Amelioration of Cisplatin-Induced Kidney Injury by Pometia pinnata

Adrian1, RA Syahputra2,*, Sukirman Lie3, SE Nugraha4, PC Situmorang5

ABSTRACT

INTRODUCTION

Cisplatin is one of the most effective anticancer drugs. But using cisplatin can cause serious nephrotoxicity and acute kidney injury (AKI). Pometia pinnata (PE) or commonly referred to as matoa is a typical plant, especially Papua, Indonesia. Pometia pinnata belongs to the Sapindaceae family. This study aimed to determine the nephroprotective activity of the extract ethanol pometia pinnata on rats induced cisplatin. Methods: 30 rats are divided into six groups, each group were contained 5 rats. Group I was a normal group which rats only given CMC (carboxy methyl cellulose). Group II was a negative group which rats injected 7 mg / kgbw of Cisplatin in day 3. Group III was a positive group which rats given vitamin C 1% from day 1 to 7 and in day 3 rats were injected cisplatin. Group IV-VI were extract groups (100 mg / kgbw, 200 mg / kgbw, 400 mg / kgbw) which rats orally given extract from day 1 to 7 and in day 3 rats were injected cisplatin. On day 8 rats were injected ketamine 1% which directly took the blood from the heart. Results: The result shows that EEPE on rats biochemical parameters including urea, creatinine, uric acid. Group II showed that there was a significant increase (p <0.05) compared to the normal group that was not given cisplatin and extracts. Whereas in the group given the extract in groups IV, V, and VI there was a reduction in biochemical parameters because the Pometia leaf extract had high antioxidant activity so that it had nephroprotective activity. extract ethanol pometia pinnata can reduce the level of sodium, potassium and chloride of each group after receiving cisplatin. Statistically group II that only given cisplatin has significantly different with group I (p<0,05) and also statically different with group VI (p<0,05).

Key words: Cisplatin, Pometia pinnata, Kidney injury.

INTRODUCTION

Cisplatin (cis-diaminedichloroplatinum II, CDDP) is one of the most effective anticancer drugs. But using cisplatin can cause very serious nephrotoxicity and acute kidney injury (AKI). Nearly 30-40% of cisplatin use in patients causes nephrotoxicity as a result of CDDP accumulation and kidney biontransformation. Until now, only amifostine is widely used as a nephroprotective agent during cisplatin treatment but has side effects such as hypocalcemia, hypotension, and vertigo. Cisplatin can increase biomarkers of kidney damage such as KIM-1 (Kidney injury molecule-1), cystatin C and NGAL (Neutrophil gelatinase)1-4.

Two of the largest clinical manifestations of nephrotoxicity due to the use of cisplatin are acute renal failure (20-30%) and hypomagnesemia (40-100%). Acute renal failure can be detected by increases in Blood Urea Nitrogen (BUN) and serum creatinine. Dialysis costs are expensive and kidney transplantation as a long-term therapy remains the gold standard. Cisplatin nephrotoxicity and acute kidney injury (AKI) remain a major challenge for the treatment of patients with cancer and nephrotoxicity is the most common cause of treatment-related death / apoptosis. 7 However, the clinical success of cisplatin is limited because of severe side effects and intrinsic or acquired resistance during treatment. Unfortunately, resistance has limited the effectiveness of these agents in most diseases. Resistance to platinum-based chemotherapy can be intrinsic or acquired and may be mediated by factors outside or inside cancer cells or on the cell membrane. 8,9 The toxicity due to the use of cisplatin is very dangerous, so that in its use, additional therapy is needed, both traditional and modern. Traditional therapy is often used by people, especially in Indonesia, one of which is the use of herbs.

Pomelia pinnata (PE) or commonly referred to as matoa is a typical plant, especially Papua, Indonesia. Pometia pinnata belongs to the Sapindaceae family. Matoa fruit has a characteristic and combined taste so that in its use, additional therapy is needed, both traditional and modern. Traditional therapy is often used by people, especially in Indonesia, one of which is the use of herbs.

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MATERIALS AND METHODS

Extract Ethanol Pometia Pinnata Preparation

700 g powdered dry fruit of *Pometia pinnata* dissolved using 96% ethanol then steer occasionally, then the solution is macerated for 7 days and steer occasionally every day, then the solution is filtered with whatmann paper no 1, the filter results are then forgotten using a rotary evaporator under reduced pressure and the solvent is evaporated until crude extract / extract ethanol of PE (EEPE) is obtained. Then performed phytochemical screening (alkaloids, flavonoids, tannins, saponins, glycosides, steroids / triterpenoids).

Animal Handling

30 normal health and weight between 150 - 200 g of rats were used in the experimental study. Rats are placed in plastic cages that are adjusted to a humidity of 40-60% and under dark / light cycle 12 hours. and also rats were given a pellet food from cratachm manufactoring and drink ad libitum.

Research design

30 rats are divided into six groups, each group were contained 5 rats. Group I was a normal group which rats only given CMC (carboxy methyl cellulose). Group II was a negative group which rats injected 7 mg / kg bw of Cisplatin in day 3. Group III was a positive group which rats given vitamin C 1% from day 1 to 7 and in day 3 rats were injected cisplatin. Group IV-VI were extract groups (100 mg / kg bb, 200 mg / kg bb, 400 mg / kg bb) which rats orally given extract from day 1 to 7 and in day 3 rats were injected cisplatin. On day 8 rats were injected ketamine 1% which directly took the blood from the heart

Biochemical parameters analysis

3 ml of blood from each rat were centrifugated 4000 RPM (5° C) for 10 menit after that 0.5 ml of supernatant was taken and directly put into cobas 6000 for examining the levels of Urea, Creatinine, Urine Acid. Data can be seen in table 2.

NGAL, SOD, and MDA analysis

1 gram of kidney tissue are taken and homogenized in homogenator tissue with 10 ml of PBS pH 7.4 during 5 minutes, supernatant are taken and continue to analysis the level of NGAL, SOD, and MDA by using ELISA reader at 450 nm (Abclonal, China).

Data analysis

Data analysis in this study used SPSS (statistical program for social sciences) version 21 using the one-way ANOVA (Analysis of Variance) test. p <0.05 if there is a significant difference between groups, p >0.05 if there is no difference between groups.

RESULTS

Biochemical Parameters Analysis of Urea, Creatinine, and Uric Acid

Measurement of serum biochemical parameters is required to analyze renal damage resulting from exposure to cisplatin. In this study, the measurement of levels of urea, creatinine, uric acid, Data can be seen in table 1.

Table 1 shows the effect of EEPE on rats biochemical parameters including urea, creatinine, uric acid. Group II showed that there was a significant increase (p <0.05) compared to the normal group that was not given cisplatin and extracts. Whereas in the group given the extract in groups IV, V, and VI there was a reduction in biochemical parameters because the matoa leaf extract had high antioxidant activity so that it had nephroprotective activity.

Biochemical Parameters Analysis of Sodium, Potassium, and Chloride

Measurement of serum biochemical parameters is required to analyze renal damage resulting from exposure to cisplatin. In this study, the measurement of levels of sodium, potassium and chloride, Data can be seen in table 2.

Table 2 show that extract ethanol pometta pinnata can reduced the level of sodium, potassium and chloride of each group after receiving cisplatin. Statistically group II that only given cisplatin has significantly different with group I (p<0.05) and also statically different with group VI (p<0.05).

NGAL, SOD, and MDA Analysis

Neutrophil Gelatinase (NGAL) is one of the specific parameters of kidney damage. If there is an increase in NGAL levels in serum and urine then it is an indication of damage to the kidneys. Sodium dismutase (SOD) is an endogenous antioxidant parameter used to analyze whether there is a decrease when cisplatin is given to rats. Meanwhile, Malondialdehyde (MDA) was used to analyze the occurrence of lipid peroxidation, especially in the kidneys due to exposure to cisplatin.

DISCUSSION

The parameters of kidney damage that are most often used are urea and creatinine, if there is an increase in these levels, it is feared that there will be structural and functional disorders of the kidneys. Creatinine is the end product of muscle creatine phosphate, and usually produced with a constant level (depending on muscle mass). Most of creatine excreted from the blood via the kidneys, primarily through glomerular filtration also through the proximal tubule secretion. If the filtration in the kidneys decreases, the creatinine level in the blood will increase. Every day, 12% of creatine is converted to creatinine. Serum creatinine is an important indicator of renal physiology since creatinine is a product of muscle metabolism that is excreted in unchanged form via the kidneys4. Urea or urea is a protein catalytic waste substance that is formed in the liver and is filtered and reabsorbed in the kidneys. If kidney function is impaired, urea will accumulate in the blood, a condition called uremia. This situation can be fatal. To overcome this, the cause of kidney failure must be addressed or the patient must undergo dialysis to remove urea and other waste products5. In this study, it was found that there was an increase in urea and creatinine in cisplatin-induced rats in group II (Tables 1 and 2). There are so many studies that prove that cisplatin causes kidney damage. The mechanisms that contribute to renal dysfunction were exposed to cisplatin is in the form of direct tubular toxicity in the form of apoptosis and necrosis mediated through inflammation, ROS, calcium overload, activation of phospholipase, decreased levels of glutathione, and inhibition of mitochondrial respiratory chain function. It has been reported that administration of 5 ml / kg bw cisplatin (0.1% in saline) by ip acute renal failure in mice within 72 hours after administration, while it has also been reported the occurrence of kidney failure with the same doses.
of cisplatin after five days injected. Model of cisplatin-induced renal failure in mice occurred at doses of 12 mg / kg bw, i.p; 18 mg / kg bw, i．p 40 mg / kg bw, i.p 16 ．

failure in mice occurred at doses of 12 mg / kg bw, i.p; 18 mg / kg bb, of cisplatin after five days injected. Model of cisplatin-induced renal oxidative stress so that the necessary antioxidants to cope 21 ．

cells. Thiol reactive also trigger proximal tubular cell death due to growth factor (VEGF) that penetrasi impaired glomerular endothelial cell barrier. Thiol reactive causes decreased production of vascular endothelial growth factor (VEGF) that triggers cell death due to oxidative stress so that the necessary antioxidants to cope 21 ．

Table 1: Biochemical parameters (Urea, Creatinine, Uric Acid) Levels of each Groups.

| Parameters       | Unit   | Groups (Mean ± SD) |
|------------------|--------|--------------------|
|                  |        | Group I            | Group II         | Group III         | Group IV         | Group V           | Group VI          |
| Urea             | mg/dL  | 30.41 ± 2.54*     | 98.45 ± 5.76     | 29.15 ± 2.44      | 54.58 ± 3.81     | 48.42 ± 3.16      | 32.41 ± 2.62*    |
| Creatinine       | mg/dL  | 0.97 ± 0.01*      | 3.36 ± 0.53      | 0.86 ± 0.08      | 1.47 ± 0.29      | 0.91 ± 0.073      | 0.78 ± 0.062*    |
| Uric Acid        | mg/dL  | 0.61 ± 0.04*      | 2.45 ± 0.21      | 0.58 ± 0.032*    | 1.58 ± 0.18      | 1.02 ± 0.098      | 0.65 ± 0.044*    |

*p (p < 0.05) significant different from normal group (Group I)
#(p < 0.05) significant different from control (-) group (Group II)

Table 2: Biochemical parameters (sodium, potassium, chloride) Levels of each Groups.

| Parameters       | Unit   | Groups (Mean ± SD) |
|------------------|--------|--------------------|
|                  |        | Group I            | Group II         | Group III         | Group IV         | Group V           | Group VI          |
| Sodium           | mmol   | 140.56 ± 10.22*    | 234.67 ± 20.48*  | 135.23 ± 9.84*    | 205.66 ± 19.86   | 152.88 ± 12.41    | 140.4 ± 10.51*   |
| Potassium        | mmol   | 5.42 ± 0.48*      | 23.60 ± 2.36     | 4.88 ± 0.38      | 18.48 ± 1.86     | 10.42 ± 0.84      | 5.28 ± 0.46*     |
| Chloride         | mmol   | 98.67 ± 7.46*     | 320.67 ± 18.72*  | 85.21 ± 6.34*    | 250.56 ± 12.65   | 185.18 ± 10.44    | 95.86 ± 8.03*    |

*p (p < 0.05) significant different from normal group (Group I)
#(p < 0.05) significant different from control (-) group (Group II)

Table 3: NGAL, SOD, and MDA Levels of each Groups.

| Parameters       | Unit   | Groups (Mean ± SD) |
|------------------|--------|--------------------|
|                  |        | Group I            | Group II         | Group III         | Group IV         | Group V           | Group VI          |
| Serum NGAL       | ng/mL  | 0.1304 ± 0.047*    | 0.5839 ± 0.342   | 0.1634 ± 0.036*   | 0.4237 ± 0.151   | 0.347 ± 0.019     | 0.1217 ± 0.021*   |
| SOD              | pg/mL  | 22.76 ± 1.05*     | 10.45 ± 0.58     | 24.48 ± 1.08*     | 15.67 ± 0.86     | 16.58 ± 0.93      | 24.62 ± 1.05*     |
| MDA              | μM/L   | 5.62 ± 0.06*      | 12.87 ± 0.69     | 5.41 ± 0.053*     | 10.44 ± 0.23     | 6.45 ± 0.081      | 5.47 ± 0.058*     |

*(p < 0.05) significant different from normal group (Group I)
#(p < 0.05) significant different from control (-) group (Group II)

The initial process of biosynthesis of creatine takes place in the kidneys involving amino acids arginine and glycine. Creatine is converted to creatine in an amount of 1.1% per day. On the formation of creatine no reuptake mechanism by the body, so most of creatine excreted through the kidneys. If renal dysfunction occurs, the creatinine filtration ability will decrease and the serum creatinine will increase. Increased levels of serum creatinine doubling indicates a decrease in kidney function by 50%, as well as an increase in serum creatinine levels tripled reflecting a decline in kidney function by 75% 22 ．Kidney disease or blockage of urine flow from the kidney causes increased levels of urea and creatinine. Higher mean serum creatinine levels kidneys do not work properly. Creatinine levels may rise temporarily if dehydrated, have low blood volume, eat a lot of meat or drinking certain drugs. Creatinine dietary supplements may have the same effect 22 ．

pomea pinnata is known to have high antioxidant activity and contains many secondary metabolites including flavonoids. The flavonoids found in Poemtia pinnata have an important role in reducing the radicalization process caused by cisplatin. The term flavonoids refers to the thousands of plant compounds with the same basic structure, phenylchromane, which allow the formation of several subclasses of flavonoids including flavonols, flavones, catechins, anthocyanidins, isoflavones, dihydroflavonols, and chalcones 24 ．Variable amounts of these compounds are found in vegetables, fruits, nuts, spices, herbs, red wine and tea, among others. Flavonoids are one of the main classes of polyphenols, which have many pharmacological activities, exert antioxidant effect and are known to improve cardiovascular health, but little is known about their role in kidney function and disease 25 ．

CONCLUSION

Ethanol extract of Pometia pinnata has nephroprotective effect on rats induced cisplatin by reducing the biochemical parameters such as urea, creatinine, uric acid, sodium, potassium, chloride, NGAL, and MDA while increase the SOD level.
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GRAPHICAL ABSTRACT

Pometia pinnata powder

Pometia Pinnata Ethanol Extract

CISPLATIN

UREUM
CREATININE
URIC ACID

NGAL
SOD
MDA

SODIUM
POTASSIUM
CHLORIDE
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