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Lycopene in tomato as nephrotoxic and anti-inflammatory in welding workers exposed to cadmium

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Abstract

Objective: The aim of this study were to know the effect of administration tomato powder as anti nephrotoxic and anti inflammatory on welding workers exposed by Cd.

Methods: This research use observational analytical with cross-sectional design. Research subject consisted of 30 welding workers in Purwokerto aged 25-55 years with a work period more than 3 years. Welding workers were given tomato powder at 14 packs at a dose of 30 g for consumption for 14 days. On the 0th and 15th day, blood was taken to examine kidney function and inflammatory parameters. These data analyzed by paired t-test.

Results: The results showed blood Cd levels, Creatinine, β 2-microglobuline, Tumor Necrosis Factor- α and Cyclooxygenase-2 levels after being given tomato powder were very significant difference compare to before given tomatoes.

Conclusions: It can be concluded that the administration of tomato powder has an effect on improving kidney function. Tomatoes powder decrease in both blood Cd levels and proinflammatory cytokines in welding workers exposed by Cd.

Keywords: Cadmium, lycopene, antinephrotoxic, anti-inflammatory

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INTRODUCTION

Lycopene is one type of carotenoid compound found in tomatoes and gives red color to tomatoes and is often found in processed products from tomatoes such as tomato juice, tomato sauce and others. Lycopene has 40 acyclic carbon (C₄₀H₅₆) and 11 conjugated ring bonds in a linear manner. According to some researchers, lycopene has a potential effect as an antioxidant, 2 times greater than β -carotene, 10 times greater than vitamin E and 20 times greater than vitamin C [1], [2]. The biological activity of lycopene in protecting cells from oxidative damage due to free radicals attack is by stimulated the enzymatic antioxidants activity in the body such as Super Oxide Dismutase (SOD), Glutathione Peroxidase (GPx) and Catalase. The activities of enzyme will decrease due to heavy metals pollution for example from cadmium [3], [4], [5].

Cadmium is widely used in industries, such as the electroplating industry, paint and battery industry. Both acute and chronic Cd exposure are very dangerous for human health, because Cd is one of the causes of hypertension, musculoskeletal disease, kidney failure and atherosclerotic heart disease in humans [6], [7], [8]. Cadmium in the blood will bind to metallothione and cause increasing of free radicals in the body such as superoxide (O₂⁻) anion, hydroxyl radicals (OH[•]) and hydrogen peroxide (H₂O₂) result in oxidative stress and cause inflammation [9], [10]. Contamination of Cd in human reported in Mae Sot at Northwestern Thailand because people in this area exposed Cd after consumption rice and other crops that grown in this area [11], [12]. Cadmium exposure also occurred in

welding industry. Welding workshop workers are one group of individuals who are at risk of exposure to Cd and are at risk of developing hypertension [13].

Prevention of Cd poisoning can only be done by giving antioxidant compounds such as vitamin C, Vitamin E, and Selenium. The function of antioxidants is to reduce the absorption of Cd by the kidneys and help eliminate Cd from the body without damaging the kidneys. But antioxidants in the form of food supplements are expensive and can only be obtained by the upper middle class. Even though people at high risk of exposure to Cd are industrial workers who generally come from the lower middle class. To overcome Cd poisoning in the body, it is necessary to look for alternatives using natural antioxidants that are easily available and cheap, such as tomatoes [14],[15]. Based on these research we will apply tomato which contains lycopene at dose of 30 mg/BW to welding workers as a group of Cd exposure. The aim of the study was to determine the effect of giving dried tomato powder as an anti nephrotoxic and anti-inflammatory agent in welding workers exposed to Cd.

METHODS

The research used an observational analytical design with a cross-sectional approach. The subject cases in this study were welding workers in Purwokerto with inclusion criteria: respondents with a minimum work period of 3 years who were willing to sign the Informed Consent and exclusion criteria were respondents who were not present at the time of this study. Welding workers were given tomato powder @ 14 packs at a dose of 30 g for consumption for 14 days. On the 0th and 15th day, blood was taken to examine kidney function and inflammatory parameters. The independent variables in this study were blood Cd levels in welding workers, while the dependent variables were changes in creatinine, β 2-M, TNF- α and COX2 levels in the blood of welding workers. Parameters observed: levels of Cd, creatinine, β 2-M TNF- α and COX2 in the blood of welding workers.

a. The technique of data collection

1) Making of tomato powder by maceration methods [16]

Fresh tomatoes are cut into small pieces and then dried in the sun for 30 minutes, after wilting is put into the Fries Drying machine for 3 hours then blended into tomato powder. Weighed as much as 30 mg and put in a plastic bag. Packaging dried tomato powder was given to welders to be consumed for 14 days.

2) Submission of Ethical Clearance

Before the research was conducted the researchers submitted Ethical Clearance to the Ethics Commission of the Surakarta School of Medicine UNS. No 002/UN27.6/KEPKC/EC/2018

3) Blood Cd, kidney function and proinflammatory cytokines examination

Blood Cd examination with AAS at a wavelength of 228.6 nm and current strength of 3.5mA⁰[17] Blood creatinine using the kinetic Jaffe method [18] and measured on the Riele spectrophotometer, while the β 2-M, TNF- α , and COX2 levels examination using the ELISA Sandwich method[19] and Absorbance reading by ELISA readers at a wavelength 450nm.

b. Data Analyzed

Data from creatinine, blood CD β 2-M, TNF- α and COX2 level in welding workers before and after being given tomato powder were analyzed using a paired t-test.

RESULTS

1. Blood Cd levels

Table 1. Blood Cd levels before and after being given tomato on the 15th day

Respondent	Blood Cd level (ppm)
Before giving tomatoes	1.092±0.498
After giving tomatoes	0.701±0.137

Note: n=30, p<0.05, indicate a highly significant difference

2. β -2M level

Table 2. β -2M levels before and after being given tomato on the 15th day.

Respondent	β -2M level (mg/dL)
Before giving tomatoes	13.961±5.691
After giving tomatoes	9.78±3.521

Note: n=30, p<0.05, indicate a highly significant difference

3. Creatinine levels

Table 3. Creatinine level before and after being given tomato on the 15th day.

Respondent	Creatinine level (mg/dL)
Before giving tomatoes	1.460±0.794
After giving tomatoes	0.880±0.327

Note: n=30, p<0.05, indicate a highly significant difference

4. TNF α levels

Table 4. TNF α level before and after being given tomato on the 15th day

Respondent	TNF α level (ng/ml)
Before giving tomatoes	12.552±4.099
After giving tomatoes	9.58 ±3.521

Note: n=30, p<0.05, indicate a highly significant difference

5. COX2 levels

Table 5. COX2 level before and after being given tomato on the 15th day

Respondent	COX2 level (ng/ml)
Before giving tomatoes	7.03±2.842
After giving tomatoes	5.26±2.569

Note: n=30, p<0.05, indicate a highly significant difference

DISCUSSION

These results from the average of Cd exposure in welding workers were 1,092 ±0.498 (Table 1). The normal value of Cd exposure was less than 1 ppm but in this research Cd value was higher than >1ppm. It was indicated that welders had experienced exposure to Cd. In the welding, process smoke is generated containing Cd²⁺ and Cd oxide (CdO) which can enter the body of the welding workers through inhalation pathways. Approximately 10 to 50% of Cd exposure comes from smoke, steam, dust and in the blood of welding workers. Cadmium exposure will cause

damage to the proximal renal tubular membrane. Kidney dysfunction causes inhibition of salt reabsorption, reduction in reabsorption of water resulting in an increase in urine volume and an increase in the amount of urine protein (proteinuria). Proteinuria can be detected by increasing low molecular proteins such as β 2 microglobulin. The level of β 2-M will increase if there is a decrease in the glomerular filtration rate. Initial β 2-M level on welding workers before administration of tomato was higher than normal value (Table 2). The normal value of β 2-M level in the human range between 9.5- 11 mg/dL [19],[20],[21]. Cadmium level after administration tomato powder decreased in average of 0.701 ± 0.137 ppm (Table 1). Tomato powder contains lycopene and beta carotene which are derivatives of flavonoids. Flavonoids will donate H^+ to free radicals that increase due to the bond Cd with Mt (Cd + Mt), so it becomes neutral [5], [14]. The human body has the glutathione S-transferase (GST) enzyme which can chelate cadmium which enters the body and is converted into mercapturic acid. The GST enzyme requires glutathione (GSH) for its activation. Initially Cd that enter the body easily binds to GSH so that GST activity will decrease because Cd ions and free radicals are too much, but by giving H^+ donors to free radicals, Cd bonded with GSH can be released so that the GST enzyme activity increases because can reuse the GSH substrate [14], [15].

The level of creatinine of welding worker increased after exposed by $CdSO_4$ (>1 mg/dL) (Table 3). Creatinine values in the case subjects exceeded the normal values of blood creatinine which are >0.7 - 1.3 mg/dL. Creatinine is a metabolic result of creatine and phosphocreatine. Creatinine is filtered in the glomerulus and reabsorbed in the kidney tubules. If kidney dysfunction occurs and LFG decreases due to Cd exposure, kidney filtration ability to creatinine will decrease so that serum creatinine will increase. A doubling of blood creatinine levels indicates a decrease in kidney function by 50% [22],[23]. After the administration of tomato powder containing lycopene, the glomerular filtration rate increases, because free radicals that increase as O_2^- and OH^- due to Cd + Mt bonds can be neutralized by the administration of H^+ donors from lycopene, so that the β 2-M levels decrease. Giving tomato powder for 14 days to welding workers causes a decrease in blood creatinine levels. The biological activity of lycopene in protecting cells from oxidative damage due to attacks by free radicals is to stimulate the activity of enzymatic antioxidants in the body such as Super Oxide Dismutase (SOD), Glutathione Peroxidase (GPx) and Catalase, which levels decrease due to exposure to heavy metals from environments such as cadmium. Increase in antioxidant enzymes in welding worker can prevent kidney damage and improve the Glomerular Filtration Rate, so that the creatinine levels decrease [3], [24].

Cadmium exposure causes inflammation of the kidneys. In the inflammatory reaction, $TNF-\alpha$ cytokines will activate the macrophages in the kidneys, namely mesangial macrophage, leading to inflammation in the renal proximal tubule. This causes an increase in $TNF-\alpha$ levels (Table 4). $TNF-\alpha$ produced by macrophages were also activates the formation of adhesion molecules E-selectin and IL-1 activates the ICAM-1 adhesion, this causes an increase in vascular permeability and it will cause inflammation got worse [25],[26]. In the next process, macrophages will degrade the phospholipid membrane in kidney proximal tubules and with the help of phospholipase A2 enzyme phospholipid converted to arachidonic acid. Furthermore, arachidonic acid will be converted into prostaglandin by the cyclooxygenase-2 enzyme. The increasing of COX-2 level in welding workers blood due to an inflammatory process induced by Cd exposure. The COX-2 enzyme converts arachidonic acid into prostaglandins, one of the inflammatory mediators, with the aim of overcoming inflammation caused by exposure to Cd. This causes an increase in COX-2 levels [27],[28].

After the welders consumed tomato $TNF-\alpha$ level increase (Table 4). Lycopene contained in tomato powder can inhibit activation of nuclear factor Kappa β (NFkB) which is a mediator of proinflammatory $TNF-\alpha$ cytokines so that excessive inflammation can be controlled. Lycopene in tomatoes also contains vitamin C and vitamin E which can break the chain of lipid peroxidation and neutralize exposure to Cd. This is consistent with the opinion of [1] which states that lycopene contains carotenoids (α - β - and γ -carotene, lutein) and flavonoids. The number of double bonds conjugated to lycopene causes lycopene to have a very strong strength as an antioxidant and anti-inflammatory [15], [29], [30]. Giving tomato powder for 14 days can also reduce COX-2 levels in welders (Table 5). Tomato powder in addition to lycopene also contains flavonoids. Flavonoid compounds can inhibit the activity of

cyclooxygenase-2 and lipooxygenase, so that it can inhibit the formation of arachidonic acid and the release of proinflammatory mediators namely prostaglandins and leucotrien so the COX-2 level will decrease [14], [31].

Tomato powder given to welding workers at a dose of 30 mg for 14 days can reduce blood Cd levels, creatinine, β 2-M levels, TNF- α levels, and COX-2 levels. Lycopene in tomato powder has an anti nephrotoxic and anti-inflammatory effect in exposed individuals Cd represented by welding workers.

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