



The Effect of Ethanol Extract of Basil Leaves (*Ocimum sanctum*) on Urea and Creatinine Levels in Wistar Strain White Rats (*Rattus norvegicus*) Induced by Cisplatin

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Article History :

Received date : 2026/06/09

Revised date : 2026/07/15

Accepted date : 2026/08/23

Published date : 2026/09/21



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E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



ABSTRACT

Background: Cisplatin is the most frequently used antineoplastic agent. Its administration may give rise to a range of adverse effects, among which nephrotoxicity is prominent. Urea and creatinine are biomarkers capable of indicating the presence of renal injury. Basil leaves (*Ocimum sanctum*) are known to possess a high antioxidant content and may therefore hold potential as an alternative herbal therapy for the prevention of renal injury arising from cisplatin administration.

Objective: To determine the effect of the administration of ethanol extract of basil leaves on urea and creatinine levels in Wistar strain white rats (*Rattus norvegicus*) induced by cisplatin.

Methods: This was an experimental study employing a post-test randomised controlled group design, using 25 rats allocated into five groups. Group 1 served as the negative control (1% CMC); group 2 as the cisplatin positive control (5 mg/kg body weight); group 3 as treatment group 1, receiving basil extract at a dose of 100 mg/kg body weight; group 4 as treatment group 2, receiving

basil extract at 200 mg/kg body weight; and group 5 as treatment group 3, receiving basil extract at 300 mg/kg body weight. Treatment groups 1, 2 and 3 received basil leaf extract orally for 10 days and were induced with a single intraperitoneal dose of cisplatin on day 5. Urea concentration data were analysed statistically using the one-way ANOVA test followed by the post hoc Tamhane test, whereas creatinine concentration data were analysed using the Kruskal–Wallis test followed by the Mann–Whitney test.

Results: Administration of ethanol extract of basil leaves at all doses reduced serum urea and creatinine levels in rats induced with cisplatin 5 mg/kg body weight. The mean urea and creatinine concentrations at a dose of 100 mg/kg body weight demonstrated the greatest reduction, with a mean urea value of 119.78 and a mean creatinine value of 1.775.

Conclusion: Administration of ethanol extract of basil leaves reduced serum urea and creatinine levels in cisplatin-induced rats, although the reduction was not statistically significant.

Keywords: Cisplatin; nephrotoxicity; urea; creatinine; *Ocimum sanctum*; antioxidants

INTRODUCTION

Cancer is one of the leading causes of death worldwide, accounting for 8.8 million deaths in 2015. The most common causes of cancer-related death are cancers of the lung, liver, colon and rectum, stomach and breast.¹ At the national level, the prevalence of cancer among the population of all ages in Indonesia in 2013 was 1.4%, or an estimated 347,792 persons. The Special Region of Yogyakarta recorded the highest prevalence of cancer, at 4.1%. Based on estimates of the absolute number of cancer patients, the provinces of Central Java and East Java were the provinces with the largest estimated number of patients with cancer, at approximately 68,638 and 61,230 persons, respectively.²

Cisplatin (*cis*-diamminedichloroplatinum (II), CDDP) is the antineoplastic agent most frequently used in cancer chemotherapy and constitutes a standard treatment regimen for head and neck cancer, testicular cancer, lung cancer, bladder cancer, and ovarian and cervical cancer. Cisplatin may, however, give rise to a variety of severe adverse effects, one of which is nephrotoxicity. During early clinical use, cisplatin-induced acute renal failure occurred in 14%–100% of patients.³ Cisplatin induces nephrotoxicity through increased generation of reactive oxygen species (ROS) and TNF- α .⁴ Nevertheless, cisplatin continues to be widely prescribed to this day, amid ongoing efforts to identify alternatives of equivalent efficacy but lesser toxicity.⁵

Urea is the end product of protein and amino acid catabolism, produced by the liver and distributed through the intracellular and extracellular fluid into the blood, from which it is subsequently filtered by the glomerulus.⁶ Creatinine is the breakdown product of muscle creatine phosphate, produced constantly by the body in proportion to muscle mass. Creatinine concentration is related to muscle mass and to renal function.⁷ Nephrotoxicity may manifest as acute renal failure, characterised by elevated serum creatinine and urea levels. In parallel with the increasing use of cisplatin, various efforts have been undertaken to prevent nephrotoxicity. One approach to preventing nephrotoxicity is to lower serum creatinine and urea levels. Compounds capable of lowering serum creatinine and urea levels include flavonoids, alkaloids and phenolics.⁸

Basil leaves (*Ocimum sanctum*) represent one of the natural plants readily obtainable in Asia, including in Indonesia.⁹ Basil (*Ocimum sanctum*) is among the plants known to possess high antioxidant capacity. The natural antioxidant compounds contained in basil leaves comprise phenolic compounds (tocopherols, flavonoids and phenolic acids), nitrogenous compounds (alkaloids, chlorophyll derivatives, amino acids and amines), and ursolic acid.¹⁰ Basil leaves contain 70% eugenol and 21% methyl eugenol. Basil leaves contain vitamin C, vitamin A and several minerals such as calcium, zinc and iron, together with numerous other phytonutrients. Basil leaves also contain constituents with biological activity, such as saponins, tannins, triterpenoids and flavonoids.¹¹

Given the antioxidant content of basil leaves and its nephroprotective potential, it is anticipated that the adverse effects of cisplatin administration associated with serum urea and creatinine levels may be minimised. On this basis, the investigators were interested in testing the effect of the ethanol extract of basil leaves on the serum urea and creatinine levels of male Wistar strain white rats elevated as a consequence of cisplatin induction.

METHODS

Instruments

The instruments used in this study were a rat weighing balance, 250 cc and 500 cc beakers, a stirring device, a gastric gavage tube, 1 cc and 3 cc syringes, a centrifuge, haematocrit tubes, micropipette tips, a micropipette, a cool box, a spectrophotometer, labels, microtubes, vacutainers, rat cages, and feeding and drinking equipment.

Materials

The materials used in this study were ethanol extract of basil leaves, gloves, AD2 rat feed and drinking water for the experimental animals, husk bedding, 1% CMC, distilled water, cisplatin, and reagents and standard kits for urea and creatinine.

Experimental Animals

The experimental animals used in this study were male Wistar strain rats (*Rattus norvegicus*, Wistar strain) obtained from the experimental animal breeding facility MS. BRAM MOUSE

FARM, Kalimanah, Purbalingga. The rats used were 2–3 months of age, weighed 150–220 grams, and were free of physical defects.

Method

This study was an experimental study employing a post-test randomised controlled group design. The study was conducted at two sites: animal husbandry and treatment were carried out at the pharmacology laboratory of the Faculty of Medicine, Universitas Jenderal Soedirman, while measurement of urea and creatinine levels was performed at the Biofit clinical laboratory, Purwokerto. The study was conducted from December 2017 to January 2018 over a period of 19 days: 7 days for acclimatisation of the experimental animals; 10 days for administration of the basil leaf extract (including administration of cisplatin on day 5); 1 day for measurement of urea and creatinine levels following treatment; and 1 day for termination of the experimental animals.

The number of rats used in this study was 30 (25 rats as the principal sample and 5 rats as reserves). The rats were allocated into five groups: group 1 as the negative control (1% CMC); group 2 as the cisplatin positive control (5 mg/kg body weight); group 3 as treatment group 1, receiving basil extract at a dose of 100 mg/kg body weight; group 4 as treatment group 2, receiving basil extract at 200 mg/kg body weight; and group 5 as treatment group 3, receiving basil extract at 300 mg/kg body weight. Treatment groups 1, 2 and 3 received basil leaf extract orally for 10 days and were induced with a single intraperitoneal dose of cisplatin on day 5.

Data Analysis

Statistical analysis was performed using SPSS statistical processing software. Serum urea concentration data for each sample were analysed statistically using the one-way ANOVA test in order to determine the presence of a significant difference in means across all groups. A post hoc Tamhane test was subsequently performed in order to identify the groups exhibiting a significant effect. Serum creatinine concentration data, by contrast, were analysed statistically using the Kruskal–Wallis test in order to determine the presence of a significant difference in means across all groups. The Mann–Whitney test was subsequently performed between each pair of study groups in order to identify the groups exhibiting a significant effect. A p value < 0.05 was considered significant (95% confidence level).

RESULTS

Analysis of the effect of basil leaf extract on serum urea levels

The data obtained from the laboratory measurements were subjected to the Shapiro–Wilk test and to a homogeneity test using the Levene test. The normality test yielded a value of $p > 0.05$, signifying that the distribution of urea concentration data in the five groups conformed to a normal curve. The data were subsequently analysed using one-way ANOVA. On the basis of the analysis of urea concentrations, the mean urea level was 33.76 with a standard deviation of 9.41 in the negative control group (NC); 200.88 with a standard deviation of 76.87 in the positive control group (PC); 119.78 with a standard deviation of 45.08 in treatment group 1 (TG1); 166.24 with a standard deviation of 127.96 in treatment group 2 (TG2); and 137.22 with a standard deviation of 66.71 in treatment group 3 (TG3), as shown in Figure 1.

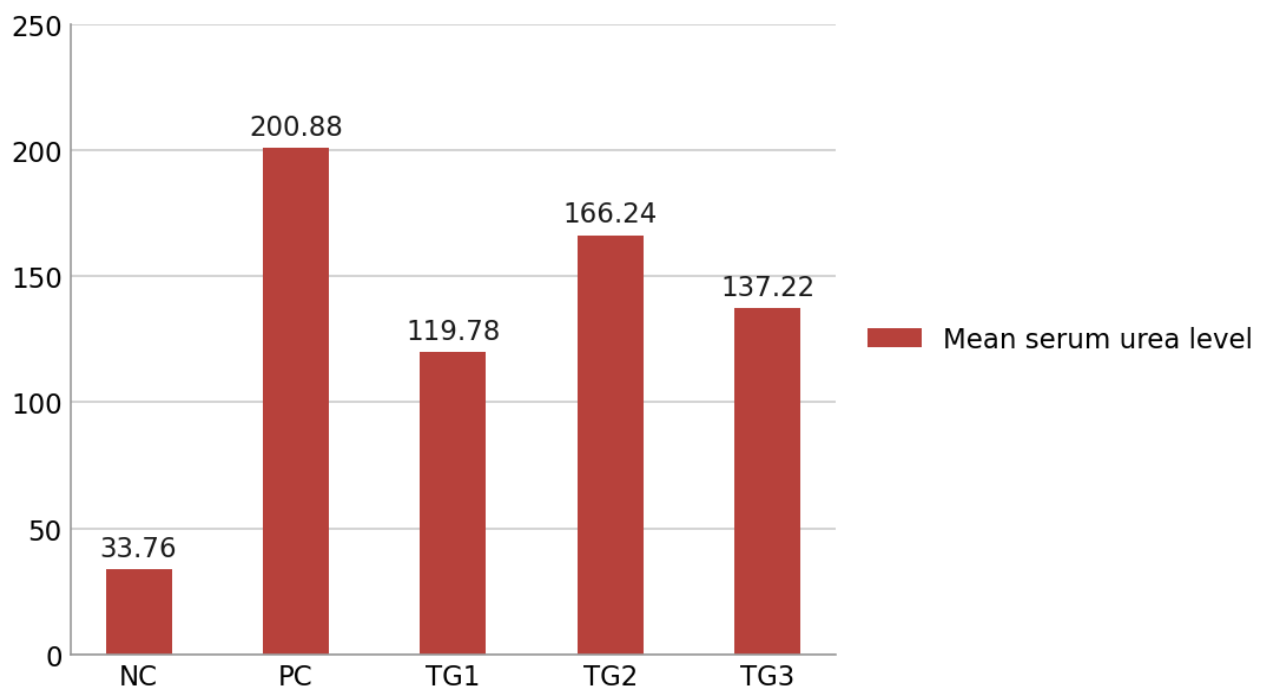


Figure 1. Mean serum urea levels in the study groups

The results of the one-way ANOVA are presented in Table 1. The mean urea levels in the NC, TG1, TG2 and TG3 groups were lower than that in the PC group. The analysis yielded an asymptotic significance value of 0.00 ($p < 0.05$); it may therefore be concluded that a difference

existed in the mean serum urea content of the rats between the treatment groups and the control groups.

Table 1. Results of the one-way ANOVA of urea levels in each group.

	N	Mean $\pm$ SD	P*
NC	5	33.76 $\pm$ 9.41	0.00
PC	5	200.88 $\pm$ 76.87	
TG1 (100 mg/kg BW)	5	119.78 $\pm$ 45.08	
TG2 (200 mg/kg BW)	5	166.24 $\pm$ 127.96	
TG3 (300 mg/kg BW)	5	137.22 $\pm$ 66.1	

*The Kruskal–Wallis test indicates a significant difference where $P < 0.05$.

On the basis of the one-way ANOVA results, it may be concluded that a difference existed in the mean serum urea content of the rats across the five treatment groups studied. The table demonstrates that treatment group 1 constituted the most effective treatment in reducing urea levels in Wistar strain white rats, with a mean of 119.78.

The analysis was subsequently extended by a post hoc test using the Tamhane test, given the presence of an effect and of differences between treatments. The post hoc test was performed in order to determine which differences between one treatment and another were statistically significant in the reduction of urea levels.

Table 2. Results of urea testing between treatment groups.

Group pair		P	Conclusion
Negative control (NC)	PC	0.001*	Significant
	TG1	0.003*	Significant
	TG2	0.229	Not significant
	TG3	0.008	Significant
Positive control (PC)	NC	0.001*	Significant
	TG1	0.453	Not significant
	TG2	0.991	Not significant
	TG3	0.823	Not significant
Treatment group 1 (100 mg/kg BW)	NC	0.003*	Significant
	PC	0.453	Not significant

Group pair		P	Conclusion
Treatment group 2 (200 mg/kg BW)	TG2	1.000	Not significant
	TG3	1.000	Not significant
	NC	0.229	Not significant
	PC	0.991	Not significant
	TG1	1.000	Not significant
Treatment group 3 (300 mg/kg BW)	TG3	1.000	Not significant
	NC	0.008*	Significant
	PC	0.823	Not significant
	TG1	1.000	Not significant
	TG2	1.000	Not significant

*The post hoc Tamhane test indicates significance where $P < 0.05$.

On the basis of the statistical analysis presented in Table 2, significant differences were obtained between the NC and PC groups, between the NC and TG1 groups, and between the NC and TG3 groups. No significant difference was obtained between the PC group and the treatment groups.

Analysis of the effect of basil leaf extract on creatinine levels

The data obtained from the laboratory measurements were subjected to the Shapiro–Wilk test. The normality test yielded a value of $p < 0.05$, indicating that the creatinine concentration data were not normally distributed, that is, did not follow a normal distribution. As the data were not normally distributed, the alternative statistical approach adopted was a non-parametric test, namely the Kruskal–Wallis test, followed by the Mann–Whitney test. The creatinine values are presented in Table 3.

Table 3. Median values (minimum–maximum) of creatinine levels in each group.

	N	Median (min–max)	P*
NC	5	0.7025 (0.627–0.778)	0.013
PC	5	3.343 (1.175–5.511)	
TG1 (100 mg/kg BW)	5	2.515 (1.164–3.866)	
TG2 (200 mg/kg BW)	5	2.787 (0.852–4.722)	

	N	Median (min–max)	P*
TG3 (300 mg/kg BW)	5	2.25 (1.232–3.268)	

*The Kruskal–Wallis test indicates a significant difference where $P < 0.05$.

On the basis of the Kruskal–Wallis analysis, it may be concluded that a difference existed in the mean serum creatinine content of the rats across the five treatment groups studied. The table demonstrates that the lowest median creatinine level was found in treatment group 3, at a dose of 300 mg/kg body weight, namely 2.25.

As an effect and differences between treatments were present, the analysis was subsequently extended by the Mann–Whitney test in order to determine which treatments exerted an effect.

Table 4. Results of creatinine testing between treatment groups.

Group pair		P	Conclusion
Negative control (NC)	Positive control (PC)	0.009*	Significant
Negative control (NC)	Treatment group 1 (TG1)	0.009*	Significant
Negative control (NC)	Treatment group 2 (TG2)	0.009*	Significant
Negative control (NC)	Treatment group 3 (TG3)	0.009*	Significant
Positive control (PC)	Treatment group 1 (TG1)	0.347	Not significant
Positive control (PC)	Treatment group 2 (TG2)	0.251	Not significant
Positive control (PC)	Treatment group 3 (TG3)	0.456	Not significant
Treatment group 1 (TG1)	Treatment group 2 (TG2)	0.917	Not significant
Treatment group 1 (TG1)	Treatment group 3 (TG3)	0.347	Not significant
Treatment group 2 (TG2)	Treatment group 3 (TG3)	0.754	Not significant

*The Mann–Whitney test indicates significance where $P < 0.05$.

On the basis of the Mann–Whitney analysis presented in Table 4, a significant effect was obtained between the NC and PC groups, between the NC and TG1 groups, between the NC and TG2 groups, and between the NC and TG3 groups. No significant effect was present among the remaining group pairs. The mean serum creatinine levels of the rats in each group are presented in Figure 2.

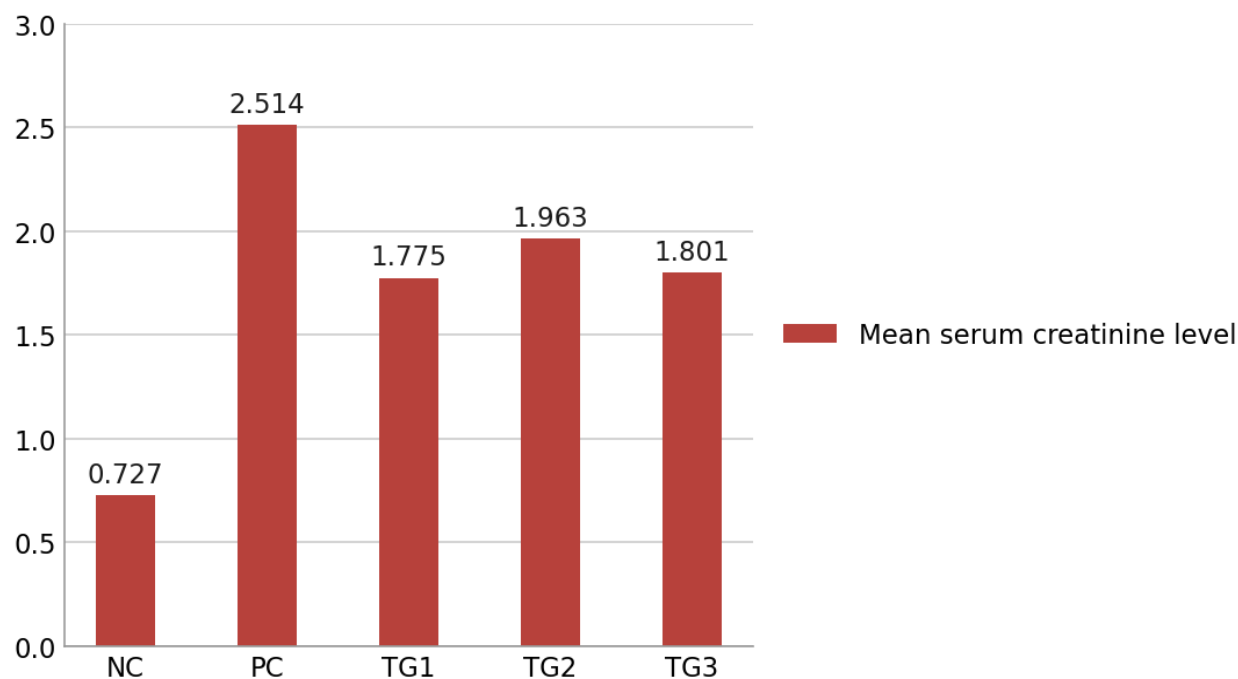


Figure 2. Mean serum creatinine levels in the study groups

On the basis of the mean serum creatinine levels presented in Figure 2, the lowest creatinine level was found in treatment group 1, at a dose of 100 mg/kg body weight, namely 1.775.

DISCUSSION

This study demonstrated a significant difference in serum urea and creatinine levels between the positive control and negative control groups, in which the mean urea and creatinine values in the group of rats induced with cisplatin were significantly higher than those in the group of rats without cisplatin induction (negative control). These findings indicate that cisplatin induction is capable of causing an elevation in serum urea and creatinine levels, which constitute markers indicative of renal injury.

Injury to, or impairment of the function of, the kidney may be detected by determining serum urea and creatinine levels. These findings are consistent with the study conducted by Ezz-Din *et al.* (2011), which demonstrated that the administration of a single intraperitoneal dose of cisplatin (5 mg/kg body weight) is capable of damaging and impairing renal function, as characterised by

elevated urea and creatinine levels together with injury to the renal parenchyma as observed on histopathological examination.¹²

The administration of cisplatin causes an increase in lipid peroxide levels and a reduction in the activity of antioxidants that prevent or protect against lipid peroxidation within tissues. Cisplatin accumulates within the epithelial cells of the proximal renal tubules, causing nephrotoxicity characterised by morphological damage to intracellular organelles, cellular necrosis, loss of microvilli, alterations in the number and size of lysosomes, and mitochondrial vacuolisation, followed by functional alterations including inhibition of protein synthesis, glutathione (GSH) depletion, lipid peroxidation and mitochondrial damage.¹³

This study aimed to examine the effect of the ethanol extract of basil leaves in inhibiting the elevation of urea and creatinine levels. The capacity of basil leaf extract to inhibit the elevation of urea and creatinine levels demonstrates its potential as a nephroprotective agent. In the use of ethanol extract of basil leaves, it must be borne in mind that the dose–response relationship is not invariably positive, meaning that a higher dose is not always accompanied by a greater effect. This study employed graded doses, namely 100 mg/kg body weight, 200 mg/kg body weight and 300 mg/kg body weight. The lowest dose, 100 mg/kg body weight, possessed the most optimal efficacy in reducing urea and creatinine levels in the rats compared with the doses of 200 mg/kg body weight and 300 mg/kg body weight.

A non-linear relationship between an active substance and the response it elicits may indeed occur. The relationship between drug dose and response is closely related to the availability and characteristics of the receptors for that drug in producing an effect. A reduction in effect at higher doses indicates saturation of the interaction between drug molecules and their receptors, such that an increase in dose will not result in an increase in effect.¹⁴ The ethanol extract of basil leaves contains numerous active constituents; among these numerous active constituents, it is postulated that some possess similar active moieties and are therefore able to bind to the same receptor to produce a synergistic effect, such that the saturation effect becomes apparent more rapidly than with a single-active-substance drug. Several studies concerning the use of herbal medicines have demonstrated a non-linear dose–response relationship.¹⁵

Analysis of the urea data in the groups receiving basil leaf extract did not yield statistically significant results; nevertheless, the numerical values and the graph demonstrate that the groups administered basil leaf extract for 10 days had lower mean urea levels than the positive control group. Administration of the ethanol extract of basil leaves at dose 1 (100 mg/kg body weight) constituted the most effective dose in reducing urea levels, demonstrating the most marked reduction compared with the other treatment groups, with a value of 119.78.

Analysis of the creatinine data in the groups receiving basil leaf extract likewise did not yield statistically significant results; nevertheless, the numerical values demonstrate that the groups administered basil leaf extract for 10 days had lower mean creatinine levels than the positive control group. The lowest median creatinine level was found with the ethanol extract of basil leaves at dose 3 (300 mg/kg body weight), with a value of 2.25; however, in terms of the overall mean for each treatment group, administration of the ethanol extract of basil leaves at dose 1 (100 mg/kg body weight) constituted the most effective dose in reducing creatinine levels, demonstrating the lowest value compared with the other treatment groups, at 1.775. Treatment group 1 was regarded as the most effective because it was representative of the overall creatinine results across the samples within each group.

This study is consistent with the research conducted by Basith (2012), which reported that basil leaf extract (*Ocimum sanctum*) possesses a protective effect in preventing renal cellular injury in mice (*Mus musculus*) induced with paracetamol.¹⁶ These findings demonstrate the efficacy of basil leaf extract in preventing renal injury, as characterised by a reduction in the extent of injury to the epithelial cells of the renal proximal tubules. This may be attributable to the presence of compounds with high antioxidant activity capable of preventing oxidative stress activity within renal cells.

Ocimum sanctum is known to constitute a source of flavonoids, which have been shown to possess a range of biological properties related to antioxidant mechanisms. The principal constituent of basil leaf extract (*Ocimum sanctum*) contributing to the prevention of renal injury is its antioxidant content. The principal antioxidative constituents of basil leaves (*Ocimum sanctum*) are ascorbic acid (vitamin C), tocopherol (vitamin E), β -carotene, β -sitosterol, eugenol, palmitic

acid, ursolic acid, phenolic compounds (flavonoids, phenolic acids) and nitrogenous compounds (alkaloids, chlorophyll derivatives, amino acids and amines).¹⁷

Eugenol, carvacrol, sesquiterpenes, apigenin, isothymusin, rosmarinic acid, cirsilineol, orientin and vicianin are phenolic compounds possessing antioxidant capacity. These compounds act through several mechanisms: first, through hydrogen atom transfer (HAT), that is, by donating a hydrogen atom; and through single electron transfer (SET), by transferring an electron in order to reduce metal ions, radicals and carbonyls. The mechanism operating through hydrogen transfer, when present in large quantities, may delay or prevent the initiation step by reacting with lipid radicals, or may directly inhibit the propagation step by reacting with peroxy radicals or alkoxy radicals.¹⁸

The functional groups of flavonoid compounds may act as scavengers of hydroxyl (OH) free radicals, such that these radicals do not oxidise lipids, proteins and DNA within the cell. Renal cell death may thereby be prevented. The capacity of flavonoids to scavenge free radicals is 100 times more effective than that of vitamin C and 25 times more effective than that of vitamin E.¹⁶

The limitations of this study were that urea and creatinine levels were not measured prior to the commencement of the study, and that no other biomarkers of renal function were examined.

CONCLUSION

It may be concluded from the results of this study that a single intraperitoneal injection of cisplatin at a dose of 5 mg/kg body weight is capable of causing an elevation of serum urea and creatinine levels in Wistar strain white rats (*Rattus norvegicus*). The administration of ethanol extract of basil leaves (*Ocimum sanctum*) had no statistically significant effect on urea and creatinine levels in Wistar strain white rats (*Rattus norvegicus*) induced with cisplatin; numerically and graphically, however, a reduction in urea and creatinine levels was observed.

ACKNOWLEDGEMENTS

I wish to express my gratitude to the Faculty of Medicine, Universitas Jenderal Soedirman, for providing the facilities for the husbandry and treatment of the experimental animals; to Biofit

Clinic for providing the facilities for the measurement of urea and creatinine; and to the Faculty of Medicine, Universitas Muhammadiyah Purwokerto, for supporting the preparation of this article.

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