



Effectiveness Rosy Periwinkle (*Catharanthus roseus L.*) Decoction Toward Urea and Creatinine Serum Levels of Male Wistar Strain Rats with Acute Kidney Failure Model

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ABSTRACT

Acute kidney failure is a disorder that occurs suddenly in the ability of the kidneys to infiltrate blood, which is characterized by increased levels of urea and creatinine within a few hours or days. This study aims to determine the effectiveness of the Rosy Periwinkle (*Catharanthus roseus L.*) on the levels of urea and creatinine in male Wistar Strain with acute kidney failure models. The object of the study were 30 male Wistar Strain Rats aged 2-3 months with a weight of 180-200 grams per rat. The study was divided into three groups, namely the treatment group, positive control group, and negative control group. Each group consists of 10 male rats. Tread leaves taken as much as 5.2 grams are boiled in 300 cc of water until the remaining 100 cc of boiled water. The treatment group and positive control group induced gentamicin 12 mg in 0.3 cc intraperitoneal / rat / day for 7 days. The treatment group was given boiled water for as much as 3.6 cc / day orally for 7 days. Giving a gentamicin injection to damage the kidneys. Data collection on urea and creatinine levels was calculated using the SPSS program version 24 One Way ANOVA test to compare creatinine urea levels. The results showed that there were significant differences in creatinine urea levels between the treatment group and the positive control group ($p < 0.05$). The conclusion of this study is that the boiled water of Rosy Periwinkle (*Catharanthus roseus L.*) is effective in reducing the level of urea and creatinine of male Wistar Strain Rats with acute kidney failure models.

Keywords: Gentamicin, Urea, Creatinine, Rosy Periwinkle (*Catharanthus roseus L.*)

INTRODUCTION

The prevalence of kidney failure in the world according to the Global Burden of Disease in 2015 amounted to 1.2 million, people who died with an increase of about 32% since 2005. Every year there are about 1,7 million people died caused by acute renal failure. It means there are around 5-10 million people die every year from kidney disease. In 2010 there were 2.62 million people in the world undergoing dialysis, which will double by 2030 (WHO bulletin, 2015).

In Indonesia, according to the results of Basic Health Research (2018) from the Indonesian Ministry, the prevalence of kidney failure in 2013 was 2.0 ‰ (499,800 people) which increased to 3.8 ‰ in 2018. The province with the highest incidence of kidney failure was North Kalimantan (Borneo). According to data from the 10th Report of Indonesia Renal Registry (2017), the proportion of patients diagnosed with acute renal failure undergoing hemodialysis is 8%.

According to a statement from Nurani & Mariyanti, the costs required for the treatment of kidney disease in terms of kidney transplantation and hemodialysis are very high, whereas according to Suryati, Dillasamola, & Rahadian herbal plants are believed to be an alternative treatment for various diseases that classified as cheap and easily accessible by community (quoted in Azizah, Santi, Marlian, 2019).

Because of this, researchers are interested in examining the effect of the rosy periwinkle (*Catharanthus roseus*, L.) decoction on toward urea and creatinine level in male rats with acute renal failure.

LITERATURE REVIEW

Acute kidney failure is a disorder that suddenly occurred in the ability of the kidneys to filter the blood, which is characterized by the increase of urea and creatinine levels within a few hours or several days (LeMone, Burke, and Bauldoff , 2015).

Acute kidney failure has signs and symptoms that is the oliguria phase (amount of urine less than 500 cc / 24 hours) where a little urination causes excess fluid in the body, hyperkalemia where potassium builds up in the body, triggering arrhythmias. During the diuretic phase, increased urinary discharge occurs which makes the body dehydrated, triggering hypokalemia (potassium deficiency) and arrhythmias, headaches, nausea and vomiting, the body becomes weak, the body weight increases due to the volume of fluid in the body restrained, anorexia (eating difficulties), stomatitis, metal taste caused by the existence of urea in saliva, symptoms of metabolic acidosis, hyperphosphatemia, hypocalcemia, symptoms of anemia, signs of osteoporosis, there is also uremic frost where there are urea crystals that makes skin irritation, the color of the urine changes to brown, radish or black (Hurst, 2015).

Things that cause kidney damage are consumption of drugs (gentamicin and NSAID), rabdiomyolysis, acute glomerulonephritis, sepsis, and hypevolemia (Rajak, Loho, and

Lintong, 2016). Gentamicin is an antibiotic (aminoglycoside) which has a toxic effect, one of which is nephrotoxicity that can damage the kidneys (Rosdahl and Kowalski, 2014).

The process of gentamicin damaging the renal tubules is by activating proteases that cause tubular epithelium into oxidative and capillary endothelial injury caused by the formation of Reactive Oxygen Species (ROS). Gentamicin with a high concentration can cause tubular cells to become necrotic both directly and indirectly in the mitochondria, thus interfering with the formation of ATP which is characterized by nucleated cells. Damaged cells will accumulate which causes cast on the lumen. Cast formation occurs due to ATP depletion which causes disruption of the proximal tubular epithelial cytoskeletal and displacement of integrin locations from the basal surface to the apical surface. As a result, the kidneys experience a decrease in sodium reabsorption and sodium buildup in the lumen and cast in the microvilli causing distal tubule obstruction (Rajak, Loho, and Lintong, 2016).

The way to measure the occurrence of kidney failure is by checking the levels of urea and creatinine. Normally, urea and creatinine, which is a part of metabolic waste products, are excreted from the body through urine. If acute renal failure occurs, urea and creatinine levels will increase rapidly within 1-2 days from the beginning of symptoms (LeMone, Burke, and Bauldoff , 2015).

The result of protein metabolism in the body is urea, whereas createne produces the final product, creatinine. Both are excreted through the kidneys out of the body (Laksmil, Dada, and Damriyasa, 2014).

The following is an illustration of rosy periwinkle classification based on Whiting, Connor, Jones, McMulkin, L. Potts, The International Plant Names Index, Royal Botanic Gardens (quoted in Nejat, Valdiani, Cahill, Tan, Maziah, Abiri, 2015):

1. Kingdom: Plantae: plants.
2. Division: Magnoliophyta: flowering plants.
3. Class: Magnoliopsida: dicotyledons.
4. Order: Gentianales.
5. Family: Apocynaceae: dogbane.
6. Genus: *Catharanthus* G. Don.
7. Specific epithet: *roseus* (Linnaeus) G. Don.
8. Botanical name: *Catharanthus roseus* (Linnaeus) G. Don (1837)

Rosy periwinkle comes from Madagascar and spread to areas with tropical climate. The parts of this plant that can be used are roots, leaves and flowers. (Laksmil, Dada, and Damriyasa, 2014).

Rosy periwinkle grows in many villages with a tropical or desert climate. Rosy periwinkle has a round rod with a small diameter. The Rosy periwinkle has a single leaf with an ovoid shape. The Rosy periwinkle has flowers that are shaped like a trumpet and have fine hairs on the surface of the flowers. These Rosy periwinkle in regional languages are often called as *kembang sari cina*, *cakar ayam*, *usia*, or *rutu-rutu*. Not only that, the soles have a slightly bitter and cool taste (Bangun , 2012).



Figure 1. Rosy Periwinkle

According to Kabesh et al., Rosy periwinkle contains alkaloids, tannins, polyphenols, terpenoids, saponins, sterols, quinines (quoted from Purbosari and Puspitasari, 2018). Alkaloid derivatives include vinblastine (VLB), leurosine (VLR), leurosidine, vincristine (VCR), vincadioline, lochnerine, and catharantine which function as anti-cancer. Not only that, alkaloid derivatives as hypoglycemic substances such as lochnerine, tetrahydroalstonine, catharantine, vindoline, leurosin, and vindolinine (Bangun, 2012) can also reduce the blood sugar level. As Mishra et al (cited in Muharram, Adnan, Faqih, Jihadi, 2019) states that the roots of the plan are able to produce antihypertensive alkaloid namely ajmalicin, reserpine, and serpentine. According to Farnsworth et al. ; Holdsworth; Joy et al. (cited in Muharram et al., 2019) Rosy periwinkle has a phytochemical compounds which is capable to treat dyspepsia, hypertension, menorrhagia, arthritis, cancer, digestive disorders, menstrual disorders, diarrhea, antiviral, and skin diseases.

According to research by Risa Rahma Putri, Rachmi Fanani Hakim, Sri Rezeki (2017), Rosy periwinkle leaves can accelerate wound healing which is characterized by a decrease in the number of fibroblasts in the oral mucosa. Tread virgin also functions as an anticancer, antiviral, antifungal, antihyperglycemic, antidiarrheal, antioxidant, antibacterial (Arifuddin, Bone, Iswahyudi, Ibrahim, Rijai, 2017).

Rosy periwinkle leaves can reduce blood sugar levels in diabetes mellitus because due the to existence of alkaloid chemical compounds which able to help inhibit the absorption of sugar so that it can prevent hyperkalemia. Alkaloid-derived compounds, such as lochnerin, leurosin, tetrahydroalstonin, vindolini, katarantin, and vindolin can help to produce insulin hormone by stimulated pancreatic beta cells so that blood sugar levels decrease (Soriton , Yamlean, and Lolo, 2014).

According to research from Agung Giri Samudra (2017), Rosy periwinkle can reduce fever because they contain flavonoid that work to inhibit the cyclooxygenase enzyme in prostaglandin biosynthesis so that body temperature decreases.

METHODS

This research is laboratory experimental research. The research was conducted in July 2019. The object of this study was 30 male Wistar strain rats with age of 2-3 months with a weight of 180-200 grams / rat. Male wistar strain rats were adapted for 7 days, treated 12 hours dark and 12 hours light, by being fed and drinking as usual. After being adapted for 7 days, male wistar strain rats were weighed with no change in body weight not exceeding $\pm 10\%$. 30 male Wistar strain rats were divided into 3 groups, namely the negative control group, the positive control group, and the treatment group. The negative control group does not suffer for kidneys damaged and fed and watered as usual, while the kidney of the positive control group was destroyed his with gentamicin 0 , 3 cc (12 mg) intraperitoneally / day for 7 days and this group was not given the therapy, and the treatment group with damaged kidneys causes by induction of gentamicin as much as 12 mg in 0.3 cc intraperitoneal / day for 7 days then given boiled water as much as 5.2 grams of water in 100 cc of water and given as much as 3.6 cc per oral / rat for 7 days.

Making Rosy Periwinkle Decoction

Rosy Periwinkle (*Catharanthus roseus*, L.) was taken from the Parongpong area, West Bandung with purple flowers. The part of the plant that is used are the leaves, roots, stems,

and flowers. First the plant are washed clean then cut into pieces. After that the soles are dried indirectly (room drying). After drying, the treads are taken 5,2 grams and boiled in 300 cc of water for 9 minutes so that it becomes 100 cc of water. The tread boiled water was given as much as 3.6 cc / oral / rat for 7 days.

Ways of making Wistar strain male rat models of acute renal failure becomes damaged is by injecting gentamicin to the mice as much as 0,3 cc intraperitoneally/ day/ rat for 7 days so that mice undergoing nephrotoxic characterized by increased levels of urea and creatinine. Gentamicin is given to the positive control group and the treatment group at the same dose.

Research Procedure

The research objects were 30 male Wistar strain rats which were divided into 3 groups:

1. The negative control group, the kidney in this group was not being damaged and feed and watered as usual.
2. The positive control group, , the kidney in this group is being damaged by inducing gentamicin as much as 0.3 cc intraperitoneal / rat and no therapy was given.
3. The treatment group the kidney in this group is being damaged by inducing gentamicin as much as 0.3 cc intraperitoneal / rat and given boiling water therapy 5.2 grams in 100 cc of water and given as much as 3.6 cc / oral / rat.

Male Wistar strain rats were adapted for 7 days. On the 8th day male rats were weighed and there was no change of $\pm 10\%$, the kidney of the positive control group and the treatment group were damaged with gentamicin 12 mg in 0.3 cc intraperitoneal / rat for 7 days while the negative control group was given food and drink as usual for 7 days. On the 15th day all three groups were tested for urea and creatinine levels. As a result of the pre-test, the treatment group was given rosy periwinkle (*Catharanthus roseus*, L.) decoction therapy as much as 5.2 grams in 100 cc of water and given as much as 3.6 cc / oral / rat for 7 days. On the 22nd day the level of urea n creatinine of the three groups were tested and analyzed with SPSS version 24, One Way ANOVA is used to compare the urea and creatinine levels in the three groups in both pre-posttest.

RESULTS

The results of the test with One Way ANOVA, the levels of urea and creatinine before and after therapy of rosy periwinkle (*Catharanthus roseus* L.) therapy in male rats wistar strain model of acute renal failure.

| Dependent Variable | (I) group | (J) group | Mean Difference (IJ) | Std. Error | Sig. | 95% Confidence Interval | |
|--------------------|------------------|------------------|----------------------|------------|------|-------------------------|-------------|
| | | | | | | Lower Bound | Upper Bound |
| Urea Pre | Control Negative | Positive Control | -40.72000 * | 2.42176 | .000 | -46.7246 | -34.7154 |
| | | Treatment | -45.65000 * | 2.42176 | .000 | -51.6546 | -39.6454 |
| | Control Positive | ControlNegative | 40.72000 * | 2.42176 | .000 | 34.7154 | 46.7246 |
| | | Treatment | -4.93000 | 2.42176 | .123 | -10.9346 | 1.0746 |
| | Treatment | Negative Control | 45.65000 * | 2.42176 | .000 | 39.6454 | 51.6546 |
| | | Positive Control | 4.93000 | 2.42176 | .123 | -1.0746 | 10.9346 |
| Urea Post | Control Negative | Positive Control | -136.86000 * | 13,15071 | .000 | -169.4661 | -104.2539 |
| | | Treatment | -17.13000 | 13,15071 | .406 | -49.7361 | 15.4761 |
| | Control Positive | Negative Control | 136,86000 * | 13,15071 | .000 | 104.2539 | 169,4661 |
| | | Treatment | 119.73000 * | 13,15071 | .000 | 87,1239 | 152,331 |
| | Treatment | Negative Control | 17.13000 | 13,15071 | .406 | -15.4761 | 49.7361 |
| | | Positive Control | -119.73000 * | 13,15071 | .000 | -152,331 | -87,1239 |
| Creatinine Pre | Control Negative | Positive Control | -1.81800 * | .14514 | .000 | -2.1779 | -1.4581 |
| | | Treatment | -1.70100 * | .14514 | .000 | -2,0609 | -1.3411 |
| | Control Positive | Negative Control | 1,81800 * | .14514 | .000 | 1.4581 | 2.1779 |
| | | Treatment | 11,700 | .14514 | .703 | -.2429 | 4769 |
| | Treatment | Negative Control | 1.70100 * | .14514 | .000 | 1.3411 | 2,0609 |
| | | Positive Control | -.11700 | .14514 | .703 | -.4769 | 2429 |
| Creatinine Post | Control Negative | Positive Control | -3.28800 * | .27575 | .000 | -3.8775 | -2.6985 |
| | | Treatment | -.73100 * | .27575 | .013 | -1.3205 | -.1415 |
| | Control Positive | Negative Control | 3,28800 * | .27575 | .000 | 2.6985 | 3.8775 |
| | | Treatment | 2.55700 * | .27575 | .000 | 1.9675 | 3.1465 |
| | Treatment | Negative Control | .73100 * | .27575 | .013 | .1415 | 1.3205 |
| | | Positive Control | -2.55700 * | .27575 | .000 | -3.1465 | -1.9675 |

* The mean difference is significant at the 0.05 level.

DISCUSSION

In this study, two measurements of urea and creatinine were carried out, namely before and after the rosy periwinkle (*Catharanthus roseus*, L.) decoction therapy to determine the

comparison of the results of urea and creatinine serum levels in the negative control group, positive control group and treatment group.

Results from statistical data using the SPSS version 24 program with the One Way ANOVA test were performed to compare the levels of urea and creatinine before and after being treated with rosy periwinkle (*Catharanthus roseus*, L.) decoction in male wistar strain rats with acute kidney failure model. Following are the results of the One Way ANOVA test analysis:

Table 1. Comparison of the results of the urea level in male wistar strain rats on the 15th day before being given therapy of rosy periwinkle (*Catharanthus roseus*, L.) decoction.

| Dependent Variable | (I) group | (J) group | Mean Difference (IJ) | Std. Error | Sig. |
|--------------------|------------------|------------------|----------------------|------------|------|
| Urea Pre | Negative Control | Positive Control | -40.72000 * | 2.42176 | .000 |
| | | Treatment | -45.65000 * | 2.42176 | .000 |
| | Positive Control | Negative Control | 40.72000 * | 2.42176 | .000 |
| | | Treatment | -4.93000 | 2.42176 | .123 |
| | Treatment | Negative Control | 45.65000 * | 2.42176 | .000 |
| | | Positive Control | 4.93000 | 2.42176 | .123 |

In table 1, it was found that the comparison of urea levels between the negative control group and the positive control group showed a significant difference ($p < 0.05$) and the comparison between the negative control group and the control group showed a significant difference ($p < 0.05$). Comparison of pre-therapeutic urea between the positive control group and the treatment group showed a non-significant difference ($p = 0.123$). This indicates that the positive control group induced kidney damage as well as the comparison between the negative control group and the treatment group because both groups were induced by 0.3 cc Intraperitoneal gentamicin for 7 days so that they experienced kidney damage which was marked by increased levels of urea serum.

Table 2. Comparison of the results of the urea serum level in male wistar strain rats on the 22nd day after treatment of rosy periwinkle (*Catharanthus roseus*, L.) decoction.

| Dependent Variable | (I) group | (J) group | Mean Difference (IJ) | Std. Error | Sig. |
|--------------------|------------------|------------------|----------------------|------------|------|
| Urea Post | Negative Control | Positive Control | -136.86000 * | 13,15071 | .000 |
| | | Treatment | -17.13000 | 13,15071 | .406 |
| | Positive Control | Negative Control | 136.86000 * | 13,15071 | .000 |
| | | Treatment | 119.73000 * | 13,15071 | .000 |
| | Treatment | Negative Control | 17.13000 | 13,15071 | .406 |
| | | Positive Control | -119.73000 * | 13,15071 | .000 |

Reviewing the results of table 2, the comparison of post-therapeutic urea levels between the negative control group and the positive control group showed a significant difference ($p < 0.05$), which means that the positive control group's urea levels did not decrease to the normal value of the negative control group's urea level this condition happen because the positive control was not get the water therapy. Comparison of post-therapy of urea levels in the negative control group and the treatment group experienced an insignificant difference ($p = 0.406$) which means that the ureum level of the treatment group approached the normal value of the negative control group marked by decreasing urea serum levels, whereas the comparison of the positive control group and the treatment group experienced significant difference with ($p < 0.05$). This indicates that the control group was positive to have a permanent kidney damage, while the treatment group after getting the therapy of rosy periwinkle decoction as much as 3, 6 cc show a decrease of urea levels approaching to normal values of the negative control group, it indicates that the water decoction of rosy periwinkle can reduce levels of urea in male wistar rats with acute renal failure model that previously had increased urea levels.

Table 3. Comparison of creatinine levels in wistar strain rats on the 15th day before giving boiled water therapy of rosy periwinkle (*Catharanthus roseus*, L.)

| Dependent Variable | (I) group | (J) group | Mean Difference (IJ) | Std. Error | Sig. |
|--------------------|------------------|------------------|----------------------|------------|------|
| Creatinine Pre | Negative Control | Positive Control | -1.81800 * | .14514 | .000 |
| | | Treatment | -1.70100 * | .14514 | .000 |
| | Positive Control | Negative Control | 1.81800 * | .14514 | .000 |
| | | Treatment | 11.700 | .14514 | .703 |
| | Treatment | Negative Control | 1.70100 * | .14514 | .000 |
| | | Positive Control | -.11700 | .14514 | .703 |

Seeing the results of table 3, the comparison of creatinine levels in the pre-therapy of rosy periwinkle decoction in the negative control group and the positive control group showed a significant difference ($p < 0.05$). Comparison of the negative control group and the treatment group showed a significant difference ($p < 0.05$), while the comparison of the positive control group and the treatment group showed no significant difference ($p = 0.703$). This is because both groups induced by gentamicin 0,3 cc intraperitoneally for 7 days so that kidney was damaged which characterized by increased levels of creatinine.

Table 4. Comparison of creatinine levels in male Wistar strain rats on the 22nd day after treatment of rosy periwinkle (*Catharanthus roseus*, L.) decoction.

| Dependent Variable | (I) group | (J) group | Mean Difference (IJ) | Std. Error | Sig. |
|--------------------|------------------|------------------|----------------------|------------|------|
| Creatinine Post | Negative Control | Positive Control | -3.28800 * | .27575 | .000 |
| | | Treatment | -.73100 * | .27575 | .013 |
| | Positive Control | Negative Control | 3.28800 * | .27575 | .000 |
| | | Treatment | 2.55700 * | .27575 | .000 |
| | Treatment | Negative Control | .73100 * | .27575 | .013 |
| | | Positive Control | -2.55700 * | .27575 | .000 |

Looking at the results from table 4, it was found that the creatinine levels of the negative control group and the positive control group had a significant difference ($p < 0.05$). Comparison of the negative control group and the treatment group there was no significant difference ($p = 0.013$). This indicates that the positive control group have permanent kidney damage without undergoing therapy, while the treatment group after the therapy of rosy periwinkle decoction as much as 3, 6 cc / orally per day for 7 days help to decrease creatinine levels and make the creatinine level approaching normal values of the negative control group. It showed that the rosy periwinkle decoction had an effect in decreasing creatinine levels in male Wistar strain rats with acute renal failure. This was also confirmed that the results of the comparison of creatinine levels in the positive control group and the treatment group had a significant difference ($p < 0.05$), even though before therapy did not show a significant difference ($p = 0.703$).

Conclusion

From the results of the study it can be concluded that the induction of gentamicin as much as 12 mg in 0.3 cc for 7 days carried out on male wistar strain rats can damage kidney function which causes the release of excess ureum and creatinine levels, which is characterized by increased levels of urea and creatinine.

And the next conclusion is 5.2 grams of rosy periwinkle (*Catharanthus roseus*, L.) which is boiled in 300 cc of water until the remaining 100 cc and given as much as 3.6 cc / oral / day for 7 days can reduce urea and creatinine levels in male wistar strain rats with acute kidney failure model.

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