

# Green Coconut Water against the Risk of Contrast Induced Nephropathy

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**Submission date:** 26-Mar-2021 11:04AM (UTC+0700)

**Submission ID:** 1542701450

**File name:** A2\_-\_Green\_Coconut.pdf (517.35K)

**Word count:** 3031

**Character count:** 15489

# Green Coconut Water against the Risk of Contrast Induced Nephropathy

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## ABSTRACT

**Aim:** to prove that young green coconut water (YGCM) reduces the risk of Contrast Induced Nephropathy (CIN) through the change of Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ). Malondialdehyde (MDA). Neutrophil gelatinase-associated lipocalin (NGAL) and renal tubular cell histopathology.

**Study Design:** Experimental research with pre- and post-test control group design.

**Method:** As many 30 rats were randomly divided into 5 groups (K1-K5). Green coconut water was given for 3 (three) days after Iodine Contrast Media (IoCM) induction. Samples were measured at 2, 24 and 48 hours after injection. and rats were terminated with anesthesia and cervical dislocation. Examination of samples using ELISA and analyzed by Linier General Model (LGM). and Fisher Exact

**Result:** Young Green coconut water decreased TNF- $\alpha$  levels by 3.9% in K-1. 19.7% in K-2 and 2.8% in K-3. reducing MDA levels by 28.7% in K-1. 26.7 % for K-2 and 30.6% for K-3. The decreased also occurred in NGAL by 0.1% on K-1. 9.9% on K-2 and 6.8% on K-3. while the histopathological picture of renal tubular cells explained that there was no pathological change in K-1 and K-3. there is NET on K-2 and there is NIPV on K-4. Statistically. the difference in the effect of YGCM on the reduction of TNF- $\alpha$ . NGAL. MDA and histopathological changes between groups was not significant ( $p > 0.05$ ).

**Conclusion:** Young Green Coconut Water lowers TNF- $\alpha$ . MDA. NGAL and potentially to be used on the risk of CIN prevention.

**Keywords:** Green coconut water. Iodine Contrast Media. Tumor Necrosis Factor- $\alpha$ . Malondialdehyde. Neutrophil gelatinase-associated lipocalin

## INTRODUCTION

Intravascular radiological contrast media has nephrotoxic properties and can cause condition of Contrast Induced Nephropathy (CIN)<sup>1-3</sup>. Patients develop CIN if the increase of serum creatinine (sCr)  $\geq 25\%$  or  $20.3 \text{ mg/dL}$  which occurs within 3 days after administration of intravascular contrast media without any other cause<sup>2,4-6</sup>. Previous study has reported that the incidence of CIN may occur 2-5 days after the patient underwent a contrast radiological examination<sup>7</sup>.

The incidence of CIN was reported in 11.1% of the 1,196 patients who underwent radiological examinations<sup>6</sup>. As much as 2% of patients who experience CIN have a 15-fold risk of experiencing Major Adverse Cardiac Events<sup>8</sup> during hospitalization than patients who do not experience CIN. CIN increased the incidence of myocardial infarction 6 times. and the risk of death increased 22 times compared to patients who did not experience CIN<sup>9</sup>.

Increased level of sCr is a strong predictor of CIN and kidney damage occurs within 30 days post of exposure with contrast media and causes a decrease in the Glomerular Filtration Rate (GFR)<sup>10,11</sup>. Disorders of the glomeruli filtration rate are also caused by an increase in Tumor Necrosis Factor Alpha (TNF- $\alpha$ ) and Interleukine-6 (IL-6) in plasma<sup>12,13</sup>.

Currently the use of sCr is less specific for detecting AKI,<sup>14-16</sup> potential parameters are needed, namely *N-acetyl D-glucosaminidase*, Neutrophil Gelatinase-Associated Lipocalin (NGAL)<sup>15</sup>, Kidney Injury Molecule-1 (KIM-1) and Interleukin-18 (IL-18)<sup>17</sup>. NGAL in urine is one of the most widely used biological markers of AKI today. NGAL also

known as lipocalin-2 that first identified as a protein contained in human neutrophil granules and it turns out that in animal studies it has a very promising potential as an early marker of ischemic and nephrotoxic kidney injury<sup>17</sup>.

Efforts on reducing the risk of CIN have been carried out, by providing premedication drugs of N-Acetyl Cysteine<sup>13</sup> and hydration techniques after giving Iodine contrast media. Providing premedication and hydration was able to reduce sCr levels and increase GFR, but the results were unsatisfactory<sup>18</sup>. Therefore, other efforts are needed as an alternative by providing natural antioxidants.

Antioxidants are defined as molecules that inhibit the oxidation of other molecules. Oxidation reactions can produce free radicals that work in chains. The chain reactions taking place in cells cause cell damage or death. Antioxidants stop this chain reaction by removing free radical intermediates, and inhibiting other oxidation reactions<sup>19</sup>.

The use of natural antioxidants is highly recommended considering that the use of these antioxidants does not have significant side effects<sup>20</sup>. The reason for using natural antioxidants is believed to protect cells from damage caused by free radicals (ROS) exposure, inhibit degenerative diseases and lipid peroxidation<sup>21</sup>. One of the natural antioxidants and is believed without side effects is Young Green Coconut Water (YGCM). YGCM contains several minerals, vitamins, antioxidants, amino acids, enzymes, and growth hormones<sup>22,23</sup>.

## METHODS

Ethical approval was issued by the Research Ethics Committee of Medicine Faculty, Universitas Diponegoro (No. 1010-EC/H/FK-UNDIP/IV/2020). Experimental research with pre- and post-test control group design. A total of 30 (thirty) Sprague Dawley (SD) rat, male, weighing 250-300 g, healthy, and 43 months old. The rats were placed in metabolic cage with free access to food and drinking water. The rats were kept at 25±2°C with humidity 50-70% and maintained on 14-h light and 10-h dark. The rats divided randomly into 5 (groups).

K1: loCM + YGCW

K2: loCM + NAC + YGCW

K3: loCM + NAC + mineral water

K4: loCM + mineral water

K5: Mineral water

Young Green coconut water (YGCW) and mineral water were given for 3 (three) days after loCM induction. Samples were measured at 2, 24 and 48 hours after loCM injection. and the mice were terminated with anesthesia and cervical dislocation. Examination of samples using ELISA and analyzed by Linier General Model (LGM). and Fisher Exact.

## RESULT

The reduction in TNF-α levels due to YGCW varied between groups. as shown in table 1.

Table 1: The decrease in TNF-α levels was 1.730 (3.9%) in K1, 4.277 (19.7%) in K2, and 1.463 (2.8%) in K3. The difference in the percentage reduction in TNF-α levels was not significant ( $p > 0.05$ ).

The reduction in MDA levels due to the provision of YGCW varied between groups. as shown in table 2.

Table 2: The decrease in MDA levels was 0.038 (28.7%) in K1, 0.036 (26.7%) in K2, and 0.040 (30.6) in K3. the difference in the percentage reduction in TNF-α levels was significant ( $p < 0.05$ ).

LSD analysis. shows that there is no significant difference between groups as shown in Table 3.

Table 3: There is no significant difference ( $p > 0.05$ ) between groups on the provision of YGCW on the decrease in MDA.

The reduction in NGAL levels due to the provision of YGCW varies between groups. as shown in table 4.

Table 4 :The decrease in NGAL was 0.034 (0.1%) on K1, 0.351(6.8%) on K3, while NGAL increase of 0.376 (9.9%) on K2. The differences percentage of NGAL decrease was not significant ( $p > 0.05$ ).

The effectiveness of YGCW in repairing renal tubular cells  
The provision YGCW on K1 caused all samples have no pathological changes (normal), except tubular necrosis (NET) on K2. There was no change in tubular cells in K3, but there was interstitial perivascular nephritis (NIPV) on K4 as shown in table 5.

Table 1. The Effect of YGCW TNF-α levels

Group	B	p	CI 95% B		Eta Square
			Lower	Upper	
K1	-1.730	0.381	-5.757	2.297	3.9%
K2	-4.277	0.038	-8.303	-0.250	19.7%
K3	-1.463	0.457	-5.490	2.563	2.8%
K4	Negative control				

Table 2. The effect of YGCW on MDA level

Group	B	p	CI 95% B		Eta Square
			Lower	Upper	
K1	-0.038	0.010	-0.067	-0.010	28.7%
K2	-0.036	0.014	-0.065	-0.008	26.7%
K3	-0.040	0.008	-0.068	-0.012	30.6%
K4	Negative control				

Table 3. Mean difference of MDA level

Group	Mean difference	Std. error	p	95% mean difference	
				Upper	Lower
K1 K3	0.000	0.006	0.989	-0.013	0.013
K2 K3	0.002	0.006	0.804	-0.011	0.014
K1 K2	0.001	0.006	0.814	-0.011	0.014

Table 4. The effect of YGCW on NGAL level

Group	B	p	CI 95% B		Eta Square
			Lower	Upper	
K1	-0.034	0.916	-0.716	0.648	0.1%
K2	0.376	0.254	-0.306	1.059	9.9%
K3	-0.351	0.347	-1.127	0.426	6.8%
K4	Negative control				

Table 5. The effect of YGCW on renal tubular cells

Group	Histopatology			Total
	NET	NIPV	NORMAL	
K1	0	0	6	6
	0.00%	0.00%	100.00%	
K2	2	0	4	6
	33.30%	0.00%	66.70%	
K3	0	0	6	6
	0.00%	0.00%	100.00%	
K4	0	1	5	6
	0.00%	16.70%	83.30%	
Total	2	1	21	24
	8.30%	4.20%	87.50%	

Fig.1: Histopathology of tubuli cells Normal (K1 and K2)

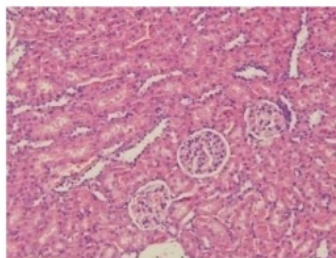
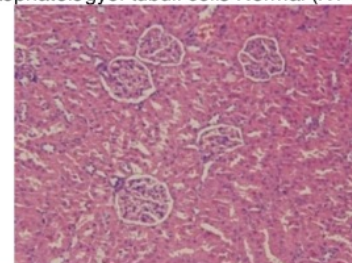


Fig.2 Histopathology tubuli cells with NIPV (K4)



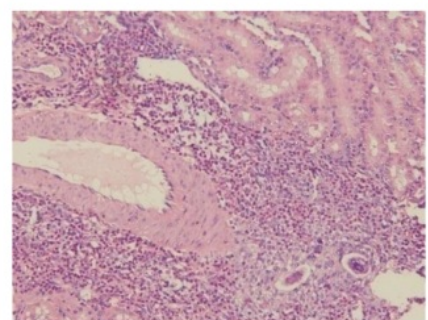
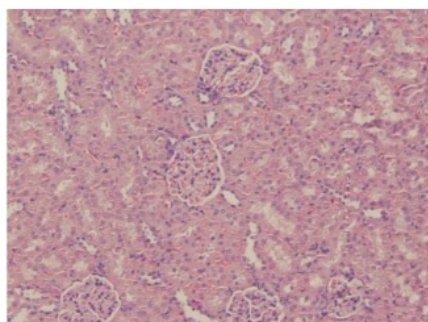
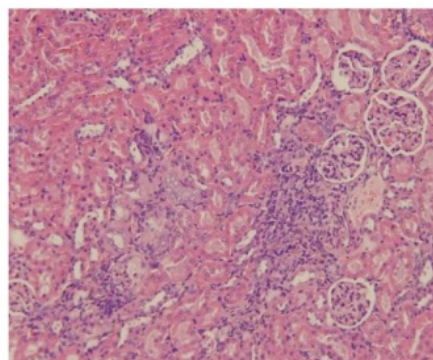
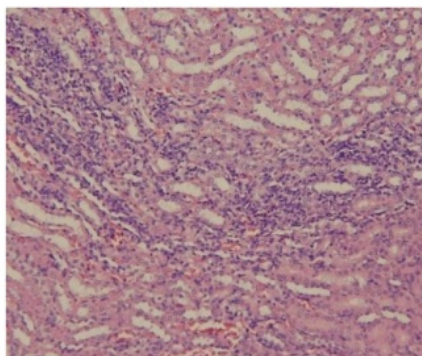


Fig.3 .Histopathologyof tubuli cells with NET(K-2)



## DISCUSSION

The nephrotoxic of IoCM has an effect on increasing the TNF- $\alpha$ , MDA, and NGAL through an increase in free radicals, inflammatory pathway, and hypoxic medullary pathway<sup>5,11</sup>.

IoCM is an intravascular contrast medium made from Iodine with a non-ionic amide radical group (-CONH<sub>2</sub>).<sup>15</sup> vision these substances into the body potentially cause free radicals as Reactive<sup>18</sup> Oxygen Species (ROS). Free radicals met enzymes or long-chain unsaturated fatty acids (Polyunsaturated Fatty Acids) will result in lipid peroxidation process. This process produces several end-products including malondialdehyde (MDA). The excess of free radicals cause an increase of lipid peroxidation process and will increase MDA production<sup>24</sup>.

IoCM causes decrease of Nitric Oxide (NO) levels in the blood, increases the oxygen (O<sub>2</sub>) need and has a direct toxicity effect on renal tubular cells. This process occurs<sup>14</sup> cause of the use of IoCM will increase oxidative stress/ Reactive Oxygen Species (ROS) in the blood<sup>25-27</sup>. The formation of ROS triggers an increase of Malondialdehyde (MDA) and lipid peroxidation in the kidneys<sup>28-31</sup>. Physiologically, the formation of ROS triggers the superoxide ion (O<sub>2</sub><sup>-</sup>) and hydroxyl radicals (OH<sup>-</sup>)<sup>29</sup>. Increased of ROS will decrease antioxidants in the body. The reduced antioxidants role will reduce the activity of ROS prevention. ROS cause decrease of Glutathione Peroxide (GPx), Superoxide Dismutase<sup>32</sup> and Catalase (CAT) activities<sup>21,28,29,33,34</sup>.

Young Green Coconut Water contains<sup>2</sup> many minerals and vitamins including Fe, Mg, Zn, Se, Vitamin C, L-Arginine. The content of chemical compounds in coconut water will increase endogenous or primary antioxidant status. Bhagya. et.al explained that the provision of young coconut water in rats experiencing a fructose diet was effective in reducing oxidative stress and increasing antioxidant status<sup>23</sup>. The previous study also showed there was a significant increase in the status of enzymatic antioxidants such as SOD, CAT, and GPx ( $p < 0.005$ ) between mice given green coconut water and controls<sup>23</sup>. The increase of antioxidants in the body is needed to ward off oxidant attacks from in and outside the body.

## CONCLUSION

Provision of YGCW to experimental animals induced by IoCM reduced levels of TNF- $\alpha$ , NGAL and MDA<sup>17</sup> and repaired renal tubular cells, although the difference were not statistically significant ( $p > 0.05$ ). YGCW has the same effectiveness as NAC and potentially used as an alternative of prevention the CIN incidence.

Further research is needed on the duration of giving YGCW not only for 3 (three) days but up to 1 week in order to thoroughly determine the effect of YGCW on free radical decrease. Future studies could be scaled up to human subjects or diagnostic and/or interventional radiology patients.

**Acknowledgment:** Special thanks to Francisca Sri Wiryaningsih as a responsible of Veteriner Technology Laboratorium Universitas Gadjah Mada and also to Vocational School of Universitas Gadjah Mada.

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