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Comparative Analysis of Sharia and The Effects of Black *Garlic (Black Allium sativum)* on Creatinine Levels in Tuberculosis-Infected Mice (*Mus Musculus*)

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Abstract : There is a high prevalence of tuberculosis (TB) in Indonesia, which is the second country with the highest TB cases in the world. Tuberculosis is an infectious disease that can attack various organs of the body and is the main cause of death among other infectious diseases. Garlic (Allium sativum) contains the compound allicin which has high antibacterial activity, equivalent to penicillin and modern antibiotics such as chloramphenicol, so it can be used to prevent and treat various diseases including tuberculosis. This study aims to determine the benefits of black garlic (*Black Allium sativum*) in controlling creatinine levels in mice (Mus musculus) infected with TB, considering that black garlic is known to have various medical properties including antioxidant, anti-inflammatory and anticancer. The research design used is Quasi-Experimental Design, namely a non-random repeat experimental design carried out with a post-test and having a control group and an experiment determined using a non-random method. The mice used were divided into several groups, including a healthy group, a group infected with tuberculosis, a group that received black garlic treatment, and a group that was given a combination of black garlic + OAT. Mice infected with TB were given black garlic, and creatinine levels were measured to determine the effectiveness of the treatment. A statistical test was carried out using the One Way Anova test on the creatinine levels of a group of tuberculous mice given black garlic. The average creatinine levels in the four treatment groups of mice were within normal limits, with the lowest value being 0.24 mg/dL and the highest value being 0.59 mg/dL. Next, a statistical test was carried out using the One Way Anova test and the results showed a P value of 0.807. This P value>0.05 indicates that the administration of black garlic does not affect creatinine levels in mice infected with tuberculosis.

Keywords: Black Garlic, Creatinine, Tuberculosis.

INTRODUCTION

According to the World Health Organization (WHO), India is the country with the highest number of Tuberculosis (TB) cases in the world. This has led to a total of 10.6 million cases of tuberculosis worldwide. India accounted for 28%, or more than 2.59 million cases. Indonesia is the country with the highest number of tuberculosis cases in the world. According to WHO, at least 9.2% of tuberculosis cases worldwide, or around 845,000 cases come from Indonesia. In 2021, the age group of 45-54 years old, which is 17.5% of the total number of TB cases in the country. Next is the age group of 25-34 years with a figure of 17.1% and the age group of 15-24 years with a figure of 16.9%.

For most people, tuberculosis attacks the lungs, but it can also be found in most organs in the body such as the brain, spine, and kidneys. Indonesia is the third country with the highest incidence rate of tuberculosis in the world, in 2017 it was found that around 420,994 cases of tuberculosis in men are three times more than in women (RI. Ministry of Health, 2018). Tuberculosis is the leading cause of death among all other infectious diseases in the world and the WHO reported that in 2010 1.1 million people died from tuberculosis. In Indonesia, Aceh province is located in eighth place with the highest incidence of tuberculosis around 0.49% higher, reaching 8,145 new cases in 2015 and this number continues to increase in 2018. In the city of Banda Aceh, 4,023 new cases were detected throughout 2015 and this number continues to increase so that the city of Banda Aceh has become the number one city with the highest incidence of tuberculosis in Aceh Province (Ministry of Health of the Republic of Indonesia, 2018). [1]

Currently, TB treatment is offered in a fixed-dose combination anti-tuberculosis drug package (OAT-KDT), which usually includes rifampicin, isoniazid, ethambutol, and pyrazinamide. The advantage of giving OAT-KDT is that it facilitates the administration of drugs and ensures the continuity of treatment until the end, but patients still have some risk of side effects. The most common side effects are indigestion, nerve inflammation, vision impairment, and liver and kidney failure. One of the risks of hepatotoxicity due to the

[1] Perdina Nursidika et al., "An Overview of Abnormalities in Patients' Liver and Kidneys," *Kartika Health Journal* 12, no. 1 (2020): 1–12.

administration of tuberculosis drugs is related to the prevalence of drug-induced hepatitis. [2]

To assess kidney function, urea, and creatinine levels are examined. Creatine is derived from metabolic waste products produced when muscle creatine breaks down and is not affected by diet, dehydration, or tissue catabolism. Urea is formed from amino acids that have been transferred to the liver reach the kidneys and are excreted [3]. Most pulmonary tuberculosis patients are successfully cured and without side effects from the treatment they undergo, but a few small parts of patients cannot be separated from the side effects, one of which is the effects of nephrotoxicity (derived from rifampicin and streptomycin) and hepatotoxicity (derived from isoniazid, rifampicin, and pyrazinamide) [4]. A study conducted in Iran showed that 45% of hospitalized pulmonary tuberculosis patients experienced side effects from the administration of anti-tuberculosis drugs. Adverse Drug Reactions (ADRs) in a study conducted in South Sulawesi found that patients treated with OAT complained more often of gastrointestinal, muscle, and joint problems during the intensive treatment phase of more than 2 weeks [5].

Gotu leaves are also a plant that can be used as an extract for consumption and inhibit the growth of *Mycobacterium tuberculosis.* According to previous research, *Centella Asiatica* leaves have long been used in Ayurvedic medicine and traditional Chinese medicine. Gotu leaves are famous for their triterpenoid content that can inhibit the growth of mycobacteria, as well as their high antioxidant content so they can also prevent lung damage in tuberculosis patients[6]. In addition, papaya is known as a plant that contains bactericidal substances that can inhibit the growth of bacteria. Papaya leaves have bactericidal properties, this is due to the antioxidant content in papaya leaves. In the previous literature, papaya leaves were found to have bactericidal

[2] Siti Aminah, "Differences in SGOT, SGPT, Urea, and Creatinine Levels in Patients With Pulmonary TB in Six Months After Treatment," *Journal of Health Analysts* 2, no. 2 (2013): 260–69.

[3] M.Tr.Kep Achmad Wahid, s.Kep., Ns. and M.Tr.Kep Dewi Retno Puspitosari, S.Kep., Ns., "Getting to Know Tuberculosis," in *Angewandte Chemie International Edition, 6(11), 951–952.*, 2021, 23–24.

[4] Ibid.

[5] Aminah, "Differences in SGOT, SGPT, Urea, and Creatinine Levels in Patients With Pulmonary TB in Six Months After Treatment."

[6] Tri Anti Permata Sari, "Potential Anti-Tuberculosis Activity of Gotu Kola Leaf Extract (Centella Asiatica L. Urban) in Inhibiting the Growth of Mycobacterium Tuberculosa," *Scientific Journal of Health Sandi HUsada* 12 (2020): 878–88, https://doi.org/10.35816/jiskh.v10i2.429.

activity against staphylococcal and streptococcal bacterial strains. Although tuberculosis bacteria have different morphological characteristics, it is possible that the toxic properties of antioxidants in papaya leaves can kill tuberculosis bacteria[7].

Garlic is effective against *Mycobacterium tuberculosis*. Garlic is known as a natural antibacterial agent. A bioactive substance that has an antibacterial effect on garlic is allicin [8]. The potential of garlic itself is known as antifungal, antiviral, antibacterial, anticancer, anthelmintic, antihypertensive, atherosclerotic, antiseptic, and also anti-inflammatory and atherosclerotic[9]. Garlic has been proven to prevent wound infections, treat influenza, malaria, cough and pulmonary tuberculosis, high blood pressure, sexually transmitted diseases, mental disorders, kidney disease, liver, asthma, and even diabetes. Allicin compounds contain sulfur components with the highest antibacterial activity. In addition, *allicin* is also responsible for other therapeutic effects of garlic, such as its antifungal and antiviral effects. The *allicin* compound found in garlic (*Allium sativum Linn*) also acts as an antimicrobial that can inhibit the bacteria that cause tuberculosis[10]. Microbiologist Louis Pasture also acknowledged garlic as an effective antibiotic. Garlic has been shown to have the same effects/activities as penicillin and modern antibiotics, including chloramphenicol[11].

The strong taste and aroma of garlic make it difficult for people to accept it. Then garlic can be processed by heating it at a certain temperature and doing a way to turn it into black garlic better known as black garlic which has a hard and odorless texture. Changes in physicochemical properties are the main cause of the increase in bioactivity of black garlic compared to fresh garlic. In addition to being consumed daily, black garlic extract has been reported in several

[7] Agam Anggoro, "The Potential of Papaya Leaves (Carica Papaya Sp.) As an anti-tuberculosis drug," *Unila Agromed Journal* 2, no. 2 (2015): 86–89.

[8] Nadya Natalia Jaya with Saputri Hutasoit, "Overview of the Effectiveness of Allium Sativum Garlic Extract in Inhibiting the Growth of Mycobacterium Tuberculosis Systematic Review," no. 31601900074 (2022).

[9] Sushma Bagde Bhatwalkar et al., "Antibacterial Properties of Organosulfur Compounds of Garlic (Allium Sativum)," *Frontiers in microbiology* 12 (2021): 613077.

[10] Hutasoit, "Gambaran Efektivitas Ekstrak Bawang Putih Allium Sativum Dalam Menghambat Pertumbuhan Mycobacterium Tuberculosis Systematic Review."

[11] Debi Kristiananda et al., "Activity of Garlic (Allium Sativum L.) As an Antibacterial Agent," *Journal of Pharmaceutical Sciences and Clinical Pharmacy* 19, no. 1 (2022): 46, https://doi.org/10.31942/jiffk.v19i1.6683.

studies to have different properties such as antioxidant, anti-allergic, anti-diabetic, anti-inflammatory, and anti-cancer effects. Tuberculosis remains a significant global health burden, despite advancements in treatment. The use of anti-tuberculosis drugs often leads to adverse side effects, including nephrotoxicity, which can be assessed by measuring creatinine levels. Black garlic, a natural compound with known antioxidant and anti-inflammatory properties, has shown promise in various health applications.

This study aims to investigate the potential of black garlic supplementation to mitigate the nephrotoxic effects of tuberculosis treatment in mice. By examining changes in creatinine levels, we aim to determine if black garlic can offer a safe and effective adjunct therapy for tuberculosis patients. The findings of this research could have significant implications for the management of tuberculosis, particularly in resource-limited settings where access to advanced medical care may be limited. If black garlic is shown to reduce the risk of nephrotoxicity, it could improve patient outcomes and quality of life. Based on the background that has been described above, researchers want to prove the effect of *giving* black garlic (*Black Allium sativum*) on creatinine levels in mice (*Mus musculus*) infected with tuberculosis.

The introduction effectively underscores the critical need for alternative treatments to mitigate the adverse effects commonly associated with traditional tuberculosis (TB) therapies. The prevalence of tuberculosis worldwide, particularly in regions with high infection rates, emphasizes the urgency of exploring supplementary therapeutic options. Black garlic (Black Allium sativum), with its proven antibacterial and antioxidant properties, represents a promising avenue for enhancing TB treatment regimens. Expanding this study's discussion on black garlic's therapeutic potential could offer valuable insights into the broader implications for human health, particularly in addressing the nephrotoxic and hepatotoxic risks posed by current anti-TB medications.

LITERATURE REVIEW

Tuberculosis

Tuberculosis is one of the chronic or chronic diseases that has been known to the public for a long time. Robert Kock's discovery in 1882 conclusively showed that tuberculosis is an infectious disease caused by a bacterium called *Mycobacteria tuberculosis*. The first person to prove that tuberculosis was an infectious disease was Villenim who lived from 1827 to 1894. Tuberculosis is

usually found in the lungs and can also be found in other organs such as lymph nodes (*lymphocytic nodes*). [12] Tuberculosis (TB) is an infectious and potentially fatal infection most often caused by *Mycobacterium tuberculosis,* but sometimes also caused by *Mycobacterium bovis* or *Mycobacterium africanum*[13]. *Mycobacterium tuberculosis* is an aerobic bacterium that often infects tissues with high oxygen content and is an acid-resistant gram-positive bacillus. It can be identified under a microscope with an acid stain called acid-resistant bacilli (BTA). *Mycobacterium tuberculosis* cell walls are rich in lipids and a thick layer of peptidoglycan containing mycholic acid slows the growth *of Mycobacterium tuberculosis*[14].

Transmission of tuberculosis is caused by *Mycobacterium tuberculosis* through airborne transmission (droplets), which is when people with tuberculosis cough and release splashes of saliva in the air, and other people breathe in the surrounding air that contains the bacteria when breathing. The source of transmission is BTA-positive pulmonary tuberculosis patients. If the patient coughs, sneezes, or talks when dealing with other people, then the tuberculosis bacteria will also come out and spread in the air and then be inhaled by the lungs of a healthy person and can then spread to other parts of the body through the bloodstream, lymphatic vessels or directly spread to other organs. In one cough it can produce about 3000 splashes of phlegm particles. The incubation period takes 3 to 6 months [15].

Creatinine

Creatinine is an endogenous metabolic product that originates from skeletal muscle and is excreted with urine through a glomerular filtration process. Creatinine levels in the blood have an important role as an indicator in assessing kidney function. These levels of creatinine are related to muscle mass, and their relative stability occurs because they are not affected by proteins from

[12] Nur Aini, Ramadiani Ramadiani, and Heliza Rahmania Hatta, "Expert System for Diagnosing Tuberculosis Disease," *Mulawarman Informatics : Scientific Journal of Computer Science* 12, no. 1 (2017): 56, https://doi.org/10.30872/jim.v12i1.224.

[13] Ibid.

[14] Achmad Wahdi and Dewi Retno Puspitosari, "MENGENAL TUBERKULOSIS Tuberkulosis, Klasifikasi TBC, Cara Pemberantasan, Asuhan Keperawatan TBC Dengan Aplikasi 3S (SDKI, SLKI & SIKI)" (2021).

[15] Irwan, *Epidemiology of Infectious Diseases*, *The Influence of Service Quality... EMBA Journal*, vol. 109, 2016.

food intake, and their concentration in plasma and excretion in the urine over 24 hours tends to remain constant [16]. The test of creatinine in the blood is used as one of the parameters to assess kidney function since its concentration in plasma and excretion in the urine over 24 hours tend to remain constant. Creatinine is the result of muscle metabolism, a muscle protein product that is released at an almost constant rate and excreted through the urine at an equivalent rate. The kidneys are responsible for the elimination of creatinine through the combined effects of the filtration and secretion processes. The concentration of creatinine in plasma is relatively stable day by day, and levels that exceed normal values indicate impaired kidney function. The normal value range for serum creatinine is usually 0.7-1.3 mg/dL. In people with diabetes mellitus, especially those who experience kidney disorders or damage, there is an increase in creatinine levels. Creatinine is synthesized in the liver and is found in almost all skeletal muscles, where it binds as creatine phosphate, an energy-storing compound[17].

Black garlic *(Black Allium Sativum)*

Black garlic, also known as black garlic, was first introduced in Japan and comes from garlic (Allium sativum). This garlic is processed by heating at a temperature of 65-80^{o}C with a humidity of 70-80% of room temperature for 30-40 days without additional treatment so that the water content decreases [18]. This heating process changes the color of garlic to black, odorless, and light because the moisture content is reduced, and can be consumed directly without the need for additional processing [19]. The results of this heating process in garlic plants

[16] Pocket Nia Nuratmini, *Overview of Serum Urea and Creatinine Levels in GGK Patients After Hemodialysis Therapy at Mangusada Hospital, Badung Regency*, *Journal of Chemical Information and Modeling*, vol. 53, 2019.

[17] M RIZKI PRAYUDA, "Hubungan Kadar Kreatinin Serum Dengan Mikroalbuminuria Pada Penderita Diabetes Melitus Tipe-2 Di Rumah Sakit Umum Daerah H. Abdul Moeloek Bandar Lampung" (2016).

[18] Agustina Dwi Prastanti et al., "Assistance in Making Black Garlic as an Effort to Prevent Coronary Heart Disease (PJK)," *Link* 16, no. 2 (2020): 136–40, https://doi.org/10.31983/link.v16i2.6411.

[19] Regina Safitri Permatasari, "Effect of Garlic Feeding on Serum MDA Levels in Male White Rats (Rattus Norvegicus strain Wistar) Fed a High-Fat and Fructose Diet," no. 1 (2018): 430–39.

include an increase in allicin compounds up to five times higher compared to fresh garlic [20].

Black Garlic Images (Important, These 9 Health Benefits of Black garlic, 2023)

Mice (*Mus musculus*)

Mice are naturally omnivorous animals that tend to be healthy, resilient, and have a high reproductive rate. The body size of mice is relatively small, and these animals have a friendly nature. In addition, mice can be obtained easily at affordable prices and require low food costs. Mice are generally not aggressive, although they can occasionally bite if held or held. Mice are often used as test animals because their reproductive, respiratory, and circulatory systems are similar to humans. The advantages of using mice as test subjects include that they have a short reproductive cycle and produce a large number of offspring. Male mice were more often selected in studies because of their high activity, and they were not affected by hormonal changes as well as female mice. The selection of male mice is based on the consideration that they do not produce a significant amount of the hormone estrogen, and their hormonal condition is more stable compared to that of female mice. This is caused by hormonal changes in female mice during the estrus, pregnancy, and lactation cycles, which can affect the psychological state of test animals. In addition, stress levels

[20] Putu Devie Sri Astari and Rizki Hanriko, "Black Garlic (Allium Sativum) Sebagai Terapi Adjuvan Potensial Pada Kerusakan Hepar Yang Diinduksi Minyak Jelantah Black Garlic (Allium Sativum) As A Potential Adjuvant Therapy In Hepar Damage Indicated By Used Cooking Oil," *Majorityl* 9 (2020): 1–6.

in female mice tend to be higher than in male mice, which can interfere with test results. [21]

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RESEARCH METHODS

This study employs a quasi-experimental design to examine the effects of black garlic (*Allium sativum*) on creatinine levels in tuberculosis-infected mice (*Mus musculus*). A total of [specify sample size] male mice, aged three months and weighing between 18-25 grams, were selected based on specific health and activity criteria.

(1) Sample Size Calculation
The sample size was determined using a power analysis to ensure sufficient sensitivity for detecting a statistically significant effect.

(2) Randomization and Group Assignment
Although this is a quasi-experimental study, an attempt was made to minimize selection bias by employing a systematic assignment to either the

[21] M. Yusuf et al., "Experimental Animal Management and Management Techniques (Understanding the Care and Welfare of Experimental Animals)," *Department of Biology FMIPA Biology Study Program*, 2022, 1–109.

[22] M. Yusuf et al., "Experimental Animal Management and Management Techniques (Understanding the Care and Welfare of Experimental Animals)," *Department of Biology FMIPA Biology Study Program*, 2022, 1–109.

control or experimental group. The control group received no treatment, while the experimental groups were given either black garlic or a combination of black garlic with anti-TB drugs (OAT). Each group was matched based on age and health status to ensure comparable baseline characteristics across groups.

(3) Control Group Description

The control group was divided into a negative control (healthy mice with no treatment) and a positive control (TB-infected mice without black garlic treatment). This structure allows a clear comparison between untreated, infected animals and those receiving black garlic, helping to clarify the compound's impact on creatinine levels.

(4) Data Analysis

Statistical analyses were conducted using the One-Way ANOVA test to compare creatinine levels among the different treatment groups. A significance level of alpha = 0.05 was set for hypothesis testing. Univariate analysis assessed the distribution of variables within each group, while bivariate analysis was used to compare the creatinine outcomes between the control and experimental groups, directly addressing the research questions and hypotheses.

RESEARCH RESULT

A. Univariate Test Analysis

Univariate analysis explained the frequency, mean value, minimum value, and maximum value of creatinine levels in the negative control mice group, positive control mice, mice fed black garlic, and mice given a combination of black garlic and OAT.

1. Creatinine Up to Mean

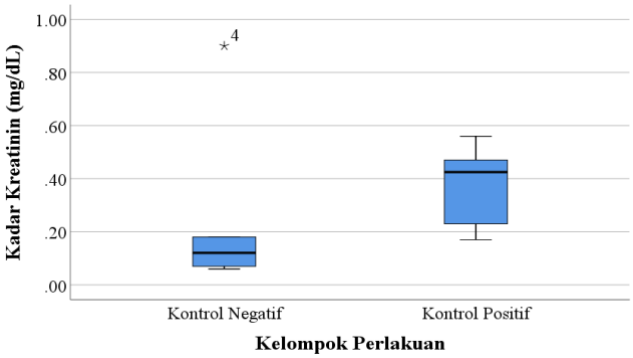
Table 1. Creatinine Levels in Each Rat Treatment Group

Creatinine	The treatment group of mice			
	K1	K2	K3	K4
Creatinine Up to Mean mg/dL	0,24	0,38	0,25	0,59
Min-Max Value	0,06-0,9	0,17-0,56	0,05-0,49	0,02-2,18

Source: Primary data, 2024

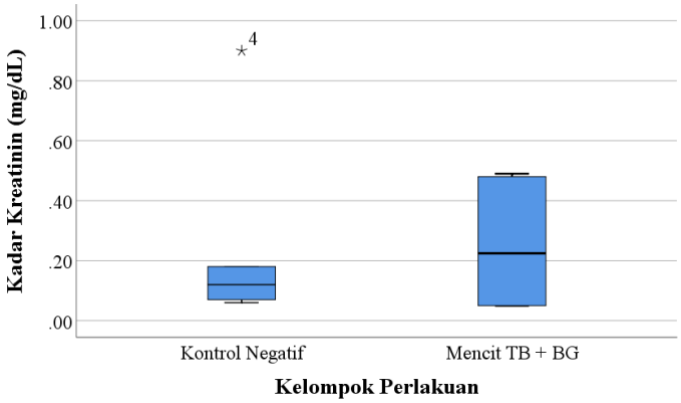
Normal creatinine levels in mice ranged from 0.2-0.8 mg/dL [23]. Based on the graph above, the overall results show that the average creatinine levels in mice are within the normal range, with the lowest value of 0.24 mg/dL and the highest value reaching 0.59 mg/dL.

2. Difference in Creatinine Levels Between Groups



Graph 1. Mean creatinine levels of the negative control group with the positive control group

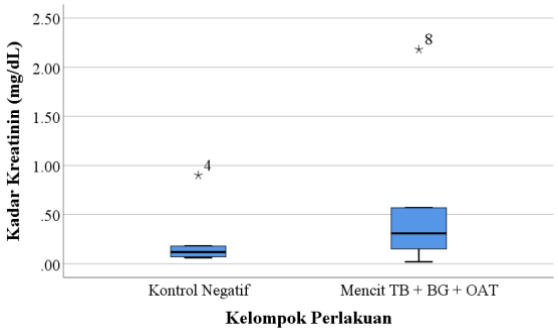
Based on Graph 1, the average difference between creatinine levels in the negative control mice group and the positive control mice group was 0.14 mg/dL.



Graph 2 Average creatinine levels of negative control mice with TB + Black garlic mice

[23] Suwahyuni Mus et al., "Acute Toxicity Test of Ethanol Extract Of Sembuk Leaf (Paederia Foetida L.) On Blood Urea Nitrogen And Creatinine Levels Mfile:///C:/Users/Ny 07/Downloads/Aguseditor,+Test-Brine.PdfENCIT (Mus Musculus)," *Pharmacy and Pharmacology Magazine* 2023, no. special issue (2023): 34–36, https://doi.org/10.20956/mff.Special.

Based on graph 2, the average difference between creatinine levels in the negative control mice group and the TB + black garlic mice group was 0.1 mg/dL.



Graph 3 Mean creatinine levels of the negative control mice group with the TB + Black garlic + OAT mice group.

Based on Graph 3, the average difference between creatinine levels in the negative control mice group and the TB + black garlic + OAT mice group was 0.35 mg/dL.

B. Bivariate Analysis

1. Normality Test

The data obtained from this study was analyzed by normality test using the Shapiro-Wilk test that had been transformed. Then, a homogeneity test is carried out to ensure the distribution of data. The data are considered normal and homogeneous if P>0.05. Furthermore, data analysis was carried out using the One Way Anova parametric test. The results of the normality test of creatinine levels in each group of mice are presented in the table below with the meaning of normal distribution (P>0.05).

Tabel 2 Hasil Uji Normalitas Up Creatinine

Treatment Groups	P value	Meaning of Test
Negative Control Mice	0,173	Normally distributed
Positive Control Mice	0,266	
Mice TB + *Black garlic*	0,130	
Mice TB + *Black garlic* + OAT	0,841	

Source: Primary Data, 2024

The normality test on each group of mice showed that P>0.05, which means that the data were normally distributed.

2. *One Way Anova Test*

Furthermore, the analysis of data on the effect *of black garlic* administration on creatinine levels in mice infected with tuberculosis bacteria using the One Way Anova test showed a P value of 0.807. The value of P>0.05 indicates that black garlic does not affect creatinine levels in mice infected with tuberculosis.

Table 3 Results of the One Way Anova Test in TB Mice on Creatinine Levels

Nilai P Value (< 0,05)		
Treatment of Mice	**P value**	**Meaning of Test**
TB mice (positive control) Mice TB + Black garlic	0,807	There was no effect of giving black garlic to male mice infected with tuberculosis.

Source: Primary Data, 2024

The comparison between the positive control mice group and the TB + black garlic mice group resulted in a P value of 0.807 (P>0.05), indicating that there was no significant change. Thus, it can be concluded that there is no effect between the positive control mice group and the mice group given TB + black garlic.

DISCUSSION

Table 1 shows the average creatinine levels in mice based on the treatment group. Group 4 (mice infected with tuberculosis and given a combination of black garlic and OAT) had the highest creatinine levels with an average of 0.59 mg/dL. Group 3 (mice infected with tuberculosis and given black garlic) had an average of 0.25 mg/dL. Group 2 (positive control) had an average of 0.38 mg/dL, and Group 1 (negative control) had the lowest creatinine levels with an average of 0.24 mg/dL. These data showed that the combination of black garlic and OAT increased creatinine levels more significantly than other treatments.

The group of mice infected with tuberculosis and given a combination of black garlic and OAT showed an average creatinine level of 0.59 mg/dL, higher than the group that was only given black garlic (0.25 mg/dL). This increase in creatinine levels is due to the effects of antituberculosis drugs, although it is still within normal limits thanks to the protective effects of black garlic. The negative control group, which consisted of healthy mice without infection, had the

lowest average creatinine levels of 0.24 mg/dL because they did not experience any infection or additional treatments.

The results of the study in Table 3 show that black garlic research has the potential as a supportive therapy in reducing nephrotoxicity due to tuberculosis in mice when used with anti-tuberculosis drugs (OAT). However, statistically, the administration of black garlic did not show a significant decrease in creatinine levels (P = 0.807). Black garlic and OAT are given orally as much as 0.5 ml, twice a day, for 14 days, but these doses may still be too low to have a significant effect. Further research with varying doses is needed to evaluate the potential of black garlic as a nephroprotective agent in the treatment of tuberculosis. Based on the Guidelines for Tuberculosis Management Medical Services, TB treatment consists of two stages: initial and advanced. The initial stage lasts for 2 months with daily administration of medication to reduce the number of germs in the body and overcome germs that may already be resistant. The advanced stage aims to kill the remaining persistent germs for 4 months by administering medication every day. This study shows that the administration of OAT is not optimal because the dosage is not under the recommendation, affecting the decrease in creatinine levels in TB mice given a combination of black garlic + OAT.

Researchers identified several factors that may have caused the insignificance of the decrease in creatinine levels in mice infected with tuberculosis and given black garlic suspension. First, the selection of 3-month-old mice does not eliminate the influence of genetic factors, which can lead to age-related bias and weight of the mother mice. Second, the different physiological responses and stress levels in each mice to tuberculosis bacterial infection also contributed [24]. Third, the garlic variety is used in the manufacture of black garlic, where compound garlic has a lower content of active compounds than single garlic, which is usually used in the manufacture of black garlic. The ratio of active compound content in 1 single clove of garlic is equivalent to 5-6 cloves of compound garlic because all the active substances are concentrated in that single clove [25].

[24] Pipit Festi Wiliyanarti and Metro Gali Wahyullah, "Effect of Black Onion Extract on Lowering Blood Glucose Levels in Mice," *The Journal of Muhammadiyah Medical Laboratory Technologist* 4, no. 1 (2021): 49, https://doi.org/10.30651/jmlt.v4i1.7269.

[25] Iesha Kinanti Adhuri, Tri Nur Kristina, and Arlita Leniseptaria Antari, "Differences in Antibacterial Potential of Single Garlic and Compound Garlic Against Salmonella Typhi," *Diponegoro Medical Journal* 7, no. 2 (2018): 415–23.

Another factor to consider is the process of making the black garlic suspension. The content of allicin and other thiosulfate compounds tends to be higher in extracts that use ethanol than in equates. This is because allicin, which is the main component of thiosulfate and the strongest antibacterial agent in garlic, is almost insoluble in water. Water-soluble thiosulfinites, such as S-allylmercaptocysteine (SAMC), are formed only from the reaction of allicin with the -SH group. In addition, in extracts that used aquades as solvents, about 72% of allicin and other thiosulfinates decomposed on day 15. However, in extracts that use ethanol, allicin and other thiosulfate compounds are formed over 15 days. The concentration of the compound continues to increase over a specified period and begins to decrease after 8 days. Therefore, it can be concluded that other allicin and thiosulfate compounds are more stable in ethanol solvents[26].

The administration of black garlic shows its potential as an antioxidant and antibacterial agent because it contains allicin compounds that act as immunomodulators, as well as reduce the side effects of the use of tuberculosis drugs. In addition, the ajoene compounds in black garlic can activate the IRE1a-JNK-ROS pathway, which stimulates macrophages to perform phagocytosis and autophagy against bacteria. Tannin compounds can inhibit the growth of *Mycobacterium tuberculosis*, while flavonoid compounds, saponins, and alkaloids have the potential to disrupt bacterial metabolism and activity, thereby preventing growth and causing bacterial death [27]. Increased serum creatinine levels are not affected by diet or fluid intake. Serum creatinine levels reflect the balance between production and excretion by the kidneys, which are produced stably based on muscle mass and are not affected by diet, dehydration, or tissue catabolism processes. As a marker of kidney function, creatinine levels are considered more accurate than Blood Urea Nitrogen (BUN). An increase in creatinine in the blood indicates a decrease in kidney function, as a healthy kidney will excrete creatinine from the blood into the urine [28].

[26] Ibid.

[27] Elvina Veronica et al., "Potential of Black Onion Extract as an Antitubercular Mycobacterium Tuberculosis," *Health Echoes* 13, no. 1 (2021): 9–18, https://doi.org/10.47539/gk.v13i1.163.

[28] M. Fery Harison, "Overview of Urea And Creatinine Levels In Pulmonary Tuberculosis Patients Who Receive Anti-Tuberculosis Drug Therapy (Oat) At The Hospital. Especially For The Lungs Of South Sumatra Province In 2019," *Proceedings of the Institution of Mechanical Engineers, Part J: Journal of Engineering Tribology* 224, no. 11 (2019): 122–30.

Rifampicin, as one of the antibiotics in the combination of antituberculosis drugs (OAT-KDT), has potential kidney-related side effects, including interstitial nephritis and acute kidney failure. These side effects arise as hypersensitivity reactions, although such events are rare. Therefore, the use of OAT-KDT recommended by the government is still considered safe if used under the rules set and closely supervised by health workers. This surveillance ensures that patients receive the right dosage and minimizes the risk of serious side effects, as well as monitors the body's response to treatment as a whole [29]. During the study, the mice cage used was made of plastic with a size of about 40 cm x 30 cm x 18 cm for 6 mice. The cage is cleaned and the husk is replaced once every 3 days to prevent disease. Mice feed should contain carbohydrates, proteins, fats, minerals, and vitamins, be easy to digest, and be preferred by mice. The need for feed is about 10% of the body weight per day, and the need to drink about 15-30 mL of water per day. The feed tray is in the form of a small basin that is resistant to cuttings, and the drinking place can use hamster drinking utensils made from glass bottles, small pipes, and glue, ensuring that it does not leak. The cage is placed in a clean room, protected from wind, rain, and direct sunlight, with good air circulation, temperature 20-25°C, and humidity 45-55%. [30] At the time before taking blood samples, mice are first anesthetized with ketamine drugs.

Measurement of creatinine levels post-treatment is important to assess kidney function and the effects of various treatments on the kidney health of mice infected with tuberculosis. By carrying out these systematic and controlled steps, the study aims to provide accurate data on the effect of black garlic administration, either alone or in combination with OAT, on creatinine levels in mice infected with tuberculosis. The results of this study are expected to provide deeper insights into the potential of black garlic as an adjunct therapy for tuberculosis and its effect on kidney function. Overall, the analysis of creatinine levels in these different groups of mice provides important insights into the impact of tuberculosis and therapeutic interventions on kidney function, as well as the potential use of black garlic as a companion therapeutic agent in the treatment of tuberculosis.

[29] Aminah, "Differences in SGOT, SGPT, Urea, and Creatinine Levels in Patients With Pulmonary TB in Six Months After Treatment."

[30] Rudy Agung Nugroho, "Getting to Know Mice as Laboratory Animals," 2018, 282.

CONCLUSION

Based on the research that has been conducted on 24 experimental animal samples in the form of mice (*Mus musculus*), it can be concluded that: 1) The average creatinine levels in all treatment groups are within the normal limit; a) The negative control group had an average of 0.24 mg/dL, with a maximum value of 0.9 mg/dL and a minimum value of 0.06 mg/dL. b) The positive control mice group had an average of 0.38 mg/dL, with a maximum value of 0.56 mg/dL and a minimum value of 0.17 mg/dL. c) The TB + black garlic mice group had an average of 0.25 mg/dL, with a maximum value of 0.49 mg/dL and a minimum value of 0.05 mg/dL. d) The TB + black garlic + OAT group had an average of 0.59 mg/dL, with a maximum value of 2.18 mg/dL and a minimum value of 0.02 mg/dL. 2) There was no effect of black garlic administration on creatinine levels in all experimental animal groups.

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