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NEFROPROTECTOR EFFECT OF CURCUMIN (CURCUMA LONGA) AND VITAMIN E (α-TOCOPHEROL) IN WISTAR STRAIN RATS AFTER CISPLATIN TREATMENT

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ABSTRACT

Objective: *To analyze the effect of curcumin and vitamin E on kidney function and inflammatory response of Wistar strain rats that received cisplatin.* ***Material & Methods:*** *An experimental laboratory study with a post-test only control design, using male Wistar strain rats (Rattus norwegicus). Rats were randomized using the simple randomized sampling method. Samples were treated with cisplatin 5 mg/kg (positive control group), vitamin E 100 mg/kg, curcumin 100 mg/kg body, and a combination of both (treatment group), to evaluate its effect on and kidney function and inflammatory response as measured by tumor necrosis factor-α (TNF-α), blood urea nitrogen (BUN) and serum creatinine.* ***Results:*** *There were differences in TNF-α levels in the positive control group (cisplatin 5 mg/kg) against each treatment group ($p<0.05$). Further analysis showed that there was a significant difference between the treatment group that received vitamin E and curcumin from the treatment group that received a combination of both ($P<0.05$). In addition, there were differences in BUN and serum creatinine levels in the positive control group (cisplatin 5 mg/kg) against each treatment group ($p<0.05$). However, there was no significant difference in BUN levels in the treatment group that received vitamin E with the treatment group that received curcumin or a combination of both ($p>0.05$). No differences were found in serum creatinine levels between treatment groups receiving vitamin E, curcumin, or a combination of both.* ***Conclusion:*** *Vitamin E 100 mg/kg, curcumin 100 mg/kg, and the combination of both have a nephroprotector feature in Wistar rats exposed to cisplatin.*

Keywords: *Blood urea nitrogen, cisplatin, curcumin, nephroprotector, serum creatinine, TNF-α, vitamin E.*

ABSTRAK

Tujuan: *Menganalisis pengaruh curcumin dan vitamin E terhadap fungsi ginjal dan respon inflamasi tikus strain Wistar yang mendapatkan cisplatin.* ***Bahan & Cara:*** *Studi eksperimental laboratoris dengan post test only control design, menggunakan hewan coba tikus putih (Rattus norwegicus) jantan strain Wistar. Tikus dirandomisasi menggunakan metode simple ramdomized sampling. Hewan coba diberikan perlakuan berupa paparan cisplatin 5 mg/kg BB (kelompok kontrol positif), dengan vitamin E 100 mg/kg BB, curcumin 100 mg/kg BB serta kombinasi keduanya (kelompok perlakuan), untuk melihat pengaruhnya terhadap fungsi ginjal dan respon inflamasi yang diukur dengan marker blood urea nitrogen (BUN) dan serum kreatinin.* ***Hasil:*** *Terdapat perbedaan kadar TNF-α pada kelompok kontrol positif (cisplatin 5 mg/kgBB) terhadap masing-masing kelompok perlakuan ($p<0.05$). Analisis lanjutan menunjukan bahwa terdapat perbedaan yang signifikan terhadap kelompok perlakuan yang mendapatkan vitamin E maupun curcumin dengan kelompok perlakuan yang mendapatkan kombinasi keduanya ($p<0.05$). Selain itu terdapat perbedaan kadar BUN dan serum kreatinin pada kelompok kontrol positif (cisplatin 5 mg/kgBB) terhadap masing-masing kelompok perlakuan ($p<0.05$). Namun, tidak ada perbedaan kadar BUN yang signifikan terhadap kelompok perlakuan yang mendapatkan vitamin E dengan kelompok perlakuan yang mendapatkan curcumin maupun kombinasi keduanya ($p>0.05$). Perbedaan juga tidak ditemukan pada kadar serum kreatinin antar kelompok perlakuan yang mendapatkan vitamin E, curcumin, maupun kombinasi keduanya.* ***Simpulan:*** *Vitamin E 100mg/KgBB, curcumin 100mg/KgBB dan kombinasi keduanya memiliki fungsi sebagai nefroprotektor pada tikus putih Wistar yang terpapar cisplatin.*

Kata Kunci: *Blood urea nitrogen, cisplatin, curcumin, nefroprotektor, serum kreatinin, TNF-α, vitamin E.*

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INTRODUCTION

Bladder carcinoma is the ninth most common malignancy in the world. In 2012 the were around 430 new cases.[1] Bladder carcinoma is the seventh most common malignancy in men and seventh in women worldwide.[2] The incidence of bladder carcinoma per 100.000 male population is 10.1 while in women the incidence is 2.5.[3] Based on the 2018 Globocan data, the incidence of bladder carcinoma in Indonesia in men are 3.5-5.8 and women are ≤ 2.3 per 100.000 population. Cancer is an age-related disease. As getting older, the risk increases.

The number of cancer cases that occur in children and adults have a higher life expectancy by providing multimodal therapy, namely surgery, chemotherapy, and radiation.[4] One cancer therapy uses chemotherapy like cisplatin.

The history of cisplatin using has been started since 1844 and began to be used as a cancer therapy in 1978.[5] Cisplatin is an anti-tumor drug used as a therapy for various malignancies, for example in the field of urology such as the bladder, testicular and penile cancers.[6] Cisplatin (DDP, cis-diamminedichloro platinum II) is an effective antitumor agent with a broad spectrum in treating solid tumors.[7] However, cisplatin administration has nephrotoxic side effects in patients because it causes necrosis of proximal tubules and apoptosis from distal nephrons.[8] Clinically, nephrotoxicity appears 10 days after administration of cisplatin with c cal manifestations of decreased GFR, BUN, and serum creatinine increases, and decreases in serum magnesium and potassium levels. Cisplatin enters the kidney cells passively. Exposure to cisplatin in tubular cells activates signaling pathways that cause cell death (MAPK, p53, ROS, etc.) or cytoprotective (p21). Cisplatin induces TNF-α production in tubular cells, which triggers an inflammatory response explosion, which in turn causes tubular cell injury and death. Cisplatin is also able to induce vascular injury resulting in tubular cell death and decreased R. This situation resulted in acute kidney failure.[9] The prevalence of cisplatin nephrotoxicity is quite high with one-third of patients undergoing cisplatin therapy w find a decrease in glomerular filtration function, an increase in serum creatinine, and a decrease in serum magnesium and potassium levels.[10] Significant increases in serum creatinine and non-significant increases in Blood Urea Nitrogen (BUN) after cisplatin administration are found to be five times greater than before treatment.[11]

BUN and serum creatinine are the result of metabolism, both markers are good screening tests for evaluation of kidney function and are useful for assessing the progression of the disease.[12] The mechanism of nephrotoxicity by cisplatin is complex and is a manifestation of various multifactorial such as inflammation, production of Reactive oxygen species (ROS), Reactive Nitrog Species (RNS), and cellular apoptosis.[8] One of the e effects of cisplatin in cells other than tumors is the formation of free radicals and Reactive oxygen species (ROS) su as superoxide anions and hydroxyl radicals. Reactive oxygen species (ROS) are produced by normal cell metabolism and in balance with prooxidants.[13] Besides cisplatin induces a decrease in antioxidant vels in plasma, this causes the phenomena of the failure of the antioxidant defense mechanism to fight oxidative damage induced by antitumor drugs.[14] Recent studies have focused on tubular cell apoptosis and many apoptotic pathways, including tumor necrosis factor receptors (TNFs) or extrinsic pathways, mitochondrial intestinal pathways (Bax pathways) controlled by Bcl-2 exits, and endoplasmic stress reticulum pathways, have been described as related renal tubular cell death.[15]

Vitamin E is a fat-soluble vitamin that is included in non-enzymatic antioxidants.[16] Vitamin E supplements are useful in reducing and slowing kidney damage that occurs due to increased oxidative stress, also vitamin E prevents the decrease in levels of other antioxidants in the kidneys such as GSH, CAT, and SOD caused by cisplatin.[17] The protective effect against ROS, other antioxidants, and the anti-inflammatory effect of vitamin E might reduce TNF-α levels in the kidneys caused by cisplatin administration.

Curcumin (C21H20O6) was first isolated in 1815. Then in 1910, curcumin was obtained in crystal form and could be dissolved in 1815.[18-19] Curcumin ha effects as antioxidants, anti-inflammatory, and anti-cancer properties and has been prescribed as a neuroprotective agent for patients with neurological disorders.[20] Curcuminoids work as strong anti-oxidants by inhibiting the formation of ROS and free radicals (O2- and OH-). The anti-inflammatory effect of curcumin occurs by inhibiting the LOX, iNOS, matrix metalloproteinase-9 (MMP-9), and COX-2 arachidonic acid production. As an anti-inflammatory, curcumin also inhibits the NF-kB and

MAP kinase pathways. Chemoprotective effects are also associated with anti-inflammatory effects.[21]

Curcumin and vitamin E have been widely studied as antioxidant agents when oxidative stress occurs and as anti-inflammatory. The use of curcumin and vitamin E in chemotherapy based on the use of cisplatin is still very limited. the researchers wanted to further evaluate the role of curcumin and vitamin E in inducing a reduction in oxidative stress, a marker of inflammatory factors, and nephrotoxicity in the kidneys as well as their relationship with BUN, serum creatinine, and TNF-α in mice.

OBJECTIVE

To analyze the effect of curcumin and vitamin E on kidney function and inflammatory response of Wistar strain rats that received cisplatin.

MATERIAL & METHODS

This research is an experimental study that uses male Watsar strain (Rattus norvegicus) white mouse. The experimental animals were treated with cisplatin and a combination of curcumin, vitamin E also a combination of both.

The design of this research study was an experimental laboratory with a post-test only control group design, with the evaluation of kidney function as measured using BUN, serum creatinine, and TNF α which are performed after the animal was treated. The grouping of experimental animals was carried out by randomization, with the repetition of 5 experimental animals in each group and there was a control group as a comparison (positive control and negative control).

Samples of male white rats (Rattus norwegicus) Wistar strains were obtained from the Department of Biochemistry of the Faculty of Medicine, Airlangga University, Surabaya, beginning with the process of adaptation in a cage/research environment for 2 weeks with a 12-hour light cycle, 12 hours dark. The control group in this study included a negative control group (CN), which was given a normal injection of 0.9% 1cc 1x intra-peritoneal saline on the 7th day as a placebo, then on the 12th day the blood sample was taken directly. The positive control group (CP), which was given cisplatin treatment (Cisplatin, Kalbe Farma, Indonesia) at a dose of 7 mg/kg intraperitoneal 1x on the 7th day, then blood was taken on the 12th day for further measurements of BUN parameters, serum creatinine, and TNF-α. Whereas in the treatment group there were three treatment groups, group P1, the group that given 100 mg/kgBW of Curcumin treatment for 9 days after starting the treatment, combined with cisplatin (Cisplatin, Kalbe Farma, Indonesia) 7 mg/kgBW intraperitoneal 1x on the day 7. The second treatment group P2, the group that was given vitamin E treatment (Blackmores, Catalent Australia) 100 mg/kgBB for 9 days after starting the treatment, then blood samples were taken on day 12 to measure BUN parameters and serum creatinine with the automatic analyzer and TNF-α measurement.

Kidney function data that was characterized by BUN and serum creatinine and TNF-α data will be tested for normality to determine whether the data is normal or not and will also be tested for variance to find out the same or not data variants. The type of hypothesis that will be used in this study to determine differences in kidney function measured using BUN and serum creatinine and TNF-α data in the control group and the treatment group is determined based on the results of the normality test and variance data. If the data distribution is normal and the data variance is the same, then the One Way Anova hypothesis test is used.

The hypothesis is determined based on the significance value obtained. If the significance value <0.05, then the next step is to do a multiple comparison test or Post Hoc Test by Tukey, which is to find out in more detail the pairs of treatment groups that are significantly different and those that are not significantly different.

If it does not meet the Anova test requirements, the following statistical test steps are taken[22]: (1) Efforts are made to transform the data so that the distribution becomes normal and the variants become the same (2) If the variables resulting from data transformation are not normally distributed or the variants remain unequal, then the alternative is chosen by the Kruskal-Wallis test (3) If the Kruskal-Wallis test produces a p-value <0.05, then the Mann-Whitney test is continued.

If there are differences, then proceed with the next statistical test to find out different data pairs (to see differences from each group). This test uses Mann Whitney as a further Kruskal-Wallis test.

This study is significant if the p-value <0.05.[22] All data processing techniques are analyzed using Statistical Product and Service Solution 20 for Windows (SPSS 25) software.

RESULTS

Table 1. Rat body weight distribution.

Group	(Mean ± SD)	Normality	p-value
CN	177.2 ± 4.868	0.643	0.146
CP	178.6 ± 5.941	0.616	
P1	179.0 ± 2.738	0.833	
P2	183.0 ± 1.871	0.111	
P3	177.0 ± 2.449	0.563	

Negative Control; CP = Positive Control; P1 = Treatment with Vitamin E 100mg/KgBW; P2 = Treatment with Curcumin 100 mg/KgBW; P3 = Treatment with a combination of Vitamin E 100mg/KgBW and Curcumin 100mg/KgBW.

Table 2. Comparison of Tumor Necrosis Factor-α (TNF-α) levels in study subjects.

Group	(Mean ± SD)	Lower Bound-Upper Bound	Normality	p-value
CN	15.61 ± 3.67	5.40 – 25.81	0.387*	0.0001*
CP	333.68 ± 33.49	240.68 – 426.68	0.617*	
P1	197.98 ± 19.87	142.80 – 253.16	0.474*	
P2	161.22 ± 12.79	125.69 – 196.75	0.190*	
P3	92.47 ± 3.84	81.80 – 103.15	0.705*	

Table 3. Comparison of Tumor Necrosis Factor-α (TNF-α) levels between treatment groups.

Comparison of TNF-α levels between groups	Mean Difference	Confidence interval 95%		P- value
		Lower bound	Upper bound	
CN Vs CP	318.07*	263.53	372.61	0.000
CN Vs P1	182.37*	127.83	236.91	0.000
CN Vs P2	145.61*	91.07	200.15	0.000
CN Vs P3	76.86*	22.32	131.40	0.008
CP Vs P1	135.70*	81.16	190.24	0.000
CP Vs P2	172.45	117.91	226.99	0.000
CP Vs P3	241.20	186.66	295.74	0.000
P1 Vs P2	36.75	17.78	91.29	0.175
P1 Vs P3	105.50	50.96	160.04	0.001
P2 Vs P3	68.74	14.20	123.28	0.016

In this study, sampling was done by randomization using the simple randomized sampling method. To assess homogeneity in this study, the Shapiro Wilk test was performed on data obtained from sampling. The results of normality t weight data of research subjects showed no nificant difference in body weight of rats, which showed that the sample data was normally distributed (p>0.05). Further analysis using the One-way ANOVA parametric test was carried out to assess differences in mean body weight of rats between groups. The results found no mean difference between treatment groups (p>0.05).

In this study, the normality test was carried out using the Shapiro Wilk test, the results of th data distribution in this study were normal (p>0.05), therefore One Way ANOVA parametric test was carried out to see the mean difference between oups. One Way ANOVA parametric test results showed that there were significant mean differences between groups with p<0.05. Mean data between groups were further analyzed to determine whether

Table 4. Comparison of BUN levels in study subjects.

Group	(Mean ± SD)	Lower Bound -Upper Bound	Normality	P-value
CN	13.20 ± 0.96	10.50 – 15.89	0.747*	0.0001*
CP	132.00 ± 4.43	119.67 – 144.32	0.562*	
P1	99.00 ± 2.79	91.24 – 106.75	0.898*	
P2	97.60 ± 3.62	87.52 – 107.67	0.503*	
P3	99.60 ± 2.74	91.96 – 107.24	0.457*	

Table 5. Comparison of BUN levels between treatment groups.

Comparison of BUN Levels Between Groups	Mean Difference	Confidence interval 95%		P-Value
		Lower bound	Upper bound	
CN Vs CP	118.80*	109.55	128.05	0.000
CN Vs P1	85.80*	76.55	95.05	0.000
CN Vs P2	84.40*	75.15	93.65	0.000
CN Vs P3	86.40*	77.15	95.65	0.000
CP Vs P1	33.00*	23.75	42.25	0.000
CP Vs P2	34.40*	25.15	43.65	0.000
CP Vs P3	32.40*	23.15	41.65	0.000
P1 Vs P2	1.40	-7.85	10.65	0.755
P1 Vs P3	0.60	-8.65	9.85	0.894
P2 Vs P3	2.00	-7.25	11.25	0.657

there were differences in variability using the Leven's Test and the results were that there were no significant variants between groups with p>0.05. The Post Hoc LSD test was carried out to compare the mean differences between study groups.

From the results of Post Hoc LSD statistical analysis, it was found that there were differences in the mean TNF-α levels in the negative control group and the positive control group and each treatment group with a p-value <0.05. In this study, there were no differences in TNF-α levels in treatment 1 and treatment 2 groups which were statistically significant with p>0.05. However, there was a significant difference in treatment group 1 and treatment 3 with p<0.05 and also in treatment group 2 and treatment group 3 with p<0.05.

In this study, the normality test was carried out using the Shapiro Wilk test, the results of the data distribution in this study were normal (p>0.05), therefore One Way ANOVA parametric test was carried out to see the mean difference between groups. One Way ANOVA parametric test results showed that there were significant mean differences between groups with p <0.05. Mean data between groups were further analyzed to determine whether there were differences in variability using the Leven's Test and the results were that there were no significant variants between groups with p>0.05. Post Hoc LSD tests were performed to compare mean differences between study groups.

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Table 6. Comparison of creatinine serum levels in study subjects.

Group	(Mean ± SD)	Lower Bound -Upper Bound	Normality	P-value
CN	0.59 ± 0.01	0.56 – 0.62	0.980*	0.0001*
CP	1.71 ± 0.07	1.50 – 1.92	0.552*	
P1	0.93 ± 0.03	0.83 – 1.03	0.134*	
P2	0.91 ± 0.03	0.82 – 0.99	0.769*	
P3	0.96 ± 0.04	0.83 – 1.09	0.066*	

Table 7. Comparison of Creatinine Serum Levels between Treatment Groups.

Comparison of Creatine Serum Levels Between Groups	Mean Difference	Confidence interval 95%		P-Value
		Lower bound	Upper bound	
CN Vs CP	1.12*	0.98	1.25	0.000
CN Vs P1	0.33*	0.20	0.47	0.000
CN Vs P2	0.31*	0.17	0.44	0.000
CN Vs P3	0.36*	0.23	0.50	0.000
CP Vs P1	0.78*	0.65	0.91	0.000
CP Vs P2	0.81*	0.67	0.94	0.000
CP Vs P3	0.75*	0.62	0.88	0.000
P1 Vs P2	0.02	-0.11	0.15	0.713
P1 Vs P3	0.03	-0.10	0.16	0.624
P2 Vs P3	0.05	-0.07	0.19	0.394

significant variants between groups with p>0.05. Post Hoc LSD tests were performed to compare mean differences between study groups.

From the results of Post Hoc LSD statistical analysis, it was found that there were differences in the mean serum creatinine levels in the negative control group and the positive control group and each treatment group with a p-value <0.05. In addition, there were also significant differences in serum creatinine levels in the positive control group for each treatment group with p<0.05. However, in this study treatment group, 1 did not differ significantly from treatment group 2 and treatment 3 with p>0.05. Likewise in treatment group 2 when compared with treatment group 3 with p>0.05.

DISCUSSION

Cisplatin or Peyronie chloride was synthesized in 1845 by Michele Peyrone. Cisplatin is used for the treatment of testicular, ovarian, bladder, head and neck cancer, esophagus, lungs, breast, cervix, stomach, prostate cancer, Hodgkin's and non-Hodgkin's lymphoma, melanoma, and mesothelioma. Cisplatin can activate the apoptotic pathway and cause cell damage through oxidative stress and inflammation.[23-24]

Previous studies have suggested that pro-inflammatory cytokines such as TNF-α were involved in cisplatin-induced nephrotoxicity.[25] The source of TNF-α that contributes to cisplatin nephrotoxicity remains unclear. TNF-α is produced by various tissues and cells, including immune and intrinsic kidney cells, such as mesangial cells, glomerular and tubular epithelial cells, and endothelial cells. Other studies have shown that cisplatin stimulates renal epithelial cells to produce TNF-α in vitro, this increased the likelihood that renal parenchymal cells were the main source of TNF-α in cisplatin nephrotoxicity.[26]

The use of cisplatin (7 mg/kgBB) in this study has shown a significant increase in TNF-α levels compared to controls. The results of this study were in accordance with the results of previous studies which showed that the cisplatin chemotherapy agent had the effect of nephrotoxicity through an increase in pro-inflammatory cytokines TNF-α.[25,27]

Nephrotoxicity due to cisplatin can be caused by mitochondrial dysfunction and increases the production of reactive oxygen species (ROS) through a respiratory chain that is disrupted by the cytochrome P450 (CYP) system.[28] Various studies have been conducted to find antioxidant agents that

could prevent cisplatin nephrotoxicity without reducing its effectiveness. Vitamin E (α-tocopherol) is a natural antioxidant that can protect the integrity of cell membranes throughout the body from oxidation reactions caused by ROS.[29] Several studies have shown the protective effect produced by vitamin E and its derivatives on nephrotoxicity and ototoxicity due to cisplatin. Giving vitamin E as a single agent or in combination with other antioxidant agents can cause changes in biomarkers of oxidative stress such as decreased levels of malondialdehyde, decrease in serum urea and serum creatinine, and also increase the antioxidant activity of the kidney antioxidant enzymes renal catalyst glutathione S-transferase and superoxide dismutation.[30]

In the results of this study exposure to low doses of vitamin E (100 mg/kgBW) gave a statistically significant difference in TNF-α levels compared to groups exposed to cisplatin alone. This is in line with previous studies that Vitamin E could reduce nephrotoxicity due to the cisplatin chemotherapy agent without interfering its effectiveness.[31-32] There was the research that says otherwise, that vitamin E could not be a nephroprotector against cisplatin toxicity. But in that study, a rat sample was given estrogen supplements, which could increase cisplatin toxicity.[17]

Research shows curcumin is a pleiotropic molecule that can interact with various molecules associated with inflammation. Curcumin modulates the inflammatory response by suppressing the activity of cyclooxygenase-2 (COX-2), lipooxygenase, and induced nitric oxide synthase (iNOS). Inhibiting the production of tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-2, IL-6, IL-8, IL-12, monocyte chemoattractant protein (MCP), and migration inhibiting proteins; and suppresses mitogen-activated and kinase Janus. Inhibition of COX-2 and iNOS is most likely achieved by suppressing the activation of nuclear factor kappa B (NK-KB). NK-KB, an eukaryotic transcription factor involved in the regulation of inflammation, cellular proliferation, transformation, and tumorigenesis. Curcumin is thought to suppress the activation of NK-KB and pro-inflammatory gene expression by inhibiting the factor l-kappa B kinase (lKB). Suppression of activation of NK-KB further suppresses COX-2 and iNOS expression, inhibiting the inflammatory process and tumorigenesis. In inflammation in animal models, curcumin also inhibits arachidonic acid metabolism and inflammation in the epidermal skin of mice by suppressing the cyclooxygenase pathway and lipoxygenase pathway.[33]

In the results of this study administration of curcumin at a dose of 100 mg/kgBW could provide a statistically significant difference in TNF-α levels compared to groups exposed to cisplatin alone. This is in line with previous research that curcumin could reduce nephrotoxicity due to cisplatin chemotherapy agents.[34] There was the research that says otherwise, that curcumin could not be a nephroprotector against cisplatin toxicity.[35] But in this study rats were not only given cisplatin, so there might be other factors that could increase toxicity to the kidneys.

Several natural products could inhibit the oxidative process of cisplatin. The combination of vitamin E with curcumin has been done to reduce the oxidative reactions of various chemotherapy drugs. However, studies on the combination of vitamin E with curcumin on alpha TNF levels in cisplatin samples are still rare. In this study, the combination of vitamin E with curcumin was shown to significantly reduce serum TNF alpha levels when compared to samples that only received vitamin E alone or curcumin alone. This is in line with other studies where the combination of natural products could reduce levels of alpha TNF as a marker of oxidative reactions in the body.[36]

Nephrotoxicity has been reported to contribute about 8-60% of AKI hospital-acquired cases.[28,37-38] Giving cisplatin in solid tumors starts from a dose of 40-50 mg/m^2 body surface area with a gap between doses for at least three weeks. The total dose reaches 100-120 mg/m^2 either as a single drug or in combination with other chemotherapy.[39] Protection strategies in cisplatin therapy in an attempt to be renoprotection are to increase drug elimination by intravenous hydration; selecting osmotic diuretics and reducing the use of nephrotoxic drugs.[40]

The use of cisplatin in this study has shown significant damage to the kidneys which was marked by an increase in serum BUN and creatinine levels compared to controls. These results were consistent with the results of previous studies which showed that cisplatin has a nephrotoxicity effect. Cisplatin can cause tubular damage, inflammatory damage in the interstitium, and vascular injury.[41] Exposure to cisplatin to tubular cells activates the activation of signaling pathways that cause cell death (MAPK, p53, ROS, etc.) or cytoprotective (p21).[15]

Cisplatin induces activation of NF-αB causing transcription of inflammatory mediators

including TNF-α and then inducing the expression of other inflammatory cytokines into kidney tissue.[42] Curcumin interventions significantly inhibit the expression of NF-αB, a transcription factor that activates pro-inflammatory cytokines TNF-α and IL-6 in response to oxidative stress, and restores IL-10 levels, which are currently considered as one mechanism for this nephroprotective role in cisplatin-induced nephrotoxicity. This finding is parallel with the histopathological results that show the ability of curcumin to reduce inflammatory cell infiltration and renal necrosis.[43]

The combination of curcumin and vitamin E also shows promising therapeutic effects. Like studies by Gevrek and Erdemir (2018), it has been shown that therapy with curcumin and vitamin E either singly or in combination could have antiapoptotic effects on cisplatin-induced cell apoptosis. Curcumin was given by the intraperitoneal route at a dose of 200 mg/kg for 5 days at the same time. Vitamin E was also given on the first day as a single dose of 50 mg/kg ip. This condition was immunohistochemically demonstrated by decreased caspase-3 expression which was an indicator of cisplatin-induced cell apoptosis, decreased Cas-3 and Bax expression, and increased expression of anti-apoptotic protein Bcl-2 expression after administration of the antioxidant compounds curcumin and vitamin E.

One mechanism of AKI that is induced by cisplatin is oxidative stress. Oxidative stress is an imbalance between free radical production and consumption. AKI caused by Cisplatin due to 3 things, namely, the formation of reactive oxygen species (ROS), accumulation of lipid peroxidation products in the kidney, and decreased antioxidant systems.[15,44]

In the results of this study exposure to vitamin E at a dose of 100 mg/kgBW gave a statistically significant difference in BUN and serum creatinine levels compared to the group exposed to cisplatin. Likewise with the administration of curcumin (100mg/KgBW), as well as the combination of vitamin E with curcumin could provide statistically significant differences in BUN and creatinine levels when compared to groups that were only exposed to cisplatin. However, this study could not prove that curcumin even the combination of curcumin and vitamin E was better than vitamin E alone in the group exposed to cisplatin. This is consistent with the study conducted by Venkatanarayana et al. which showed a significant increase in BUN levels in samples that received vitamin E or curcumin and a combination of the two products. The study also stated that the combination of vitamin E and curcumin did not differ significantly in reducing BUN levels compared to the group that only got curcumin alone. However, in the study serum, creatinine levels differed significantly with the combination of the two substances when compared with curcumin alone. Furthermore, the study did not use cisplatin but instead used carbon tetrachloride as its nephrotoxicity agent.[45]

Research conducted by Volarevic et al. showed that the main mechanism of cisplatin in inducing nephrotoxicity was by increasing the production of reactive oxygen species (ROS) through the respiratory chain that is disrupted by the cytochrome P450 (CYP) system which in turn affects the mitochondrial cell dysfunction which will ultimately result in apoptosis of renal tubular cells.[28] Vitamin E which is a natural antioxidant plays a role in increasing the ability of mitochondria to fight ROS and fat peroxidation.[46] Curcumin has a slightly different pathway from vitamin E in its role as an antioxidant through inhibition of NF-KB pro-inflammation.[43] Even so, ultimately pro-inflammatory NF-KB will play a role in mitochondrial dysfunction.[47]

In this study BUN and serum creatinine levels in the group that received curcumin, Vitamin E and cisplatin did differ significantly from the group that received cisplatin but did not differ significantly from the group that received curcumin and cisplatin only and those who received vitamin E and cisplatin alone. This is confirmed by research conducted by Subudhi et al. where the administration of vitamin E or curcumin could increase the effectiveness of the mitochondrial respiration complex of cells exposed to ROS exposure. However, in this study, it was proven that the combination of vitamin E and curcumin did not provide a significant difference to the increased effectiveness of the mitochondrial respiration complex of cells exposed to ROS exposure.[48] Therefore, it is possible that the antioxidant effect given by vitamin E 100 mg/kgBW or curcumin 100 mg/kgBW can already reach the maximum point of the effectiveness of mitochondrial cells. This is supported in previous research conducted by Yohan et al. where BUN and serum creatinine levels did not differ significantly in the group that received vitamin E 100 mg/kgBW and vitamin E 200 mg/kgBW. Other studies are also in

line with this statement, where the combination of curcumin and vitamin E did not show a significant difference in the apoptosis index of cells exposed to cisplatin exposure.[49]

In this study, TNF-α levels were significantly different in the group that received a combination of vitamin E and curcumin when compared to the group that received vitamin E or curcumin alone. This is different from the results obtained from the combination of the two antioxidant agents on BUN and serum creatinine levels. TNF-α is produced by macrophage cells and monocytes as an inflammatory response. The inflammatory response can be triggered by the presence of free radicals such as ROS.[50] The role of the effectiveness of the mitochondrial respiration complex is not needed in the process of reducing TNF-α levels by vitamin E and curcumin. Furthermore, the process of increasing TNF-α occurs long before the occurrence of cell apoptosis.[51]

CONCLUSION

1. There was a significant increase in serum TNF-α, BUN, and creatinine levels in Wistar strain white rats exposed to Cisplatin compared with controls.
2. Curcumin administration could reduce TNF-α, BUN, and serum creatinine levels and in Wistar strain white rats exposed to Cisplatin exposure.
3. Vitamin E administration could reduce levels of TNF-α, BUN, and serum creatinine and in Wistar strain white rats exposed to Cisplatin exposure.
4. Giving a combination of Curcumin and Vitamin E could reduce levels of TNF-α, BUN, and creatinine serum and in Wistar strain white rats exposed to Cisplatin exposure.
5. The combination of Curcumin and Vitamin E did not give significantly different results on BUN and serum creatinine levels in Wistar strain white rats exposed to Cisplatin.

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