi et al., 2018). Tubular necrosis and parenchyme renal injury are a key role of acute kidney injury (Sanchez et al., 2018) and cell death in renal disease caused by damage to the mechanism of tubular (Priante et al., 2019).

The liver is an important organ system and performs numerous vital functions, such as detoxifying the blood before it is supplied to the brain and

break down proteins and lipids to maintaining blood chemistry tools neutralize and regulate the circulation of hormones, regulate blood composition containing fat, sugar, protein and other substances (Schulze et al., 2019) and maintain homostasis (Nagarajan et al., 2019). Hepatocytes are the cells parenkimal main on the liver that plays a role in many metabolic pathways. Hepatocytes are very actively synthesize proteins and lipids for secreted, and has a lot of the endoplasmic reticulum and the Golgi bodies (Schulze et al., 2019).

In the case of liver failure, a liver transplant may be the best choice in the future and can be seen from the progress of current research and the sophistication of the laboratory equipment required and the progress of technology (Rinella, 2015; Kholodenko and Yargin, 2017; Asrani et al., 2018). Although with the lack of progress, but there is no available targeted therapy, but the method of treatment of hepatitis keep using the treatment methods in the era of 40 years ago to keep the nutrients balanced and the treatment with korticosteroid (Gao and Bataller, 2011).

Liver damage caused by metal and nano-titanium exposure in the environment, carcinogenic and the other substances that can cause oxidative stress (Yun et al., 2013; Nino and Chaverri, 2014; Hong and Zhang, 2016). Disorders of the liver was always associated with necrosis of the cells and the administration of antioxidants exogen, it may be advantageous to protect can protect and nourish the liver. The natural antioxidant is known to have a particularly favorable effect in liver disorders. The provision of andaliman can reduce the damage to the liver and kidneys (Situmorang et al., 2019; Ranawat et al., 2010). For andaliman experience content important function in the health of the cells of the body. Andaliman has the properties of a unique taste and bioactive compounds. Chemical compounds in herbs are monoterpenes, hydrocarbon monoterpenes, volatile compounds main in the andaliman geranyl acetate, and limonene (Limsuwan et al, 2009; Pramodh et al, 2008). The andaliman has a negative impact on the liver histology of rats (Sabri et al, 2018).

A lot of the nucleus cells arise from cells of hepatocytes in the liver. The process when the toxic substances such as benzopyrene get into the hearts of the nucleus will die even more small parts of the chromatin fiber and reticular breed. Increased damage of hepatocytes from chemical compounds in the fruit andaliman. Protection herbs such as andaliman such compounds terpenoids that can be used as an insecticide and has effects very toxic in animals. The damage will cause the body's immune response, and will be directly affected by the biochemistry of the cell. Then it takes an antioxidant such as andaliman. Based on the results and discussion it is known that benzopyrene that enters into the liver and kidneys will lead to impaired function of organs and the giving of andaliman as antioxidants are one way to fix it.

CONCLUSION

Extract andaliman can repair the damage of the liver and kidney of rats induced by benzoapyrene and the provision of andaliman as antioxidants are one way to repair it. Andaliman can be recommended as a drug to repair the necrosis on the liver and kidneys caused by cancer. However, the dose andaliman need to be analyzed in further research.

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