2.14 Oxidative

by Hery Winarsi

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Improving oxidative stress and inflammation status of obese women with metabolic syndrome using phenolic-rich red kidney bean sprout milk yogurt

[1]*Winarsi, H. and [2]Septiana, A. T.

[1]*Department of Nutrition Science, Faculty of Health Sciences, Universitas Jenderal Soedirman, Purwokerto, 53123, Central Java, Indonesia*
[2]*Department of Food Technology, Faculty of Agriculture, Universitas Jenderal Soedirman, Purwokerto, 53123, Central Java, Indonesia*

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Abstract

Oxidative stress and inflammation are involved in the pathogenesis of metabolic syndrome (MetS). Antioxidant-rich food products are known for improving the oxidative stress and inflammation as well as inhibiting the development of metabolic syndrome. The present work thus aimed to determine the effects of phenolic-rich red kidney bean sprout milk yogurt (RKBSMY) on superoxide dismutase (SOD) activity, TNF-α level, and body mass index (BMI) of women with MetS. Thirty obese women with MetS, low SOD activity, and high TNF-α level served as research subjects. The 2-month intervention using red kidney bean sprout milk yogurt (RKBSMY) with 2% lactic acid bacterial starter, 10% sucrose, and 24-h fermentation was conducted to women with MetS. Results showed that RKBSMY increased the SOD activity from 5.13 to 8.02 ng/mL ($p = 0.047$), decreased the plasma TNF-α level from 60.89 to 39.77 pg/mL ($p < 0.05$), and decreased the BMI from 28.04 to 24.38 kg/m^2. Therefore RKBSMY could be beneficial for people with degenerative diseases associated with oxidative stress.

Introduction

Various factors can trigger the emergence of metabolic syndrome (MetS) which is a group of simultaneously occurring metabolic disorders. These disorders include the increase in high blood pressure, accumulation of fat in stomach, increase in blood sugar, and increase in cholesterol and triglyceride levels. These are usually triggered by the oxidative stress and inflammatory conditions.

The development of MetS may also lead to type 2 diabetes mellitus and cardiovascular disease (Alshehri, 2010). Montague and O'Rahilly (2000) added that obesity is a major MetS-causing component; however, its role is still unclear. Under the obesity conditions, adipose cells produce TNF-α active molecule, and release both interleukin-6 (IL-6) and C-reactive protein (CRP), as well as pro-inflammatory cytokines (Winarsi *et al.,* 2016). TNF-α has been recognised as a pro-inflammatory cytokine which has an important role in the pathogenesis of a number of chronic inflammatory diseases. The increase in TNF-α contributes to the development of thrombosis and insulin resistance (Nair *et al.,* 2006). Therefore, it is important to control inflammation since it is believed as the key to the development of MetS.

Additionally, obesity also triggers the systemic oxidative stress associated with high body mass index (BMI) and accumulated fat which further underlies the dysregulation of adipocytokine and development of MetS. Winarsi *et al.* (2012) reported that high oxidative stress is mostly found in women aged > 40 years. This population subgroup often has low activity of superoxide dismutase (SOD) and high levels of CRP and TNF-α (Winarsi *et al.,* 2015). Shahbazian *et al.* (2013) said that the risk of MetS in women is higher than in men. Some researchers reported that oxidative stress interferes with glucose absorption (Krishna *et al.,* 2015), decreases insulin secretion, underlies hypertension, and even damages blood vessel walls (Wu *et al.,* 2014). It is therefore imperative to tackle oxidative stress and reduce BMI of people with MetS.

Food products rich in phenolic antioxidants can improve oxidative stress, including increasing the activity of antioxidant enzymes such as SOD (Winarsi *et al.,* 2016; Şenay *et al.,* 2019), inflammation status (including decreasing the levels of cytokines such as IL-6, CRP, and TNF-alpha) (Yehuda *et al.,* 2015), and normalisation of women's weight (Guo *et al.,* 2017). Winarsi *et al.* (2019)

*Corresponding author.
Email: winarsi12@gmail.com

reported that red kidney bean sprout milk yogurt (RKBSMY) contained 993.08 ppm of phenolic antioxidants.

Phenolic acts as the direct scavengers of superoxide anion by cutting the elongation of free-radical oxidation chain or scavenging the free radicals (Rosignoli *et al.,* 2013). Flavonoids, one of the phenolic compounds, have antiradical properties especially against hydroxyl, superoxide anions, peroxyl, and alkoxyl radicals. The presence of these flavonoid compounds has a very strong affinity for Fe ions, a catalyst for free-radical formation (Fu *et al.,* 2013). Phenolics also have anti-inflammatory properties by inhibiting the synthesis of pro-inflammatory mediators, modifying eicosanoid, inhibiting the activation of immune cells, and inhibiting the activity of nitric oxide synthase (NOS) and cyclooxygenase-2 (Chuang and McIntosh, 2011). The research question of the present work was whether or not the phenolic content of RKBSMY could improve the antioxidant status, inflammation status, and BMI in women with MetS. The present work thus aimed to determine the effects of RKBSMY on SOD activity, TNF-α level, and BMI of women with MetS.

Materials and methods

The present work employed a true experimental design, and has obtained the ethical approval from the Health Research Ethics Commission (*Komisi Etik Penelitian Kesehatan; KEPK*) from the Faculty of Medicine, Jenderal Soedirman University (reference no.: 3343/KEP-K/VII/2019).

Production of RKBSMY

Sucrose (10%) and skim milk (10%) were added to red kidney bean sprout milk (RKBSM). The milk was pasteurised at 70°C for 10 min, and then cooled to 45°C. The milk was inoculated with commercial lactic acid bacteria (LAB) starters at 2% of milk's total volume. The milk was then incubated at the room temperature (27 - 35°C) for 24 h (Winarsi *et al.,* 2019).

Research subjects

A total of 30 women with MetS served as the research subjects with the following inclusion criteria: aged 45 - 80 years, having central obesity, inflammation, and oxidative stress, not leaving the research site for two months, and willing to sign the consent form. The subjects were randomly divided into three groups with a total of 10 people in each group.

RKBSMY intervention in research subjects

The first group (control) only took medication from doctor; the second group received placebo treatment; and the third group received 200 mL/d of RKBSMY regularly for two months.

Blood sampling

Blood samples (1 mL) of research subjects were taken three times (0, 1, and 2 months after the intervention). The blood samples were centrifuged at 3,000 rpm for 10 min. The blood plasma was then examined to determine the SOD activity (using Fine Test Human SOD ELISA Kits) and TNF-α level (using Fine Test Human TNF-alpha ELISA Kits). Weight (kg) and height (m) measurements were also conducted every time the blood samples were taken. BMI was calculated by dividing the weight (kg) by the height square (m^2).

Data analysis

The obtained data were analysed using *F*-test, and continued with Duncan's Multiple Range Test (DMRT) at the level of 5% if there was a significant difference.

Results and discussion

Effects of RKBSMY on SOD activity

RKBSMY increased SOD activity from 5.13 to 8.02 ng/mL (p = 0.047). The longer the intervention duration, the higher the SOD activity. The highest activity occurred after 2-months intervention in the treatment group, but SOD activity decreased in the control (p = 0.0036) and placebo group (p = 0.0058) (Figure 1).

These results are similar to the findings of Kojadinovic *et al.* (2016), who also added that 300 mL/d of pomegranate juice given for six weeks could reduce the thiobarbituric acid reactive substances in erythrocytes. A 5-year Mediterranean diet with olive oil or legume extracts also increased the plasma SOD and catalase activity (Sureda *et al.,* 2016). The increase in SOD activity is possibly related to the phenolic antioxidant content in RKBSMY.

The antioxidant potential of phenolic compounds is determined by the chemical structure, number, and position of hydroxyl groups, conjugated groups, degree of glycosylation, and presence of electron donors in the ring structure (Kumar and Pandey, 2013). It is said that phenolic bioavailability is low, but its metabolism and elimination are high.

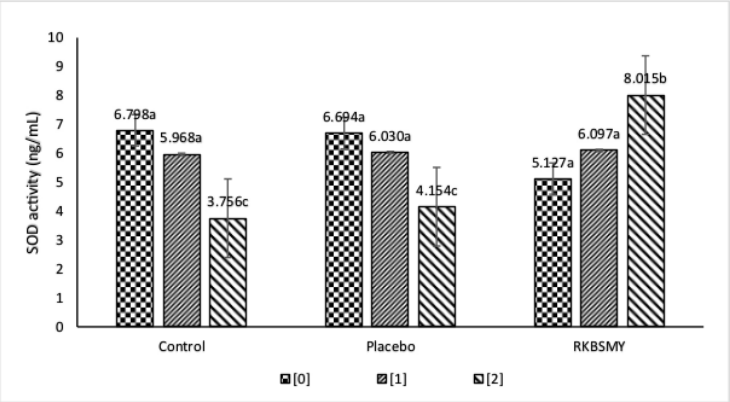

Figure 1. Effect of red kidney bean sprout milk yogurt (RKBSMY) on plasma SOD activity in women with metabolic syndrome (MetS). [0] = baseline data (before receiving the intervention); [1] = data obtained after subjects received the intervention for one month; and [2] = data obtained after subjects received the intervention for two months.

Therefore, its antioxidant effects potentially have clinical relevance. Polyphenols, one of which is phenolic, are an important dietary antioxidant. They are biomolecules found in plant products, and proven able to exert antioxidant and anti-inflammatory effects both *in vitro* and *in vivo* (Chiva-Blanch and Visioli, 2012). According to Ovaskainen *et al.* (2008), the total phenolic intake is generally estimated at 900 mg/d. In the present work, the subjects received RKBSMY at 200 mL/d, which is equivalent to 198.8 mg of phenolic/d (Winarsi *et al.,* 2019), and only 22% from the opinion of Ovaskainen *et al*. (2008), but proven able to increase SOD activity to 56.33%. In other words, phenolic RKBSMY is a potential antioxidant because it can induce the performance of plasma SOD enzyme in MetS sufferers.

There are several mechanisms by which polyphenols could increase SOD activity. Hu *et al.* (2019) have reported that polyphenols increase the expression of stress-response proteins (*e.g.,* heat shock proteins) and SOD antioxidant enzymes, and thereby suppress the reactive oxygen species (ROS) level. Polyphenols minimise the oxidative stress by cleaning the ROS, and producing more stable phenolic radicals. The radical scavenging ability of polyphenols mainly comes from the D ring in the galloyl structure (Severino *et al.,* 2009). Hydroxyl radicals and ROS are bound by polyphenols, especially through the oxidised D-ring galloyl group.

In addition, polyphenols also have indirect antioxidant effects. As reported by Feng *et al.* (2002), the administration of tea polyphenols could reduce the 8-oxoguanine level (a marker for DNA damage caused by oxidative stress), and inhibit DNA oxidative damage (by reducing the expression of cytochrome P450). Therefore, polyphenols could mitigate the symptoms related to oxidative stress by increasing antioxidant capacity.

Phenolic prevents oxidation by chelating the metal ions, and inhibiting the reaction of Fenton and Haber-Weis as the sources of oxygen free radicals. Phenolics can directly scavenge superoxide radicals (Winarsi *et al.,* 2016). It is possible that phenolic in RKBSMY could have contributed to reducing the superoxide radical reactivity at early stage, so that the compound could not turn into hydrogen peroxide which has the potential to become a radical. Therefore, there could be no oxidant build-up as indicated by the increased activity of SOD. Furthermore, the subjects received 200 mL/d of RKBSMY, which was equivalent to 198.9 mg of phenolic daily (Winarsi *et al.,* 2019). The plasma SOD activity in women with MetS increased by 56.33% at this dosage.

The effect of RKBSMY on TNF-α level

After 2-month intervention using RKBSMY, the plasma TNF-α level in women with MetS significantly decreased ($p < 0.05$) from 60.89 to 39.77 pg/mL (Figure 2). Besides its effect as an antioxidant that suppresses the oxidative stress, it turns out that the phenolic in RKBSMY also showed anti-inflammatory effects. The phenolic compounds affect the inflammation-related cell signalling pathways and gene expression. Phenolics are mostly found in beans and their processed products, including the yogurt made from red kidney bean sprouts used in the present work.

The half-life of polyphenol elimination is

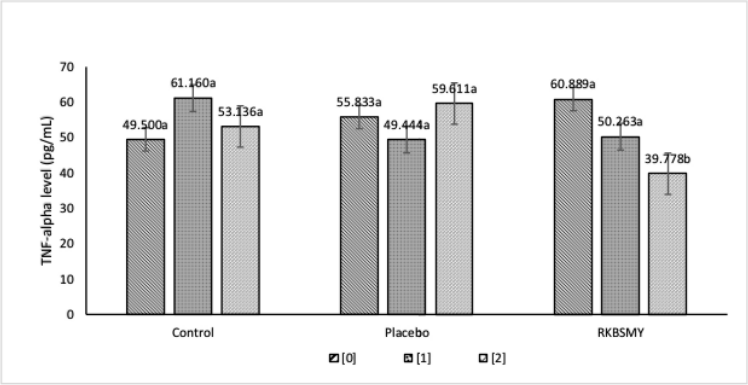

Figure 2. Effect of red kidney bean sprout milk yogurt (RKBSMY) on plasma TNF-alpha levels in women with metabolic syndrome (MetS). [0] = baseline data (before receiving the intervention); [1] = data obtained after subjects received the intervention for one month; and [2] = data obtained after subjects received the intervention for two months.

between 1 and 18 h, but most polyphenols can be excreted in less than 8 h (Manach *et al.,* 2005). This finding proves that most polyphenols are excreted from the body within one day after consumption. Therefore, the concentration of plasma and tissue polyphenols depends strongly on the consumption patterns, and their levels in plasma also vary throughout the day. The 2-month intervention utilised in the present work allowed the phenolic in RKBSMY to affect the inhibition of inflammation development, as indicated by the decrease in TNF-α level.

Some studies have shown that flavonoids, one of the phenolic types, modulate several inflammatory response mediators. Flavonoids inhibit the expression of pro-inflammatory genes (*e.g.,* cytokines, chemokines, or adhesion molecules) and that of inducible NOS (iNOS) isoforms (García-Lafuente *et al.,* 2009). The administration of products containing quercetin, one of the phenolic compounds, reduced the TNF-α in obese patients (Egert *et al.,* 2009).

González *et al.* (2011) confirmed that the anti-inflammatory activity of flavonoids occurs through several mechanisms; *i.e.,* inhibition of cyclooxygenase (COX) and lipoxygenase activities, inhibition of leukocyte accumulation, inhibition of neutrophil degranulation, and inhibition of histamine release. Inflammation occurs due to the release of chemical mediators from the damaged tissue and cell migration. Polyphenols are known able to inhibit the inflammation associated with cytokine production. According to Nair *et al.* (2006), polyphenols are one of natural ingredients which could inhibit the activation of NF-kB, thus decreasing TNF-α production. It has also been stated that polyphenol activity is specific, depending on the type of cell and its structure. Polyphenols block the release of TNF-α by modulating the MAPK pathway at various levels of signalling pathways. In epithelial cells, polyphenols block the TNF-α, and trigger the ICAM-1 by inhibiting the ERK, JNK, and p38 (Nizamutdinova *et al.,* 2007). The ability of polyphenol compounds to block the MAPK pathway makes this bioactive substance potentially therapeutic, which protects the body from the inflammatory reactions.

Concerning its role in the decrease of inflammatory cytokines, cyclooxygenase and lipoxygenase are two enzymes which have an important role as the inflammatory mediators. Both enzymes are released by the oxidised arachidonic acid, together with the initial inflammatory response. Neutrophils contain lipoxygenase which produces chemotactic compounds from the arachidonic acid to release cytokines (Kojadinovic *et al.,* 2016). Phenolic compounds can inhibit both cyclooxygenase and lipoxygenase pathways, thereby suppressing the formation of inflammatory metabolites (TNF-α).

The effect of RKBSMY on BMI

Subjects had an average BMI of 28.04 kg/m^2 at the beginning of the study, thus categorised as obese. The higher the BMI, the wider the surface of adipose tissue. This triggers the O_2 deficiency. Adipose is encouraged to release the pro-inflammatory cytokines, chemokines, and angiogenic factors under this condition to increase blood flow and vascularity (Donath and Shoelson, 2011). It is obvious that high BMI is closely related to inflammatory conditions. Prolonged (chronical) hypoxia causes a chronic release of pro-inflammatory

cytokines. Therefore, it is important to lower or normalise the BMI.

In the present work, RKBSMY decreased the BMI from 28.04 to 24.38 kg/m2. The decrease (11.57%) was greater than in the placebo (2.91%) and control (2.20%) groups. Although the decrease in BMI caused by the RKBSMY was not significant, the decreased BMI now placed the subjects in the normal weight category. Rupasinghe *et al.* (2016) stated that phenolic compounds can change fat and energy metabolisms, thereby facilitating weight loss and preventing weight gain. The decreasing BMI in women with MetS was also associated with the decreasing level of pro-inflammatory cytokine (TNF-α). Flavonoids act in the management of obesity by controlling hunger and satiety. Kim *et al.* (2013) confirmed that phenolic compounds, especially in the form of aglycones, could increase the secretion of cholecystokinin (CCK), a hormone secreted by endocrine cells in small intestine. Increasing CCK helps to control the amount of food intake. CCK encourages the release of enzymes in pancreas and bile in the gall bladder. Therefore, CCK also has the function to delay hunger and prolong satiety.

Dallas *et al.* (2008) reported that 20 mg/mL of phenolic supplement could stimulate lipolysis in adipocytes, which were then verified as free fatty acids. Phenol also has an inhibitory effect on cAMP-phosphodiesterase (Dell'Agli *et al.,* 2008). Phosphodiesterase is an enzyme that can convert cAMP to 5'AMP. The amount of cAMP increases with the inhibition of cAMP-phosphodiesterase by phenolic. High cAMP stimulates the action of protein kinase which in turn activates lipase, thus resulting in lipolysis and a decrease in fat content. The low-fat content could also lead to weight loss.

There are several mechanisms of weight loss by polyphenols. One of the mechanisms is their action in gastrointestinal tract by suppressing the digestion and absorption of macronutrients or changing the intestinal microbiota. Polyphenols inhibit anabolism after the systemic absorption occurs with the changes of intestinal microbiota. Polyphenols then stimulate catabolism in liver, muscles, adipose tissue, and other tissues (Yang *et al.,* 2015). Through these mechanisms, polyphenols can decrease body weight, improve MetS condition, and eventually reduce the risk of MetS development.

Regarding the consumption of polyphenol-rich products and their benefits in weight loss, some researchers reported that these antioxidant compounds increase lipid and total nitrogen levels in faeces, which means that polyphenols can reduce the digestion and absorption of lipid and protein (Yang and Hong, 2013). After the phenolic-rich product is consumed, lipids are then emulsified, hydrolysed, and absorbed in small intestine. Lipid transporters on the apical surface of intestine facilitate the transfer of fatty acids and cholesterol into enterocytes. The absorbed lipids are then packaged into the chylomicrons, and secreted into the lymphatic system. In this case, polyphenols interfere with the emulsification, and inhibit the action of pancreatic lipase and phospholipase, thus reducing the weight gain in rats fed with a high-fat diet (Grove *et al.,* 2012). The mechanism of polyphenols in inhibiting the protein digestion and absorption has not been frequently studied. However, there is a strong relationship between antioxidant, digested protein, and proteinase in the digestive system through H-bonds and hydrophobic interactions, thus resulting in the obstruction of the digestive working system.

The polyphenol inhibitory activity on digestive enzymes occurs in α-amylase, glucosidase, and glucose transporters. Polyphenols inhibit the glucose absorption in the intestinal cells through the competitive inhibitors of sodium-glucose co-transporter 1 (Park *et al.,* 2009). It has also been reported that consumption of polyphenol-rich products can reduce the glucose digestion and absorption due to the inhibition of α-amylase activity by these compounds (Forester *et al.,* 2012). The nutrient-decreasing digestion and absorption have an important role in weight loss, which ultimately inhibit the development of MetS.

Conclusion

Phenolic-rich RKBSMY increased SOD activity by 56.33%, decreased plasma TNF-α level by 34.67%, and decreased BMI of obese women with MetS by 11.57%, which led to normal weight. Therefore, RKBSMY could be beneficial as a healthy and functional food, and source of antioxidants and anti-inflammatory for obese women with MetS.

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2.14 Oxidative

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