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COFFEE CONSUMPTION MAY DECREASE THE SERUM CREATININE AND PLASMA MALONDIALDEHYDE LEVELS IN RATS WITH HYPERURICEMIA INDUCED BY A HIGH PURINE DIET

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ABSTRACT

The aim of this research was to determine the effect of coffee on creatinine and plasma malondialdehyde (MDA) level in rats fed on high purine diet. A total of 24 male Wistar rats divided into 4 groups of 6 rats each. Beef broth were given to 3 groups (K1, P1, P2) for thirty days. Beef broth administration were followed by giving coffee (caffeinated= P1 or by a decaffeinated= P2, 144 mg/200 g BW). Serum creatinine levels and plasma MDA were examined periodically on day 0, 15, and 30. Data were analyzed by multivariate analysis of variance or MANOVA test (CI= 95%, P<0.05). Coffee administration (caffeinated and decaffeinated) may decrease the serum creatinine (day-30, K1= 3.17± 0.69; P1= 1.63±0.11; P2= 1.14±0.08) and MDA levels (day-30, K1= 9.8±0.28; P1= 5.80±0.55, P2= 3.87±3.26) after 30 days of treatment (P= 0.000 for creatinine and MDA levels in K1, P1, P2 groups). A lower serum creatinine and MDA levels can be found in decaffeinated coffee grup. Coffee consumption for 30 days (especially decaffeinated) may decrease serum creatinine and plasma MDA in rat induced by a high purine diet.

Key words: coffee, creatinine, malondialdehyde, high-purine diet

ABSTRAK

Tujuan dari penelitian ini adalah mengetahui pengaruh konsumsi kopi terhadap kadar kreatinin dan malondialdehida darah tikus (MDA) yang diinduksi oleh diet tinggi purin. Sebanyak 24 ekor tikus Wistar jantan dibagi menjadi 4 kelompok (n= 6). Kaldu sapi diberikan kepada 3 kelompok selama tiga puluh hari (K1, P1, P2). Pemberian kaldu sapi dilanjutkan dengan pemberian kopi (berkafein= P1 atau tidak berkafein= P2, 144 mg/200 g bobot badan). Kadar kreatinin serum dan MDA plasma diperiksa secara berkala pada hari ke 0, 15, dan 30. Data dianalisis dengan uji MANOVA (CI = 95%, P<0,05). Pemberian kopi dapat menurunkan kadar kreatinin serum (hari-30, K1=3.17±0.69; P1=1.63±0.11; P2= 1.14±0.08) dan kadar MDA plasma (hari-30, K1= 9.8±0.28; P1= 5.80±0.55, P2= 3.87±3.26) setelah 30 hari perlakuan (P= 0.000 untuk kadar kreatinin dan MDA di kelompok K1, P1, P2). Kadar kreatinin dan MDA yang lebih rendah dapat dijumpai pada kelompok yang mendapatkan kopi yang tidak berkafein. Konsumsi kopi selama 30 hari (terutama yang tidak berkafein) dapat menurunkan kadar kreatinin dan MDA pada tikus yang diinduksi diet tinggi purin.

Kata kunci: kopi, kreatinin, malondialdehid, diet tinggi purin

INTRODUCTION

Kidneys are an essential organ in which 2/3 of uric acid is excreted to maintain the balance of its levels in the body. Impaired renal excretion is recognized as the main cause of hyperuricemia, while a rise in uric acid levels indirectly induces increased creatinine levels and oxidative stress. Johnson *et al.* (2018) stated that hyperuricemia can activate the renal and systemic renin-angiotensin-aldosterone system (RAAS), trigger oxidative stress, and lead to the loss of endothelial nitric oxide. Abnormally high concentrations of uric acid also stimulate the nuclear factor-kappa B (NFkB), a proinflammatory transcription factor, thereby increasing the synthesis of proinflammatory cytokines, such as interleukin-1β, interleukin-6, and tumor necrosis factor-α. As time passes, this will result in inflammation and microvascular changes in the kidney, some of which observable manifestations include a decline in the glomerular filtration rate (GFR) along with elevated creatinine levels that can eventually lead to chronic renal failure (Sautin *et al.*, 2011; Johnson *et al.*, 2018).

A study by Hall *et al*. (2018) revealed that creatinine level in hyperuricemic patients significantly increase if the kidney is damaged. The hyperuricemic condition (induced by the administration of 750 mg/kg BW oxonate acid for 12 weeks) raised the level of oxidative stress in the kidney (Cristóbal-García *et al.*, 2015). Such increase can eventually cause glomerular hypertension due to increased renal vascular resistance and decreased blood flow to the kidney (Sah and Qing, 2015). Hyperuricemic conditions can also cause by excessive consumption of a high-purine diet (Villegas *et al.*, 2012; Babiker, 2016; Hong *et al.*, 2020). Long-term consumption of a high-protein (high-purine) diet can also lowering the glomerular filtration rate and cause mild damage to the kidneys (Hong *et al.*, 2020). Elevated creatinine levels and oxidative stress in the body indicate an increased risk of kidney disorders. It is therefore important to undertake appropriate interventions to prevent further complications associated with hyperuricemia in the kidney (creatinine levels) and systemic condition (concentration of free radicals).

A cross sectional study has proved that coffee consumption can reduce serum creatinine levels. A previous study of coffee consumption habits involving 2.673 people aged 35-84 years found that the group consuming more than 2 cups of coffee per day

demonstrated lower serum creatinine levels compared to those who consumed either less than 1 cup per day or only 1 cup per day (Kim *et al.*, 2013). The effect of coffee on hyperuricemia was not affected by its caffeine content. Research shows that tea consumption (also contains caffeine) is not able lowering uric acid levels. This indicates that other compounds in the coffee such as antioxidant are responsible for lowering uric acid levels (Choi and Curhan, 2010). Chlorogenic acid and diterpenes, that are believed to be capable of combating the effect of oxidants of hiperurisemic condition (Martini *et al.*, 2016). With its antioxidant content, coffee also plays a role in reducing oxidative stress. Previous experimental research on consumption of 24 g of coffee per day for one week by 11 healthy people aged 10-31 years found a significant decline in malondialdehyde (MDA) concentrations (Yukawa *et al.*, 2004). Scientific evidence related to the potential of coffee consumption in preventing kidney abnormalities was still limited. Therefore, this study will investigate the protective effect of coffee consumption in preventing kidney disorders through observation of creatinine and serum MDA levels. To find out whether caffeine content effect on creatinine and MDA level, we used two types of coffee (caffeinated and non-caffeinated coffee). In addition, this study will also examine the duration required for the protective effect of coffee consumption on kidney function.

MATERIALS AND METHODS

The research had been approved by the Ethics Committee of the Faculty of Medicine Gadjah Mada University. The study was conducted at the Inter-University Center (PAU) Laboratory of Gadjah Mada University.

Sampling Technique

This study involved male Wistar rats (*Rattus norvegicus*) weighed 180-220 g, healthy and aged 8-10 weeks. The rats were excluded if they undergo physical changes associated with a physically-observable disease (inactive, impaired, and looking sick), refuse feeding during the study, and were involved in previous experiments. There were four grup in this study, named group K1, K2, P1, and P2. K1 group were fed by high purine diet (possitive control grup) and K2 were grup with normat diet (negative control group). P1 group were fed by high purine diet and followed by caffeinated coffee, while P2 group were fed by high purine diet and followed by decaffeinated coffee. Based on Charan and Kantharia (2013) the minimum number of samples is 14-24 rats with 4-6 rats per group. In this study, we used 24 rats (6 rats each groups, 4 groups).

Administration of High-Purine Diet and Coffee

A high-purine diet was given through oral administration of beef broth (700 mg/kg BW/day dissolved in 1 mL of water) to K1, P1, and P2 groups. The coffee was administered immediately after the administration of high-purine diet (144 mg/200 g BW dissolved in 2.7 mL of water). All the treatment (beef broth and coffee) were given once a day for 30 consecutive days. The coffee used in this study is an instant coffee which is often found in the market in Indonesia. Both types of this coffee come from the same brand, but only differ in their caffeine content.

Serum Creatinine and Plasma Malondialdehyde Test

Blood sampling for creatinine and MDA levels was conducted simultaneously at the predetermined days (day-0/ before the induction of high purine diet, day-15 and day-30). The experimental animals were fasted for 8 hours prior to sampling. Blood was taken by penetrating the retro-orbital sinus in the eye using a microhematocrit tube. The total blood collected was 4 mL (2 mL for each test on day-0, 15, and 30). For serum creatinine levels, blood was collected in Eppendorf tubes without anticoagulant, whereas for MDA, blood was put in tubes containing EDTA. To examine the serum creatinine levels, the sample was left to coagulate and then centrifuged at 4.000 rpm for 10 minutes. The serum was drawn using a micropipette and transferred to an empty eppendorf tube. The collected serum specimen was then analyzed for the creatinine levels using the Jaffe Reaction method (Küme *et al.*, 2018). To test the plasma MDA levels, the blood specimen was centrifuged at 4.000 rpm for 10 minutes. The obtained plasma was then taken and transferred to an empty eppendorf tube to be analyzed for the MDA levels using the Thiobarbituric Acid Reactive Substances (TBARS) method (Fidianingsih and Ahsani, 2018).

Data Analysis

All data were analyzed by using SPSS (95% CI and 5% α). Creatinine and MDA and levels were performed as mean ± standard deviation. The MANOVA test was performed with 95% CI and 5% α. The statistical tests were significant when the p value was <0.05.

RESULTS AND DISCUSSION

This study shows that coffee consumption (both caffeinated coffee and decaffeinated coffee) may lowering the serum creatinine levels and also plasma MDA levels after 30 days of treatment. On day 15, elevated serum creatinine and MDA levels were found in the positive control group and treatment groups. Between day 15 and 30, the positive control group had considerably lower changes in serum creatinine and MDA levels compared to the coffee treatment groups. On day 30, the changes in serum creatinine and MDA levels were most evident in the group given decaffeinated coffee (P2) as opposed to those on day 15 (Figure 1). There were significant differences in

serum creatinine and MDA levels among different groups (Table 1).

Administration of beef broth leads to increased creatinine levels, which becomes the marker of impaired kidney function, as beef broth is among purine-rich proteins. Elevated creatinine levels due to administration of high-protein diet are in line with a previous study of high-protein diet administration (25% of total calories) to 164 subjects for a 6-week intervention. The results indicated a marked increase of 0.02 mg/dL in serum creatinine levels (Juraschek *et al.*, 2013). Similarly, another study comparing consumption of usual-protein diet (1.3 g/kg BW) and low-protein diet (0.575 g/kg BW) showed considerably higher serum creatinine levels in subjects consuming usual-protein diet compared to those eating low-protein diet (Tangri *et al.*, 2011).

This study found that both caffeinated coffee and decaffeinated coffee significantly lowering the creatinine and MDA levels on day 30. Research by Hall *et al.* (2018) shows that no significant differences on caffeinated and decaffeinated coffee content other than the caffeine. Coffee contains chlorogenic acid, melanoidins, trigonelline, diterpenes, cafestol, and kahweol. These compounds has an antioxidant, antihypertensive, and hypoglycemic properties that comprehensively contribute to renoprotective effects (Lew *et al.*, 2018). In general, these compounds also play a role in neutralization of reactive oxygen species (Martini *et al.*, 2016).

The effect of coffee on decreased serum creatinine levels has also been demonstrated in a number of studies. A Randomized Controlled Trial (RCT) found that coffee administration can inhibit increased serum

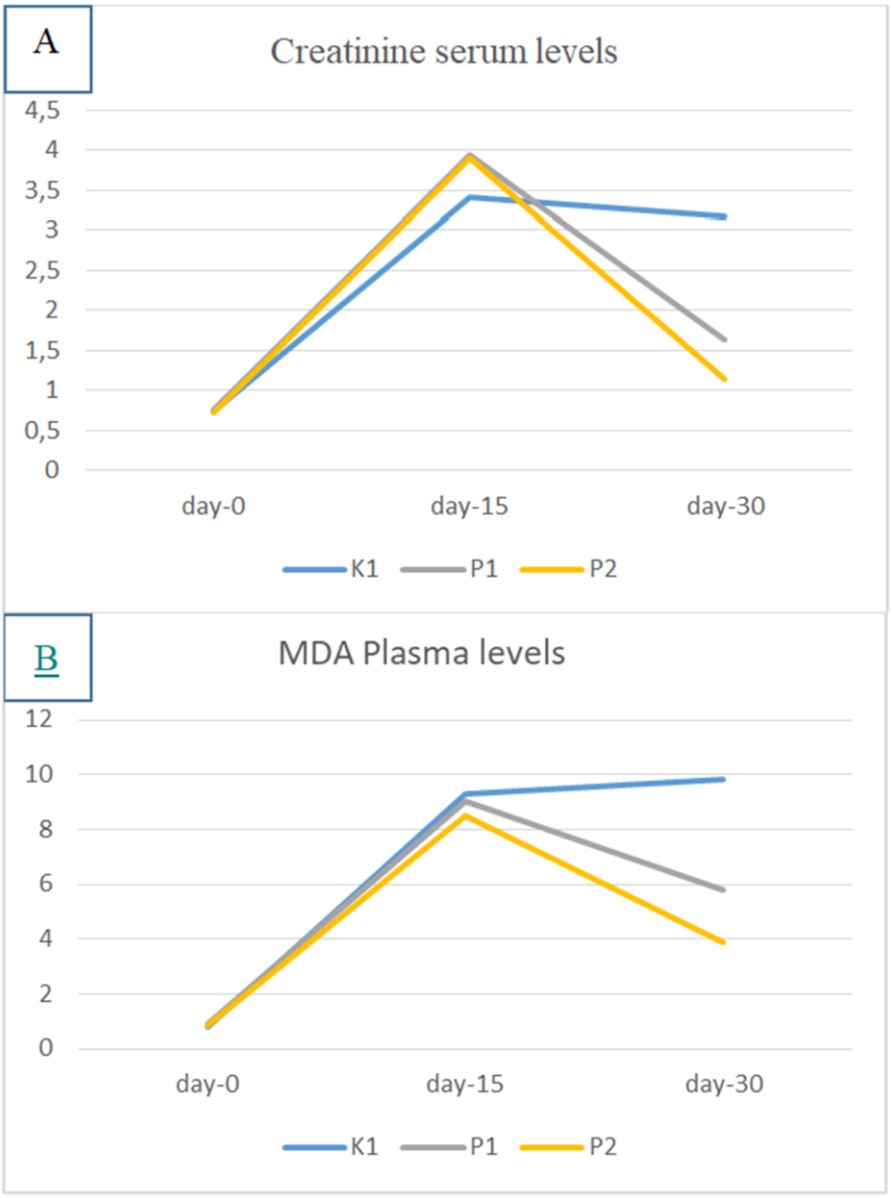

Figure 1. Serum creatinine and MDA levels in hyperurisemia induced high purine diet rats. Lower creatinine (A) and MDA level (B) can be seen in coffee consumption groups after 30 days. Decaffeinated groups (P2) has the lowest creatinine levels among three groups. K1 = Positive control (induced by high-purine diet), P1 = Induced by high-purine diet and caffeinated coffee, P2 = Induced by high-purine diet and decaffeinated coffee.

Table 1. MANOVA test of creatinine and MDA Levels

Parameter	Group	Days	n	Mean±SD	P-value
Kreatinine	K1	0	6	0.75±0.03	0.000*
		15	6	3.41±0.09	
		30	6	3.17±0.69	
	K2	0	6	0.71±0.03	0.086
		15	6	0.74±0.48	
		30	6	0.75±0.02	
	P1	0	6	0.76±0.02	0.000*
		15	6	3.95±0.02	
		30	6	1.63±0.11	
	P2	0	6	0.72±0.022	0.000*
		15	6	3.90±0.10	
		30	6	1.14±0.08	
MDA	K1	0	6	0.80±0.15	0.000*
		15	6	9.28±0.34	
		30	6	9.80±0.28	
	K2	0	6	0.89±0.15	0.022*
		15	6	0.95±0.15	
		30	6	1.20±0.22	
	P1	0	6	0.90±0.16	0.000*
		15	6	9.04±0.44	
		30	6	5.80±0.55	
	P2	0	6	0.86±0.12	0.000*
		15	6	8.51±0.39	
		30	6	3.87±3.26	

*= P<0.05, K1 = Positive control (induced by high-purine diet), K2 = negative control, P1 = Induced by high-purine diet and caffeinated coffee, P2 =Induced by high-purine diet and decaffeinated coffee

creatinine levels in alcohol-induced rats (Islam *et al.*, 2016). A cross-sectional study showed that coffee consumption habits significantly correlate with a reduced risk of kidney damage (Kim *et al.*, 2013). Equally, another study also indicated that the coffee drinker group has a significantly higher GFR compared to the group of non-coffee drinkers (Kotani *et al.*, 2010). Nakajima *et al.* (2010) also suggested that coffee drinking habits are associated with decreased serum creatinine levels and increased GFR. The results of their study indicated lower mean levels of serum creatinine in the coffee drinker group compared to those in the non-coffee drinker group although the difference is insignificant.

Beef broth administration can also increase MDA levels, which was shown in a randomized clinical trial with 8-week intervention, resulting in elevated MDA levels in the high-protein diet group and declined MDA in the standard-protein diet group (Prasetya *et al.*, 2018). The mechanism associated with the consumption of high-protein diet involves glomerular pressure and hyper filtration in the kidney, thereby affecting impairment of kidney function and the onset of oxidative stress (Martin *et al.*, 2005). Previous studies have also revealed the effect of coffee on reduced plasma MDA levels. Research by Aritanoga *et al.* (2019) suggested that the administration of Arabica-Gayo coffee can significantly reduce MDA levels. A RCT conducted by Abidah *et al.* (2017) on Robusta coffee administered to psychological stress-induced Wistar rats found significantly lower MDA levels in all treatment groups when compared to those in the stress control group.

On day 15, the treatment groups (P1 and P2) had higher serum creatinine levels compared to the positive control group (K1). In contrast, lower plasma MDA levels were found in the treatment groups as opposed to the positive control group. This is consistent with a number of previous findings in which short-term coffee consumption increases creatinine levels. Some literature mentioned that such mechanism is associated with increased of adrenaline concentration. Increased of adrenaline concentration affect the kidney function, marked by reduced GFR. However, the increased of adrenaline concentration is only be found in people who not regularly consume coffee. No increased of adrenaline concentration can be found in people who drink coffee for four weeks

(Pourshahidi *et al.*, 2016). Other studies shows that a short-term coffee consumption (6 mg/kg BW coffee for four days) may increase the creatinine levels (Grandjean *et al.*, 2000). Therefore, the higher creatinine levels on day-15 in the treatment group is likely caused by combined effects of increasing glomerular pressure, renal hyperfiltration and also adrenaline concentration due to short term of coffee consumption. On contrary to MDA levels, this studies shows that, coffee administration may lower MDA level in a short time. This is in line with Aritanoga *et al.* (2019) which show that a lower MDA levels can be found in people after one hour consuming coffee. The lowering effect of MDA level is due to chlorogenic acid. The chlorogenic acid in coffee can reduce inflammation and oxidative stress in a short time. Although both types of coffee (caffeinated and decaffeinated coffee) in this studies have a similar effect on creatinine and MDA levels in hyperuricemia induced by a high-purine diet condition. It is necessary to consider other side effects that arise from coffee use, especially in hypertensive patients and chronic kidney failure.

CONCLUSION

Coffee administration (caffeinated and decaffeinated) may decrease the serum creatinine and MDA levels after 30 days of treatment. A lower serum creatinine and MDA levels can be found in decaffeinated coffee grup.

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REFERENCES

Abidah, R.S., B. Wirjatmadi, B. Purwanto, and M. Adriani. 2017. Robusta coffee decreased malondialdehyde levels in wistar mice experiencing oxidative stress. **Health Nations.** 1(4):330-334.

Aritanoga, M., C. Effendi, and L. Herawati. 2019. Kopi arabika-gayo menurunkan MDA dan meningkatkan SOD setelah latihan fisik akut submaksimal pada pria. **J. Sumberdaya Hayati.** 5(2):58-63.

Babiker, M. 2016. Intake of purine-rich foods, total meat, seafood and dairy products and relationship to serum of uric acid. **Am. J. Biomed. Sci**. 14(3):35-43.

Charan, J. and N. Kantharia. 2013. How to calculate sample size in animal studies?. **J Pharmacol. Pharmacother.** 4(4):303-306.

Choi, H.K. and G. Curhan. 2010. Coffee consumption and risk of incident gout in women: The nurses health study. **Am. J. Clin. Nutr**. 92(4):922-927.

Cristóbal-García, M., García-Arroyo, E. Tapia, H. Osorio, A.S. Arellano-Buendía, M. Madero, B. Rodríguez-Iturbe, J. Pedraza-Chaverrí, F. Correa, C. Zazueta, R.J. Johnson, and S.L. Laura-Gabriela. 2015. Renal oxidative stress induced by long-term hyperuricemia alters mitochondrial function and maintains systemic hypertension. **Oxid. Med. Cell. Longev.** Doi:10.1155/2015/535686.

Fidianingsih, I. and D.N. Ahsani. 2018. Age-related changes of malondialdehyde, body weight and organ weight in male mice. **UnivMed.** 37(2):115. Doi: 10.18051/univmed.2018.v37.115-126.

Grandjean, A.C., K.J. Reimers, K.E. Bannick, and M.C. Haven. 2000. The effect of caffeinated, non-caffeinated, caloric and non-caloric beverages on hydration**. J. Am. Coll. Nutr**. 19(5):591-600.

Hall, S., J. Yuen, and G. Grant. 2018. Bioactive constituents in caffeinated and decaffeinated coffee and their effect on the risk of depression-A comparative constituent analysis study. **Beverages.** 4(4):79. Doi:10.3390/beverages4040079.

Hong, F., A. Zheng, P Xu, J. Wang, T. Xue,S. Dai, S. Pan,Y. Guo,X. Xie,L. Li,X. Qiao,G. Liu, and Y. Zhai. 2020. High-protein diet induces hyperuricemia in a new animal model for studying human gout. **Int. J. Mol. Sci**. Doi:10.3390/ijms21062147.

Islam, M.T., M. Islam, M. Hossain, and M. Wares. 2016. Kidney histotexure and serum creatinine level in response to concurrent administration of alcohol and coffee in mice. **Bangl. Vet.** 32(2):42-47.

Johnson, R.J., G.L. Bakris, C. Borghi, M.B. Chonchol, D. Feldman, M.A. Lanaspa, T.R. Merriman, O.W. Moe, D.B. Mount, S.L.G. Lozada, E. Stahl, D.E. Weiner, and G.M. Chertow. 2018. Hyperuricemia, acute and chronic kidney disease, hypertension, and cardiovascular disease: Report of a scientific workshop organized by the national kidney foundation. **Am. J. Kidney Dis**. 71(6):851-865.

Juraschek, S.P., L.J. Appel, C.A.M. Anderson, and E.R. Miller. 2013. Effect of a high-protein diet on kidney function in healthy adults: Results from the omniheart trial. **Am. J. Kidney Dis**. 61(4):547-554.

Kim, B.H., Y.S. Park, H. M. Noh, J.S. Sung, and J.K. Lee. 2013. Association between coffee consumption and renal impairment in Korean women with and without diabetes: Analysis of the fourth Korea national health and nutrition examination survey in 2008. **Korean J. Fam. Med.** 34(4):265-271.

Kotani, K., N. Sakane, and N. Taniguchi. 2010. Association between coffee consumption and the estimated glomerular filtration rate in the general Japanese population: Preliminary data regarding C-reactive protein concentrations. **Clin. Chem. Lab. Med.** 48(12):1773-1776.

Küme, T., B. Sağlam, C. Ergon, and A.R. Sisman. 2018. Evaluation and comparison of Abbott Jaffe and enzymatic creatinine methods: Could the old method meet the new requirements?. **J. Clin. Lab. Anal.** 32(1):e22168. Doi: 10.1002/jcla.22168.

Lew, Q.L.J., T.H. Jafar, A. Jin, J.M. Yuan, and W.P. Koh. 2018. Consumption of coffee but not of other caffeine-containing beverages reduces the risk of end-stage renal disease in the Singapore Chinese Health Study. **J. Nutr.** 148(8):1315-1322.

Martin, W.F., L.E. Armstrong, and N.R. Rodriguez. 2005. Dietary protein intake and renal function. **Nutr. Metab.** Doi:10.1186/1743-7075-2-25.

Martini, D., C.D. Bo, M. Tasooti, P. Riso, D.D. Rio, F. Brighenti, and M. Porrini. 2016. Coffee consumption and oxidative stress: A review of human intervention studies. **Molecules.** Doi:10.3390/molecules21080979.

Nakajima, K., K. Hirose, M. Ebata, K. Morita, and H. Munakata. 2010. Association between habitual coffee consumption and normal or increased estimated glomerular filtration rate in apparently healthy adults. **Br. J. Nutr.** 103(2):149-152.

Pourshahidi, L.K., L. Navarini, M. Petracco, and J.J. Strain. 2016. A comprehensive overview of the risks and benefits of coffee consumption. **Compr. Rev. Food Sci. Food Saf.** 15(4):671-684.

Prasetya, S.I., J. Jutamulia, A. N. Paranoan, F. Witjaksono, and N. Mudjihartini. 2018. Comparison of plasma malondialdehyde and glutathione levels between low calorie high protein diet to standard protein in obese individuals with weight cycling – A randomised trial. **F1000Research.** 7:446. Doi:10.12688/F1000RESEARCH.13227.1.

Sah, O.S.P. and Y.X. Qing. 2015. Associations between hyperuricemia and chronic kidney disease: A review. **Nephrourol. Mon.** Doi: 10.5812/numonthly.7(3)2015.27233.

Sautin, Y.Y., W. Imaram, K. Kim, A. Angerhofer, G. Henderson, and R. Johnson. 2011. Uric Acid and Oxidative Stress. In **Studies on Renal Disorders**. Miyata, T., K. Eckardt, and M. (Eds.). Nangaku. Humana Press, New Jersey, NJ, USA.

Tangri, N., L.A. Stevens, C.H. Schmid, Y. Zhang, G. Beck, T. Greene, J. Coresh, and A.S. Levery. 2011. Changes in dietary protein intake has no effect on serum cystatin C levels independent of the glomerular filtration rate. **Kidney Int.** 79(4):471-477.

Villegas, R., Y.B. Xiang, T. Elasy, W.H. Xu, H. Cai, Q. Cai, M.F. Linton, S. Fazio, W. Zheng, and X.O. Shu. 2012. Purine-rich foods, protein intake, and the prevalence of hyperuricemia: The Shanghai men's health study. **Nutr. Metab. and Cardiovasc. Dis.** 22(5):409-416.

Yukawa, G.S., M. Mune, H. Otani, and Y. Tone. 2004. Effects of coffee consumption on oxidative susceptibility of low-density lipoproteins and serum lipid levels in humans. **Biochemistry.** 69(1):70-74.