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Effectiveness of Boiled Cherry Leaf (muntingia calabura L) Toward Ureum Creatinine Serum of Wistar Strain Mice with Acute RenalFailure Model

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ABSTRACT

Renal failure is a clinical condition that is characterized by a decrease in kidney function with an indicator of changes in the levels of urea and creatinine. The purpose of this study is to determine the effectiveness of Boiled Cherry leaf (muntingia calabura L) on the reduction of ureum and creatinine levels. The objects in this study were 30 male Wistar strain rats aged 2-3 months with a weight of 180-200 grams. Rats were randomly grouped into 3 groups: the treatment group, positive control and negative control. The positive treatment and control group was induced gentamicin 0.3 cc IP / day for 7 days. Boiled water from 10 grams of cherry leaves (muntingia calabura) in 200 cc of boiling water to 100 cc was given as much as 3.6 cc orally for 7 days to the treatment group. Data were analyzed with SPSS version 24, One test ANOVA was performed to compare urea and creatinine levels. The results showed that there were significant differences in urea and creatinine levels between the treatment group and the positive control group ($p < 0.05$). Urea and creatinine values between the treatment group and the negative control group were not different ($p = 0.06$). As Conclusion, boiled cherry leaves (muntingia calabura) has an effect on the reduction of urea and creatinine serum in male wistar strain rats with acute renal failure models.

Keywords: Gentamicin, Ureum, Creatinine, Muntingia Calabura L.

INTRODUCTION

The use of natural ingredients has been started since ancient times since in Indonesian society traditions are common to use plants as medicine. Drugs with natural ingredients can be used to prevent disease, provide body fitness, increase endurance, and for the beauty needs. Some people have the assumption that drugs with natural ingredients are safer to consume because they have smaller side effects but this also does not mean that traditional medicine has no side effects or toxic effects. In accordance with the times of traditional medicine is expected to develop into patent medicine. (Sudharmono, 2014)

Herbal Medicine are often used against disease and play a role in the immune system because Herbal Medicine contain some chemicals substances that are safe for consumption (Tandi, Wulandari, Asrifa, 2018). Medicinal plants among the community is not a new thing.

Traditional medicine both in the form of medicinal plants and herbal medicine is believed to be able to handle a disease because medicinal plants have a pharmacological effect (Tandi , Roem , Yuliet , 2017) .

An easy natural way to make traditional medicines or medicines with natural ingredients is by boiling. Boiing is regarded as an easy way by society because this method does not require a long time, and the cost is also relatively inexpensive. People in general know how to make traditional medicine by boiling it, because the solvent used is water so that polar compounds can be attracted (Tukayo, Titihalawa, and Paepadaseda, 2018).

Cherry or in Latin called as Muntingia calabura L is a tropical fruit are often found at the edge of the road. the Name of this plant is vary in several areas such as kerukup siam in Malaysia, jamaican cherry in English, talok in Java, and Ceri in Borneo. Cherry has a size small, the tree is always green, flowering and fruiting every year (Ilkafah, 2018).

Cherry plants are rich in antioxidants that can prevent the oxidation process of other molecules. Muntingia calabura is classified as follows: Kingdom: Plantae, Division: Spermatophyta, Class: Dycotiledoneae, Order: Malvales, Genus: Munting , Species: Muntingia calabura Linn. (Damara, Sukohar, 2018).

Cherry leaves contain flavonoid, tannins, triterpene, saponins, polyphenols which show the presence of antioxidant activity. The flavonoids may lower the levels of acid uric through inhibition of the enzyme xanthine oxidase (Ilkafah, 2018). In addition, flavonoids can function as antimicrobial, antiviral, antioxidant, antihypertensive, stimulate estrogen formation and treat impaired liver function (Damara, Sukohar, 2018). Flavonoids in the leaves of cherry can be classified into several categories;flavones, flavonols , flavonones , catechins , and isoflason and its potential in lowering levels of tropical glucose (Stevani , Base, Thamrin) . The flavonoids, tannins and saponins in the leaves of cherry can help to heal the burnt wounds (Handayani, Sentat, 2016). Moreover, the ethanol in the leaves of cherry has the effect to decrease the levels of cholesterol in the blood (Princess, Yuliet, Khaerati, 2018). Ethanol extract of cherry leaves has anti- bacterial power against bacteria that cause acne (Handayani). Besides, Cherry leaves have analgesic and anti-inflammatory effects due to their flavonoid content which acts as an analgesic (Handayani, Sentat, 2016). Flavonoids, tannins and saponins, polyphenyl also play as an antioxidant and anti-bacterial and anti-inflammatory role

in the healing of puerperal perineal wounds (Iswati, Marliandiani 2017). Cherry leaves have the potential to ward off free radicals that can reduce the amount of damage to the kidney tubules (Ninditya, Miranti, Wijayahadi, 2016).

Kidney is an important organ that has a very vital function. The main function of the kidneys is to filter out dirty blood and then the filtering results are released in the form of urine, then the clean blood is re-channeled into large blood vessels to be circulated throughout the body. In addition to these functions the kidneys also work to produce urine and also remove excess water in the body in the form of urine, remove waste products from the rest of metabolism in the body, the kidneys play a role in blood formation, maintain normal blood pressure and are also able to maintain bone integrity (Situmorang, 2015). Kidney is the main pharmacokinetic organ. The kidneys have the function to excrete drugs or chemicals consumed. Kidney function itself can be disrupted by drugs or chemicals that enter the body's circulation (Sudharmono, 2014). Kidney disease is a disorder that affects the kidneys. This disease arises due to various factors, such as infections, tumors, congenital abnormalities, metabolic or degenerative diseases, and others. According to the Indonesian Ministry of Health regarding kidney failure All levels of society need to adopt a healthy lifestyle to keep their kidneys healthy, including regular physical activity, eating a healthy and balanced diet (low in sugar, salt, fat and high in fiber), control blood pressure and blood sugar levels, drink water at least 2 liters per day, do not consume drugs that are not recommended and do not smoke. Data on Basic Health Research (Riskesdas) in 2013, showed that the prevalence of Indonesian population suffering from Kidney Failure was 0.2% or 2 per 1000 population and the prevalence of Kidney Stones by 0.6% or 6 per 1000 population. The highest prevalence of kidney failure is in Central Sulawesi Province by 0.5%.

Based on gender, the prevalence of kidney failure in men (0.3%) is higher than in women (0.2%). Based on the characteristics of the age the highest prevalence is in the age category above 75 years (0.6%), which begins to increase at the age of 35 years and over. Based on education level, the prevalence of kidney failure is highest in people who are not in school (0.4%). While based on the people who live in rural areas (0.3%) the prevalence is higher compared to urban areas (0.2%) (MOH, 2018).

Gentamicin is an aminoglycoside class of antibiotics that are usually used to treat infections due to gram-negative bacteria. Aminoglycosides are almost entirely excreted through glomerular filtration in the kidneys and concentrations in urine reach 50-200 micrograms / ml.

This type of drug if used for 3-5 days can cause 5-25% of patients experience mild and reversible nephroxicity. High drug concentration in plasma is related to the severity of nephroxicity. 15% of acute kidney failure caused by nephroxicity ± 10% of cases of acute kidney failure caused by the use of antibiotics aminoglycosides. Kidney toxicity mostly results from the accumulation and retention of aminoglycosides in proximal tubular epithelial cells. On the results of renal microscopic examination in male wistar strain rats that were given gentamicin 0.3 cc / day intraperitonially for 7 days showed that tubular epithelial cells were swollen and cells were enlarged, and some epithelial cells of tubules necrosis and apoptosis and basal membrane torn. The toxic material from gentamicin can cause morphologic changes in the kidneys with acute tubular necrosis (Poppy M. Lintong, Carla F. Kairupan, Priska LN Sondakh 2012).

Acute kidney failure is a condition of damage to the kidneys that is marked by increased levels of creatinine and nitrogen products in the blood that are reversible so that it causes the inability of the kidneys to regulate the balance of fluid and electrolyte (Amelia, Lubis, Trisnawati 2014). Disturbances in the kidneys can be identified by doing a blood check and showing the occurrence of increased levels of urea and creatinine in limits that exceed normal requirements. How to identify kidney damage due to toxic substances can be done by looking at changes in histological structure that occur such as acute tubular nectosis which can be marked morphologically by proximal tubular epithelial decomposition. These proximal tubular epithelial cells are easily destroyed and sensitive to anoxia, this is because poisoning that occurs due to contact associated with chemicals will be excreted through the kidneys. Changes that occur in the structure of kidney histology are strongly influenced by the amount of chemicals that enter the body. The chemicals entered into the body will enter from the blood into the urine, then they will be accumulated in the proximal tubule but if the chemicals entered into the body are reabsorbed from the urine then it will pass through the tubular epithelial cells with high concentrations. After that the substance will experience concentration and it will become a toxic substance that will cause damage to the kidneys.

There are two types of changes that often occur in the kidneys if kidney damage caused by toxic substances, namely irreversible changes and reversible changes. Irreversible changes include changes from tubular cells including atrophy or lumen dilatation, tubular cell fibrosis, and the most severe is tubular cell necrosis, while reversible changes include tubular cell degeneration, tubular cell inflammation and cast. The most important index for damage to kidney function is the value of BUN (Blood Urea Nitrogen) which will show the function of

glomerular filtration, creatinine and urea levels in case of damage to kidney function, the concentration of urine and creatinine in the blood will exceed normal limits. Decreased kidney function can indicate kidney failure.

Creatinine is a residual product of final endogenous products from creatin phosphate tabolism which has relatively more constant levels. Whereas Ureum is the main product resulting from protein metabolism in the body. The level of urea in the serum is very dependent on the catabolism (breakdown) of protein in the liver which is then secreted into the kidneys and then excreted in urine. This parameter is the one to assess normal renal function (Tandi, Wulandari, Asrifa, 2017).

The causes of elevated creatinine levels in the blood include the use of drugs that are toxic to the kidneys, renal dysfunction with infection, dehydration, kidney disease, and uncontrolled hypertension. If there is a doubling in creatinine levels it indicates a decline in kidney function by 50% (Alfonso, Mongan, Memah, 2016).

The purpose of this study was to determine the effectiveness of boiled water of cherry leaves (muntingia calabura L) at a dose of 3.6 cc / day orally for 7 days for decreasing ureum and creatinine levels in male wistar strain rats with acute kidney failure model, induced gentamicin 0.3 cc / day intraperitonially for 7 days.

METHODS

This research uses experimental laboratory methods. In this study, the researcher measured the levels of urea and creatinine to see the level of kidney damage in male wistar rats as experimental animals that were damaged with gentamicin 0.3 cc / day intraperitonially for 7 days. The object of the study was 30 male Wistar strain rats with a body weight of 180-200 grams and with 2-3 months of age. Rats were randomly divided into 3 groups, namely the negative control group, the positive control group, and the treatment group. Before being grouped, these mice were adapted for 7 days with 12 hours of dark and 12 hours of light and the mice were given food and drink normally. Wistar strain rats body weight did not change ± 10% from the determined criteria during adaptation. The process of making dried cherry leaves is by taking cherry leaves in the Parongpong area, West Bandung, how to take it is by picking the leaf from its branch, then the leaves are washed clean and then aerated until withered after wilting the cherry leaves are cut into small pieces then sun dried. After that, the cherry leaves are measured in order to get the weight of leaves as 10 grams. Cherry leaves are then boiled with 200 ml of water as to boiling using a boiled pan until the water remains 100 ml, after that,

the boiled water was moved to a clean bottle or glass let it stand until warm and then put it into a bottle then consumed or given to male rats wistar strain orally to the group treated for 7 days with a dose of 3.6 cc / day.

The way to draw blood in order to check the urea and creatinine level of male wistar rats is to cut the tip of the rat's tail and then the rat's tail is squeezed to release its blood.

Data analysis used the One Way ANOVA Test with SPSS (Statistical Package for Social Science) version 24.

30 male Wistar strain rats after adaptation process for 7 days with the method of 12 hours dark and 12 hours of light, rats were given regular normal food and drink, rats that fit the criteria will be included in the study, rats with acute kidney failure model will be given Intra peritonial gentamicin with a dose of 0.3 cc / day (12 mg) in the positive control group and the treatment group for 7 days then ureum and creatinine were checked and all groups were then given cherry leaf boiled water at a dose of 3.6 cc / day orally for 7 days on treatment group.

The treatment for each group can be described as follows:

1. The Negative control group: 10 Rats were given normal food and drink regularly.
2. The Positive Control group: 10 Rats were given normal food and drink regularly and intraperitoneally gentamicin 0.3 cc / day for 7 days
3. The treatment group: 10 Rats were given normal food and drink regularly, intraperitoneally gemtamisin 0.3 cc / day for 7 days and the boiled water of cherry leaf as much as 3.6cc/day for 7 days.

The order in treatment is as follows:

1. Days 1-7: 30 rats were adapted at the Laboratory
2. Day 8 : check the weight of male wistar rats in all groups
3. Days 9-15: Positive control group and treatment group were given gentamicin 0.3 cc / day intraperitonially for 7 days
4. Day 16: ureum and creatinine check in male wistar rats in all groups
5. Days 16-22:
    1) The negative control group: 10 rats male Wistar strain were fed and watered regularly.
    2) The positive control group: 10 rats male Wistar strain were given food and drink regularly and intraperitoneally gentamicin 0.3 cc / day for 7 days

3) The treatment group: 10 rats rats male Wistar strain fed and watered regularly and gemtamisin intraperitoneally as much as 0.3 cc / day and the boiled water of cherry leaf as much as 3.6 cc / day for 7 days.

6. Day 23: checking the urea and creatinine rats male Wistar strain in all groups to get the post -data treatment.

The Process of producing water decoction of cherry leaves is from 10 grams of leaves of cherry (Muntingia C alabura L.) dried simmered in boiling water of 200 cc to 100 cc. Then the cherry leaf boiled water is filtered and put in a bottle and given orally to the treatment group for 7 days at a dose of 3.6 cc / day orally.

RESULTS

Table 1. **One Way ANOVA test table comparing urea levels of pre-therapeutic water to cherry leaves boiled in male rats in the Wistar strain with acute renal failure model.**

Dependent Variable	(I) GROUPS	(J) GROUP	Mean Difference (IJ)	Std. Error	Sig.
UREUM_ PRE	Control N egatif	Positive Control	-40.72000 *	303,196	.000
		Perlakuan	-45.68000 *	303,196	.000
	Positive Control	Control Negatif	40,72000 *	303,196	.000
		Perlakuan	-496,000	303,196	.248
	Perlakuan	Control Negatif	45.68000 *	303,196	.000
		Positive Control	496,000	303,196	.248

* The mean difference is significant at the 0.05 level.

From the table, above it can be concluded that the levels of urea on the 16th day s Before the given therapy of cherry leaves boiled water as much as 3.6 cc / day orally in male rats wistar strain and inducted by |gentamicin of 0.3 cc / day intraperitoneally for 7 days showed that the deference between negative control group, the positive control group and the treatment group were significant ($p < 0.05$). This happened because the positive control group and the kidney treatment group were both damaged by inducing gentamicin 0.3 cc (12 ml) / day intra peritonially for 7 days so that the ureum levels in the positive control group and the treatment group had increased while in the negative control group Urea levels are normal. But the positive control group compared to the treatment group has no significant difference ($p = 0.248$). This

occurs because of the effect of gentamicin induction as much as 0.3 cc / day by intraperitoneally for 7 days in the positive control group and the treatment group could increase urea levels in male rats wistar strain with acute renal failure models. The increasing of the urea level can occur due to dehydration, protein dietary and shock. In tubular necrosis, damage to tubular cells results in leakage of intratubular waste into the peritubular circulation, gentamicin accumulates in proximal tubular epithelial cells and persists in proximal tubules for a long time and causes nephrotoxicity (Ayuningtyas, Trianto, Fitrianingrum, 2015). Gentamicin excretion occurs entirely in the kidneys. The occurrence of toxicity is caused by the accumulation and retention of aminoglycosides in the epithelial cells of the proximal tubules. Some aminoglycosides are retained in the proximal tubule after the aminoglycosides are filtrated by the glomerulus. The toxicity of aminoglycoside in microscopic ways can be seen by the presence of necrosis in tubular epithelial cells which are the main cause of kidney damage. As a result of nephrotoxic is the damage to the kidney tubules (Azizah, Santi, Marlian, 2019). In another study it was also mentioned that the increase that occurred in the ureum level occurred after the tested animals were induced gentamicin at a dose of 80 mg / kg for 10 days. So it can be concluded that administration of gentamicin results in increased levels of ureum (Imelda, azaria, Lucretia, 2017).

Table 2. **One Way ANOVA test table comparison of post ureum levels in the water treatment of cherry leaves boiled in male rats with acute renal failure.**

Dependent Variable	(I) GROUP	(J) GROUP	Mean Difference (IJ)	Std. Error	Sig.
UREUM_POST	Negative control	Positive Control	-136.86000 *	1,306,458	.000
		Treatment	-1,246,000	1,306,458	.612
	Positive Control	Negative control	136.86000 *	1,306,458	.000
		Treatment	124.40000 *	1,306,458	.000
	Treatment	Negative control	1,246,000	1,306,458	.612
		Positive Control	-124.40000 *	1,306,458	.000

* The mean difference is significant at the 0.05 level.

Urea levels in male wistar strain rats on 23rd day or after a given therapy of cherry leaves boiled water with a dose of 3.6 cc / day orally in comparison between the negative group control and the positive group control shows a significant result (p <0.05). its happen because at the negative control group the rats were not given gentamicin but only fed and watered normally, whereas in the positive control group the rats were given gentamicin 0.3 cc / day intra peritonial for 7 days so that the level of ureum in male wistar strain rats in the positive control group increased. Then in the negative control group compared with the treatment group obtained insignificant results (p = 0. 612), because the treatment group of rats were given gentamicin 0.3 cc / day intra peritonial for 7 days which can increase ureum levels in male wistar strain rats whereas in the negative control group the rats were only fed and drinking normally. Another reason is because the male wistar strain rats in the treatment group had been given water treatment with cherry leaf at a dose of 3.6 cc / day orally for 7 days so that the ureum levels in gentamicin-induced rats decreased. This is supported by the comparison between the positive control group compared with the treatment group the results were significant (p <0.05) because in the treatment group the male Wistar strain rats were treated with cherry leaf boiled water at a dose of 3.6 cc / day orally for 7 days while in the positive control group of rats was not given water treatment with cherry leaf decoction. This shows that the level of ureum in male wistar rats after being given water treatment with boiled cherry leaves at a dose of 3.6 cc / day orally for 7 days is approaching the normal rate.

Table 3. **One Way ANOVA test table for comparison of creatinine levels before the treatment of cherry leaf boiled water in male rats with acute renal failure.**

Dependent Variable	(I) GROUP	(J) GROUP	Mean Difference (IJ)	Std. Error	Sig.
KREATININ_PRE	Negative Control	Positive Control	-2,21800 *	.23232	.000
		Treatment	-2.49800 *	.23232	.000
	Positive Control	Negative Control	2,21800 *	.23232	.000
		Treatment	-.28000	.23232	.410
	Treatment	Negative Control	2.49800 *	.23232	.000
		Positive Control	.28000	.23232	.410

* The mean difference is significant at the 0.05 level.

Table 3 shows the results of analysis of creatinine serum in the 16th day in Wistar male rats that induced by gentamicin as much as 0.3 cc / day intra peritonial for 7 days before boiled cherry leaf therapy as much as 3.6 cc / day orally for 7 days, it can be seen that between negative control group, the positive control group and the treatment group obtained significant results ($p < 0.05$) because in the negative control group the kidneys were in normal condition and the male Wistar strain rats were only fed and drinking normally whereas in the positive control group and the treatment group of rats with renal wistar strain were damaged by induction of gentamicin 0.3 cc / day intra peritonial for 7 days resulting in an increase in creatinine levels. Increased creatinine levels show a damage to kidney function, the concentration of creatinine in the blood will exceed normal limits (Alfonso, Mongan, Memah, 2016). This is supported by the comparison in the positive control group and the treatment group showing no significant difference ($p = 0.410$) because in the positive control group and the treatment group of the male Wistar strain rats were equally damaged by being given gentamicin 0.3 cc / intra- peritonial day for 7 days which can increase creatinine levels in male wistar strain rats. Increased creatinine may occur as a result of a high diet in creatine (protein), shock and urinary tract obstruction damage caused by gentamicin, which is the result of a decrease in renal blood flow, decreased GFR (glomerular filtration rate) and increased vascular resistance that cause tubular necrosis. In tubular necrosis, tubular cell damage occurs which causes leakage of residual substances that are intratubular into the peritubular circulation of gentamicin accumulation in the proximal tubular epithelial cells and persists in proximal tubules for a long time and causes nephrotoxicity (Ayuningtyas, Trianto, Fitrianingrum, 2015). In other studies, also mentioned that damage to the kidneys due to exposure to free radicals caused by gentamicin can be proven by observing reduced kidney function and damage to the histopathological structure of the kidney. Decreased kidney function can be seen from the significant increase in creatinine levels. The objects in this study were 25 mice induced with gentamicin (Normasari, Dewi, Rachmania, 2017).

Table 4. **One Way ANOVA table comparison of post- therapeutic creatinine levels of cherry leaf boiled water in male rats with acute renal failure.**

Dependent Variable	(I) GROUPS	(J) GROUP	Mean Difference (IJ)	Std. Error	Sig.

KREATININ_POST	Negative Control	Positive Control	-3.30800 *	.22142	.000
		Treatment	-.75600 *	.22142	.006
	Positive Control	Negative Control	3.30800 *	.22142	.000
		Treatment	2.55200 *	.22142	.000
	Treatment	Negative Control	.75600 *	.22142	.006
		Positive Control	-2.55200 *	.22142	.000

* The mean difference is significant at the 0.05 level.

The table 4 above shows the results of serum creatinine analysis in 22nd day in Wistar male rats with acute kidney failure model after being given a boiled water of cherry leaves as much as 3.6 cc / day orally for 7 days showed the results that in the negative control group compared with the positive control group were significant ($p < 0.05$) this happened because in the positive control group male Wistar strain rats were induced with gentamicin 0.3 cc / day intra peritonial for 7 days to damage the kidneys by increasing creatinine levels in male rats wistar strain, whereas in negative control group of rats were fed and watered normally, then in the negative control group and the treatment group were showed no significant difference ($p = 0:06$). This shows that the decoction of cherry leaves as much as 3.6 cc / day orally for 7 days can reduce creatinine levels in the treatment group in male Wistar strain rats with acute kidney failure model induced with gentamicin 0.3 cc / day intra peritonial for 7 days so that creatinine levels in the treatment group approached normal levels as in the negative control group whose kidneys were not damaged and were only given normal food and drink. The results of the comparison between the treatment group compared with the positive control group were significant ($p < 0.05$) because in the treatment group the male Wistar strain rats were induced with gentamicin 0.3 cc / day intra peritonial for 7 days to increase creatinine levels in male Wistar rats. Then given water therapy with cherry leaves boiled dose of 3.6 cc / day orally for 7 days to reduce creatinine levels after the kidney of the male Wistar strain was damaged. So that it can be concluded that the kidney was initially damaged by the effects of gentamicin 0.3 cc / day intra peritonial for 7 days has been treated with a cherry leaf boiled water is 3.6 cc / day orally for 7 days in contrast to the positive control group were tampered with gentamicin 0, 3 cc / day intra peritonial for 7 days but not get therapy.

CONCLUSION

In this study it can be concluded that given gentamicin as much as 0.3 cc (12 mg) / day intaperitonially in male wistar strain rats has the effect of increasing ureum and creatinine levels in male wistar strain rats.

A decoction of cherry leaves (Muntingia calabura L) at a dose of 3.6 cc / day orally administered for 7 days has an effect in decreasing serum ureum and creatinine in male rats in the Wistar strain.

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