# 3. Martapura River Water Leads to Hepar Alteration in Rats-Proceeding ETAR 2019

*by* Hasni Syahida

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# Martapura River Water Leads to Hepar Alteration in Rats

*Ida Yuliana[1], Husnul Khatimah[2], Lena Rosida[3], Nika Sterina Skripsiana[4]*

*[1,2,3]Biomedical Department, Faculty of Medicine, Lambung Mangkurat University, South Kalimantan, Indonesia, [4]Public Health Department, Faculty of Medicine, Lambung Mangkurat University, South Kalimantan, Indonesia*

Abstract

Martapura is an area in South Kalimantan, Indonesia that is passed by the Martapura River. This river has been polluted by various pollutants, triggering various organ disorders including hepar. To prove this, this research was conducted. The aimed of this study to evaluate alteration macroscopic and microscopic of hepar rats. Design of this study was experimental laboratory with totally 32 research subjects of male rats (Rattus novergicus) divided into 2 groups, namely the group given aquades (control) and the group given river water (treatment) for 30 days. On the 31st day the rats were sacrificed and hepar organ were made histologically with HE staining, analyzed by microscope. The results showed significant alteration of hepar size (p = 0.385), increasing number of hepatocytus (p = 0.036) and central vein (p = 0.000) and also sign of inflamation process in treatment group (odem and congesty in parencim). Conclusion of this study is administration of Martapura river water can cause alteration macroscopic and microscopic in rats hepar

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*Keywords: Martapura river water, Alteration; Hepar, Hepatocytus, Central Vein*

## Introduction

As many as 59.4% of the people along the Martapura River use river water as a source of water for household needs and around 80% of the community take river water without processing it (Fokus Batulicin, 2011; Festiani, 2015)

Based on data from the South Kalimantan regional environmental agency (BLHD) in 2010, the content of heavy metals in the Martapura River exceeded the specified quality standard (Triadayani, 2010) This was confirmed by other studies that stated that Martapura River water contained cadmium levels of 0.006 mg / l, iron of 1, 03-1.35 mg / l, mercury at 5.876 mg / l and lead at 0.125 mg / l (Wang et al, 2011; Festiani, 2015; Johan et al, 2017). These levels exceed the maximum value of the specified water quality standard ie each cadmium, iron, mercury and lead of 0.005 mg / l, 1 mg / l, 0.001mg / l and 0.05 mg / l.6 Based on the regulation of the minister of health of the Republic of Indonesia number 32 of 2017, the maximum parameters in the environmental health quality standard for water media for sanitary hygiene needs that can be used as raw water for drinking water include physical, biological and chemical parameters. Chemical parameters consist of pH and heavy metals such as iron, manganese, mercury, arsenic, cadmium, chromium, selenium, zinc, sulfate and lead (Karantika et al, 2016)

Heavy metals become dangerous pollutants because they are not easily destroyed in the body and in the environment so they tend to accumulate (Agano et al, 2017). High iron content in the body can cause poisoning (vomiting), intestinal damage and diarrhea (Widyasari et al, 2015). Lead exposure can cause kidney damage, anemia and deterioration memory (Somade et al, 2014). Effects of exposure to cadmium result in bone fragility, kidney damage and lung damage (Manoj et al, 2013). Exposure to mercury can interfere with kidney function, central nervous system and peripheral nerves (Suhartono, 2015).

Heavy metals become dangerous pollutants because they are not easily destroyed in the body and in the environment so they tend to accumulate (Harteman E, 2011). High iron content in the body can cause poisoning (vomiting), intestinal damage and diarrhea (Parulian A, 2009). Lead can cause kidney damage, anemia and memory deterioration (Irianti et al, 20117). The effects of cadmium exposure result in bone fragility, kidney damage and lung (Marwah RA et al, 2015). Exposure to mercury can interfere with kidney function, central nervous system and peripheral nerves (Muthmainnah D, 2013).

Heavy metals in the body will trigger reactive oxygen species (ROS) as a result, there will be a buildup of free radicals, resulting in a condition called oxidative stress. (Kumar V et al, 2105). Free radicals in normal cells can cause adverse pathological stimuli in the form of reversible or irreversible injury. According to Robbins and Jannette in Janardani et al, heavy metals that enter through the digestive tract will be distributed to the tissues, one of which is the hearth (Janardani NMK et al, 2018).

Heavy metals in the body will trigger reactive oxygen species (ROS) resulting in a buildup of free radicals, resulting in a condition called oxidative stress (Koyu at al, 2006). Free radicals in normal cells can cause adverse pathological stimuli in the form of reversible or irreversible injury. According to Robbins and Jannette in Janardani et al, heavy metals that enter through the digestive tract will be distributed to the tissues, one of which is the liver (Kar R et al, 2015).

Objective of the study Based on the background above, this study was conducted to determine the effect of Martapura River water administration on microscopic and macroscopic images of the liver which were assessed based on liver size, hepatocyte cell count and central venous cells. In addition, the results of this study are expected to help provide basic information and can be an educational material for the community not to consume Martapura River water or as a reference for the government to create a Martapura River water distillation program.

## Literature Review

South Kalimantan is an area surrounded by many rivers. One of the rivers is the Martapura River which has a very important role in the lives of the surrounding community for drinking, bathing, washing, transportation facilities, etc. The Martapura watershed is a sub-watershed of the Barito watershed which is part from the Barito River region. Martapura watershed has an area of 453.88 km2 or 45,388 (Sobatnu F et al, 2017).

The results of research conducted by Amalia et al at three points of observation, showed that Martapura River water contained cadmium with an average concentration of 0.004-0.006 mg / l. The third point, which is located around the Rubber Factory area, along the Basirih River which is close to the estuary area of the Martapura River, contains the highest amount of cadmium at 0.006 mg/l (Amalia WR et al, 2016). Research by Ulmi et al. Mentions that water taken from the upstream point of the Karang Intan River, Sungai Kayu River and Downstream of the Martapura River contains iron levels of 1.03-1.35 mg / l (Ulmi EI et al, 2017). Penelitian lain menyebutkan air Sungai Martapura mengandung kadar merkuri sebesar 5,876 mg/l dan kadar timbal 0,125 mg/l.5

These levels exceed the maximum value of the water quality standard determined by the regulation of the Minister of Health of the Republic of Indonesia, namely each cadmium, iron, mercury and lead levels of 0.005 mg / l, 1 mg / l, 0.001 mg / l and 0.05 mg / l. Article of the regulation of the Minister of Health of the Republic of Indonesia number 32 of 2017 states that the maximum parameters in the environmental quality standard for water media for sanitary hygiene purposes are divided into three parameters, namely physical, biological and chemical parameters (Peraturan Menteri Kesehatan RI, 2017).

Heavy metals such as low levels of iron are needed by living things to regulate various chemical functions and physiology of the body, but heavy metals can be dangerous or toxic when in excessive levels in the body. Heavy metal groups that have no function at all for the body such as lead, mercury and cadmium. These compounds are even very dangerous and are toxic to humans (Parulian A, 2009). High iron content in the body can cause poisoning (vomiting), intestinal damage and diarrhea (Irianti TT et al, 2017).

The observational data of Ade Elha et al on the histology of duck grouper liver tissue showed that lead metal can cause liver cell damage in the form of fat degeneration, hydrophobic degeneration, congestion and hepatic necrosis. Other studies on the influence of other heavy metals in the liver also show that heavy metals can cause edema and fat degeneration in liver cells (Erma Faradella Hakim, 2018).

Some theories mention the pathomechanism of cell damage to organs due to consuming heavy metals. Heavy metals in the body will trigger Reactive oxygen species (ROS) (Hazra B et al, 2011). Reactive oxygen species (ROS) are free radicals derived from oxygen which play a role in cell injury. Reactive oxygen species (ROS) cause cell injury by one of the main reactions, namely membrane fat peroxidation which results in membrane damage and will end in necrosis (Kumar V et al, 2005).

The most important damage to membranes in cell tissue is the mitochondrial membrane, the plasma membrane and the lysosome membrane. Mitochondrial membrane damage results in decreased ATP production, with various adverse effects and ends in necrosis. Damage to the plasma membrane will result in loss of osmotic balance, entry of fluids and ions and also loss of cell contents. Damage to the lysosome membrane will result in the entry of enzymes into the cytoplasm. Lysosomes contain enzymes that will cause enzymatic digestion of cell components and cells will die from damage. An enzyme that has digested

the cytoplasmic organelle will make the cytoplasm vacuol, this is called vacuolization (Kumar V et al, 2015).

If the production of reactive oxygen species (ROS) increases or the eradication system is ineffective, there will be a buildup of free radicals, resulting in a condition called oxidative stress (Janardani NMK et al, 2018). Cell abnormalities in reversible lesions can be corrected and if the stimulus disappears the cells can return to normal. Important abnormalities associated with reversible injury to cells are cell swelling that causes swelling of cell organelles and protrusion in the plasma (Kumar V et al, 2015).

The swelling of cells is a result of the failure of an energy-dependent ion pump in the plasma membrane which results in the cell being unable to maintain ion and fluid homeostasis, causing sodium to accumulate in the cell and release of potassium from the cell. The end result is the addition of water which is iso-osmotic. Microscopic features show small clear vacuoles in the cytoplasm. This pattern of injury is called vacuol degeneration. Continuous and severe injury due to prolonged heavy metal exposure will result in cells going beyond the "point of no return" to irreversible injury and cell death (Kumar V et al, 2015). The transition from reversible lesions to irreversible lesions through a process of increased cell swelling, swelling and damage to the lysosomes, damage to cell membranes and changes in the nucleus chromatin which will end necrosis with fragmentation of cell membranes and the nucleus (Kumar V et al, 2005).

Irreversible tissue is a type of cell death associated with loss of membrane integrity and leakage of cell contents resulting in cell damage. Necrosis is characterized by changes in cytoplasm and cell nuclei that undergo injury. Core change is in the form of one of three patterns. The first picture is karyolysis, the color of basophils from chromatin will fade. The second picture is picnosis, in the form of a shrinking core and increased color basophils. The third picture is karyoreksis, the picnotic core experiences fragmentation. In one or two days the dead cell nucleus will disappear. Electron microscope image shows changes in the nucleus that ends with dissolution of the nucleus (Kumar V et al, 2015).

Research Model

The study design used was an experimental study in a laboratory using a posttest only with control group research design. The research subjects used were white Sprague Dawley strain (Rattus norvegicus) strain, male, 2-6 months old, and weight 250 - 300 g. Based on the calculation, the minimum number of sample replications is 16 rats per group plus 20% risk factor for death, so the total rats used were 38 male white rats. The research group was divided into 2 groups, namely the control group (K) and treatment (P).

1. Control group (K) is a group of experimental animals that were given distilled water in libitum

2. The treatment group (P) is a group of experimental animals that were given Martapura River water on an ad libitum basis

*Materials and Research Tools*

The materials used in this study are white rats (Rattus norvegicus) Sprague Dawley strain, male, age 2-6 months and weight 250 - 300 g obtained from Banjarbaru BVET, Martapura River water, hematoxylin harris solution, eosin solution, solution liquid paraffin, xylol I, II and III solutions, 70% alcohol, 80%, 90%, 95%, 96%, distilled water, and entel. The tools used in this study are bottles, image raster software, optilab cameras, binocular light microscopes, scalpels, iron leuckharts, tissue cassettes, water heaters, slide mirrors, cover glass and microtomes.

*Research variable*

1. The independent variable in this study is Martapura River water

2. Dependent variables in this study are macroscopic and microscopic pictures of the liver which are assessed based on the size of the liver, the number of liver cells (hepatocytes), and the number of liver central veins

*Research Flow*

The process of treatment in experimental animals

When starting this study, the selection of experimental animals was carried out on the condition that the animals used in the study were healthy animals, males, age 2-6 months, and weights of 250-300 g. Then the acclimatization process was carried out on experimental animals for one week in a cage condition. Experimental animals were grouped randomly into two groups namely the control group (K) and the treatment group (P). The control group (K) was given distilled water on an ad libitum basis and the treatment group (P) was given water on the Martapura River on an ad libitum basis. Martapura River water is shaken before being given to experimental animals. The research was carried out for 30 days in accordance with

previous studies whose purpose is almost the same, namely to see the effect of giving a content to experimental animals.

*Isolation organ process*

Animals try to be sacrificed by using anesthetized methods. An autopsy was performed on the chest to isolate the liver of a white rat (Rattus norvegicus). Pieces of white rat liver (Rattus norvegicus) are immediately fixed by immersing the organ in a fixative solution (formal saline) for 24 hours or more. The fixated liver is cut transversely using a scalpel and then arranged into a cassette of tissue.

*Histological preparations process*

The next step is the dehydration process, carried out using an alcohol solution with gradations of increasing concentration, from 70% -80% -90% -95%. The process of pembeningan with xylol I, II and III. Immersion is carried out in a liquid paraffin solution. Next, a white rat liver (Rattus norvegicus) is placed in a horizontal position in a cube of 2 leuckhart iron, then poured liquid paraffin into it. Cutting the white rat liver (Rattus norvegicus) paraffin block with microtome is done serially with transverse slice thickness of 4-6 microns. Organs are cut with tissue microtomes in half. The paraffin strips obtained were then put into a water heater, with the paraffin band loop attached to the slide.

*Hematoxylin eosin (HE) staining*

Beginning with the deparafinization process by means of preparations that are ready to be soaked first in a solution of xylol I and xylol II for two minutes. The hydration process in the alcohol solution was continued with a gradation of decreased concentration of 96% -90% -80% -70% and distilled water for two minutes each. Then the preparation was incubated in a hematoxylin harris solution for 2 minutes, then rinsed with distilled water. Then the sample is put into 70% alcohol with 2 dips. The preparation was incubated in eosin 1% for two minutes. Furthermore, the dehydration process by dipping the preparation into alcohol with an increased concentration of 70% -90% -90% -96% slowly, each for two minutes. The preparations were soaked in xylol I and xylol II solutions for two minutes respectively, followed by application of adhesive on the slide as an adhesive and covered with cover glass. The preparations are ready to be observed under a binocular light microscope.

*Observation of histological preparations on a microscope*

The data collection process was carried out based on the parameters measured in this study, namely identifying microscopic morphological changes in the liver of white rat (Rattus norvegicus). The initial stage, histological preparations were examined under a binocular light microscope at a magnification of 100x, then the two histological preparations were taken from the best white rat liver (Rattus norvegicus). Micro photographs were made with an optilab camera in JPEG format, then observed using raster image computer software.

Data Analysis

The data obtained were tested for normality with the Shapiro-Wilk test followed by a homogeneity test with the Levene test then the data were analyzed by t-independent test to determine differences in microscopic images between the control data and the treatment data. using 95% confidence and $p < 0.05$.

Alteration in morphological alterations from both control and treatment groups can be seen in Table 1 and Figure 1.

**Table 1.** Morphological alterations from both control and treatment groups

| **Alteration on hepar** | **Control** | **Treatment** | **P value** |
|---|---|---|---|
| Hepar size(cm) | 8.77±1.56 | 9.17±1.45 | 0.385 |
| Numberous of hepatocytus | 10.45±2.18 | 12.00±2.82 | 0.036 |
| Numberous of centralis venous | 1.48±0.312 | 1.84±.21 | 0.000 |

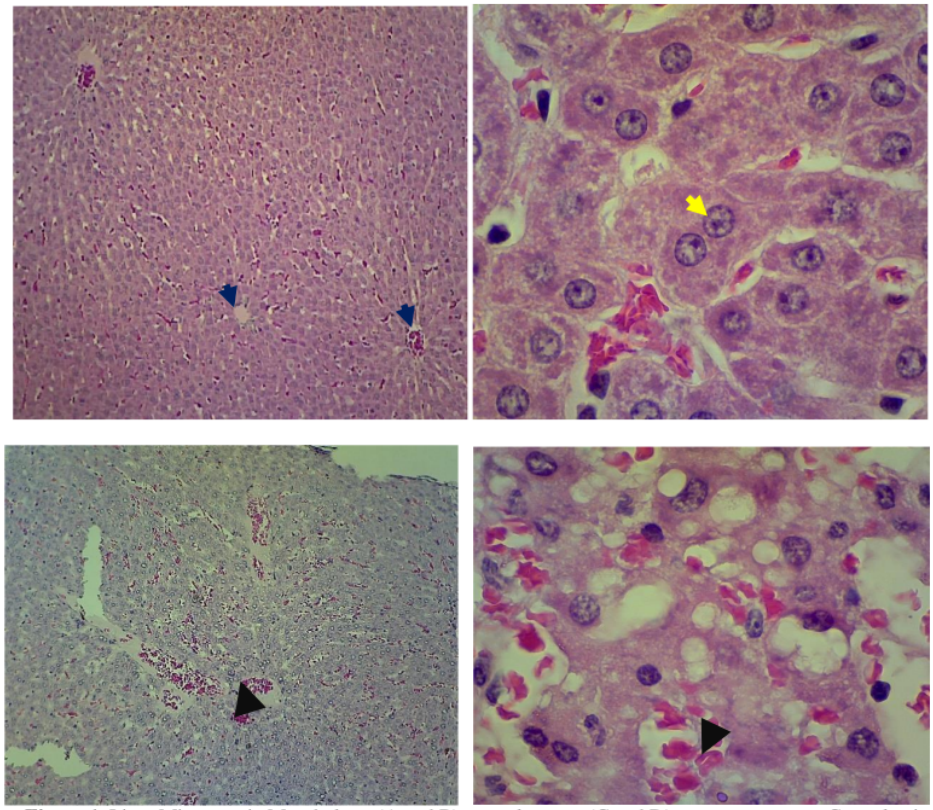

**Figure 1.** Liver Microscopic Morphology (A and B) control group; (C and D) treatment groups; Central vein (blue arrow); Hepatocytes (yellow arrows); fat generation (red arrow); congestion (black arrow); (HE staining, magnification of 100 X and 400 x, binocular microscope

## Discussion

Heavy metals such as iron in low levels are needed by living things to regulate various chemical functions and physiology of the body, but heavy metals can be dangerous or toxic when in excessive levels in the body. Heavy metal groups that have no function at all for the body such as lead, mercury and cadmium. These compounds are even very dangerous and are toxic to humans (Widyasari et al, 2015). High iron content in the body can cause poisoning (vomiting), intestinal damage and diarrhea (Somade at al, 2014). Lead poisoning can cause symptoms in the form of headaches, stomach aches, and several other related symptoms nervous system. Prolonged exposure to lead can lead to memory loss and anemia. Lead poisoning also results in impaired hemoglobin synthesis and causes damage to the proximal renal tubules. Exposure to mercury can change brain function, seizures, impaired vision and hearing, and interfere with kidney function ((Widyasari et al, 2015). Excessive cadmium intake can cause obstructive pulmonary disease and kidney toxicity, initially as tubular damage, which can develop into end-stage kidney disease. Cadmium exposure also causes bone abnormalities (Teichiro et al, 2002)

Some theories mention the pathomechanism of cell damage to organs due to consuming heavy metals. Heavy metals in the body will trigger the occurrence of Reactive oxygen species (ROS) (Suhartono, 2015). Reactive oxygen species (ROS) are free radicals derived from oxygen which play a role in cell injury. Reactive oxygen species (ROS) cause cell injury through one of the main reactions, namely membrane fat peroxidation which results in membrane damage and will end in necrosis.

Cells are able to meet normal physiological needs with homeostasis. If there are pathological stimuli, then an adaptive response arises in the form of hyperplasia, hypertrophy or atrophy in physiological and morphological cells in order to achieve new homeostasis. If the limit of the adaptive response is excessive, cell injury occurs. The lesion is reversible to some extent, but if the stimulus is permanent or severe from the start, then the lesion is irreversible and ultimately cell death (Ross Pawlina, 2006).

Reversible or irreversible lesions can be caused by heavy metals. Heavy metals in the body trigger ROS.23 Heavy metal ions that accumulate in the body cause antioxidant enzymes to be inactive so that there is an increase in ROS production. This increase causes an increase in free radical formation which triggers oxidative stress in the cell so that the cell will experience lack of oxygen or hypoxia which ultimately causes cell injury (Ross Pawlina, 2006; Junquira, 2000)

Hypoxic cells cause disruption of the plasma membrane. This causes the cells to lose osmotic balance, resulting in the failure of the sodium pump followed by potassium out and sodium and water entering. Cells that are unable to maintain this state will experience reversible swelling. Cell abnormalities in reversible lesions can be corrected and if the stimulus disappears the cells can return to normal. Important abnormalities associated with reversible lesions in cells are cell swelling that causes swelling of cell organelles and protrusion in the plasma membrane.(Koyu et al, 2015; Sheng Z et al, 2015).

The swelling of cells is a result of the failure of an energy-dependent ion pump in the plasma membrane which results in the cell being unable to maintain ion and fluid homeostasis, causing sodium to accumulate in the cell and release of potassium from the cell. The end result is the addition of water which is iso-osmotic. The transition from reversible lesions to irreversible lesions through a process of increasing cell swelling, swelling and damage to the lysosomes, damage to cell membranes and changes in the nucleus chromatin that will end necrosis with fragmentation of cell membranes and the nucleus (Spector, 2006)

The observational data of Ade Elha et al on the histology of duck grouper liver tissue showed that lead metal can cause liver cell damage in the form of fat degeneration, hydrophobic degeneration, congestion and hepatic necrosis. Other studies on the influence of other heavy metals in the liver also show that heavy metals can cause edema and fat degeneration in liver cells (Erma Faradella Hakim, 2018).

In this study found a significant increase in the number of liver cells and liver cells. In the treatment group hyperplasia condition occurs which is a condition of the adaptive process of cells undergoing injury by increasing the number of cells due to an increase in the process of mitosis. This hyperplasia is found in cells that are stimulated by increased cell workload, hormone signals, and locally generated signals in response to decreased tissue density. This condition can be exist because liver cell have ability to detocixication.

Hyperplasia can occur due to physiological processes, pathological processes and / or compensation processes. In this study it can be believed that liver cell hyperplasia and an increase in the number of central veins due to pathological processes due to the administration of Martapura river water containing heavy metals. The treatment group also showed an increase in congestion in the liver sinusoid and fat degeneration which indicates that the liver cells have reversible lesions. In the treatment group there was also a significant increase in liver size which could be expected to occur due to the process of swelling at the cellular level which was a result of the failure of the ion pump which was dependent on energy / energy-dependent plasma membranes which resulted in the cell being unable to maintain ion and fluid homeostasis, causing it to accumulate sodium in the cell and the release of potassium from the cell. The end result is the addition of water which is iso-osmotic (Kumat et al, 2015).

## Conclusion

Based on the results of this study it can be concluded that the administration of the Martapura river water causes changes in the significant alteration of hepar size ($p = 0.385$), increasing number of hepatocytus ($p = 0.036$) and central vein ($p = 0.000$) and also sign of inflamation process in treatment group (odem and congesty in parencim). That its mean the administration of the Martapura river water causes alterations on macroscopic picture of enlarged liver size and liver microscopic changes in the form of liver cells and central venous hyperplasia, congestion and fat degeneration which shows liver cells experiencing reversible lesions.

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