

## Conference Paper

# Acute Toxicity of Tomato Extract (*Lycopersicum esculentum*) on Rat' Liver

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## Abstract

Tomato extract (*Lycopersicum esculentum*) is commonly used as traditional medicine because of its antioxidant activity. As a traditional medicine, tomato extract uses for therapy. Therefore, it is important to note that the safety aspect does not cause toxic effects. This study aimed to determine the acute toxicity of tomato (*Lycopersicum esculentum*) extract on the liver of Sprague Dawley rats (SD) by looking at the activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transpeptidase (GGT) and features liver organ histopathology. Acute toxicity test was carried out by giving tomato extract orally in doses of 16, 160, 1600 and 16000 mg/ individual. Toxicity observations were carried out within 14 days after administration. The activities of AST, ALT, ALP and GGT were analyzed using Diasys kit for research purpose. The results showed that the activity of AST, ALT, ALP and GGT was not significantly different in the treatment group with the control group ( $p < 0.05$ ) and histopathology found some changes in cell structure and tissue in the liver organ but this change did not indicate the occurrence of toxic damage. The conclusion of this study is that no acute toxic effects were found from tomato extract (*Lycopersicum esculentum*) on SD rats.

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## 1. Introduction

Tomato is common vegetable that used for so many dishes and beverage. It contains very powerful antioxidants such as lycopene, vitamins C and E and carotenoids and vitamin A (Iswari & Susanti, 2016). Tomato is also can be used for dyslipidemia disease therapy because of its potential eliminating low density lipoprotein (LDL) and very-low density lipoprotein (VLDL). But, most people consumes lot of tomato without worry about its possibility of poisoning. There is no understanding and evidences before to proof the toxicity level of tomato consumption. Hence, this needs to be considered because the consumption of excess antioxidants can trigger a back reaction and increase pro-oxidant compounds in the body inside (Bártíková *et al.*, 2014), especially in the condition of the liver (Vrolijk *et al.*, 2015)

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The use of traditional plants / traditional medicines needs to be proven their safety and effectiveness through research. This is based on findings in the community regarding the use of traditional drugs that have negative effects and are toxic. Responding to these problems this study aims to establish the potential for acute toxicity by determining the liver condition in rat induced by tomato extract

## 2. Method

This research is an experimental research, Posttest Randomized Controlled Group Design. The study was conducted at the Biochemistry Laboratory of the Department of Biology, FMIPA Universitas Negeri Semarang and the Molecular Biology Laboratory, Faculty of Medicine, Universitas Gadjah Mada.

### 2.1. Tomato extraction

The total tomato extract used in this study was 500 mg / day for 30 days or as much as 15 kg of tomato extract needs. These needs were met from 30 kg of steamed tomatoes for 30 minutes at a temperature of 120 °C crushed with a blender then extracted using a maceration method with 70% alcohol. After maceration, the tomatoes are put into the oven at 40-50°C until dry, then blended dry into a rough powder. The results of the blender were sieved with no. 100 sieve, the fine powder obtained was weighed as much as 500 mg. The dissolution process was then carried out using distilled water for (Tokac *et al.*, 2015).

### 2.2. Rat supplementation

The samples of this study were Sprague Dawley (SD) *Rattus norvegicus* rats which were kept in a cage and fed 594 pellets (PT Japfa Confeed Indonesia: Grobogan, INDONESIA) on an ad libitum basis. A total of 25 healthy male SD rats, aged 12 weeks and body weight of around 200 - 300 grams, were divided into five groups. The first group (K) was a control which was given a solvent of tomato extract. The second to fifth group were treated in the form of tomato extract with a dose of 0, 16, 160, 1600 and 16000 mg / head, respectively.

### 2.3. Blood collection and serum preparation

Blood collection is carried out every three days, first taking through the retroorbital plexus (eye corner) using microhematocrit and collected in a 3 ml tube of EDTA to obtain plasma. Second, rats were anesthetized using 0.75 ml / BB ketamine. Blood taken 3 ml from the heart is then left at room temperature for 30 minutes to obtain serum. Both samples of blood taken were labeled and centrifuged at 8000 rpm for 5 minutes.

### 2.4. Liver health biomarker and histopatology

Blood plasma obtained from rats was measured by aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), Gamma glutamyl transpeptidase (GTP) using the Diagnosis System (DiaSys) GmbH for metabolic syndrome markers (Holzheim, German), with spectrophotometric techniques. Each of 10 -100  $\mu$ L of serum is used in each test. The testing is carried out in accordance with the work method and manufacturer's protocol.

Rats are sacrificed by pulling the spine, surgery using sterile and aseptic devices, starting from the abdomen to the thorax. After the abdomen until the thorax is open, the liver is removed. The organ is then weighed and analyzed for its anatomy. The data obtained were in the form of organ weight results, and organ anatomy scoring which was then used for further analysis.

### 2.5. Statistical analysis

The measurement results of the parameter were tested using One-way Anova and chi square with a 95% confidence level, if significant effect continued with the test. continued, with a 95% confidence level. Statistical analysis was performed with Statistical Product and Service Solution (SPSS) 24 data processing facilities and Windows. Data is presented in the form of processed and interpreted data.

### 3. Result and Discussion

#### 3.1. Body weight and urine production

Administration of tomato extract on *R. norvegicus* has no meaningful effect on liver condition. Significant differences occurred in the liver weight of male rats induced with tomato extract of 0 mg / Ind there was  $6,64 \pm 0,64$  in K0 group (Table 1). Although there was significantly different from K0 group to tomato treatment group. It was not indicating that the administration of tomato extract at high doses affect the change in liver condition.

TABLE 1: The liver's health biomarker.

Groups	Liver weight (gr)
K0	$6.64 \pm 0.64^a$
K1	$7.95 \pm 0.45^b$
K2	$7.64 \pm 0.78^b$
K3	$7.37 \pm 0.50^a$
K4	$7.80 \pm 0.34^b$

Note : alphabetic letter represents significant differences among group

Specific marker (ALT) and non-specific (AST) serum transaminases can be used as biomarkers of the ability of the hepatocyte plasma membrane to tolerate compounds that enter the body (Tigu & Moldovan, 2016). AST and ALT are mitochondrial enzymes found in the liver.

Based on biomarker analysis of liver chemistry showed that for Aspartate aminotransferase (AST) levels did not show significant results. Although not significantly different, the highest value of AST was obtained from the K2 group of  $18.45 \pm 0.34$  IU / L, while the lowest concentration value was obtained from K0 rats, namely sebsar  $17.98 \pm 0.36$  IU / L. significantly. The lowest GTT levels were found in the K1 and K2 groups, which were  $11.02 \pm 0.36$  IU / L, while the highest were in the K0 and K3 groups, namely  $11.19 \pm 0.31$  IU / L

Administration of tomato extracts with high concentrations is likely to lead to the production of alanine aminotransferase (ALT) and alkaline phosphatase (ALP). Based on the measurement results, ALT levels in the K4 group were  $22.94 \pm 0.40$  IU / L less than in the other groups, the K4 group had less ALT levels than the other groups. ALP levels also show significant differences. The highest level was obtained from the K2 group which was  $47.22 \pm 2.04$  IU / L followed by the K4 group at  $46.53 \pm 1.50$  IU / L

TABLE 2: The liver's health biomarker.

Group	AST* (IU/ L)	ALT (IU/ L)	GGT* (IU/ L)	ALP (IU/ L)
K0	17.98 ± 0.36	22.94 ± 0.40 <sup>ab</sup>	11.19 ± 0.31	44.46 ± 1.14 <sup>a</sup>
K1	18.33 ± 0.40	22.95 ± 0.40 <sup>a</sup>	11.02 ± 0.36	47.22 ± 2.04 <sup>b</sup>
K2	18.45 ± 0.34	23.30 ± 0.34 <sup>ab</sup>	11.02 ± 0.36	45.49 ± 1.38 <sup>ab</sup>
K3	18.33 ± 0.52	23.06 ± 0.54 <sup>ab</sup>	11.19 ± 0.31	44.80 ± 1.54 <sup>a</sup>
K4	18.21 ± 0.25	22.70 ± 0.40 <sup>b</sup>	11.02 ± 0.36	46.53 ± 1.50 <sup>b</sup>

Note : \* mark represents no significant differences, a-b letters represents significant differences among group

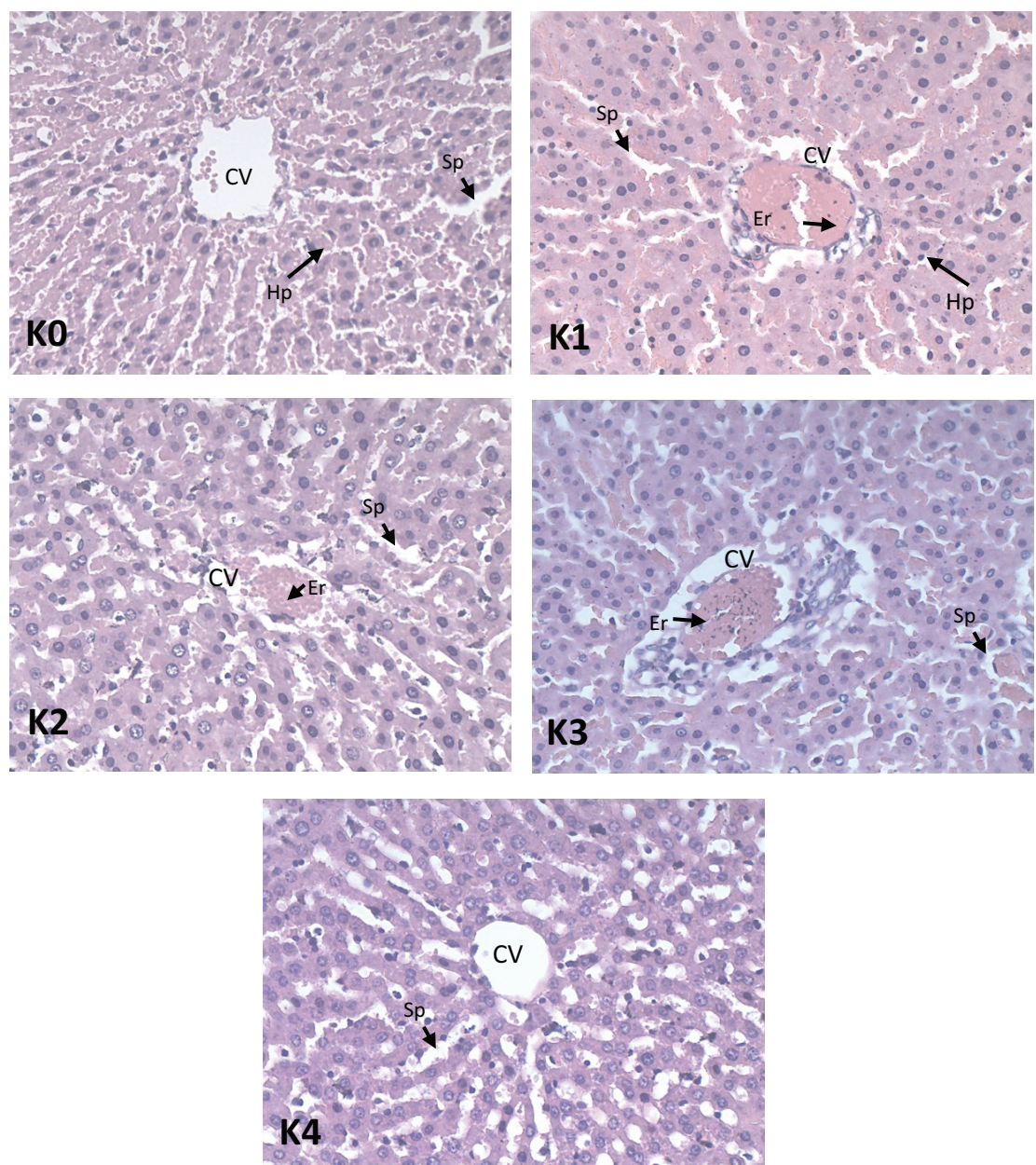


Figure 1: Histological aspects of hepatic tissue in control (K0), and treatment group (K1-K4). CV – centrolobular vein; Hp –Hepatocyte; Er – Erythrocyte; Sp – spaces between cell strands. Bar – 300 µm.

Liver damage increases the number of these two enzymes in the blood serum, the normal level of AST in the bloodstream is less than 43 IU / L, whereas ALT is less than 60 IU / L. In general, both AST and ALT are also present in the bloodstream but at low levels. AST and ALT leaks, which are marked by amounts exceeding the threshold in serum, are indicative of a disease in the liver or liver cells are damaged. Increased AST and ALT in the blood can be triggered by infection with all types of hepatitis (viral effects), alcoholic drugs and drugs or drug toxicity.

AST is usually involved in the malate-aspartate shuttle, providing NAD<sup>+</sup> for glycolysis in the cytosol, and NADH in the mitochondria, for the electron transport chain. It seems that tomato extract has not enhanced the shuttle's activity (Tigu & Moldovan, 2016).

ALP is found in many body tissues (intestine, kidney, placenta, and bone) and is produced in the bile ducts and sinusoidal membranes of the liver. Blockage of the bile duct results in an increase in ALP levels. In addition, increased ALP is also a symptom of cirrhosis, sclerosing cholangitis and liver cancer. The normal limit of ALP levels in the blood is below 115 IU / L. In addition, bone disease, congestive heart failure and hyperthyroidism cause unexpected high levels of ALP. However, the increase in ALP accompanied by GGT is the main indicator of liver damage.

However, several studies have shown that administration of lycopene which is an important component in tomatoes, in higher doses (up to 40 mg / kg) for 4 weeks, results in a decrease in serum ALT and AST (Eze et al., 2016). In addition, giving a low dose of 2.5 mg / kg of lycopene, for 7 days also gave the same effect (Baymaroglu, et al., 2013).

### 3.2. Liver histopathology

The liver is the main organ in the regulation of drugs that enter the body. Based on the results of the analysis, it was shown that the liver of K0-K4 rats had a normal structure, the lobules were separated by fibrous septa (Figure 1A). The heart preparation field also shows that the hepatocyte is still intact, not lysis. In addition, the liver organs observed did not show any inflammatory concentration indicating that the liver was healthy. This is in line with the level of biomarker of liver damage in blood serum (Table 2) which is still in normal concentration.

Some things that need to be noted are the space between cells (sp) in the K1-K4 group which tends to be wider along with the addition of tomato extract levels compared to K0. However, these conditions cannot be ascertained whether it correlates with the

condition of tomato extract toxicity. Several studies have shown that increased space between cells is common in the consumption of certain compounds even in low doses

## 4. Conclusion

Administration of tomato extract up to 16000 mg / individual on *Rattus norvegicus* rats Sprague Dawley strain showed no acute toxic effects were found from tomato extract (*Lycopersicum esculentum*) symptoms of poisoning and liver failure of SD rats

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