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Effects of kefir on paraoxanase activity (PON1), total antioxidant status (TAS), total oxidant status (TOS), and serum lipid profiles in smokers and non-smokers

Huda Oflazoglu DIKEN[1], Berjan DEMIRTAS[2*], Hacer Kayhan KAYA[1]

Abstract

Some scientific evidence indicates that antioxidant-rich diets may prevent the negative effects of free radicals. In this study, we aimed to evaluate the effects of kefir consumption on paraxonase-1 (PON1) activity, total antioxidant status (TAS), total oxidant status (TOS), and serum lipid parameters in smokers and non-smokers. At baseline, PON1 activity, TAS, and high-density lipoprotein cholesterol (HDL-C) levels were lower ($P<0.05$, $P<0.01$, and $P<0.05$, respectively) whereas TOS, triglyceride (TG), and light-density lipoprotein cholesterol (LDL-C) levels were higher (all $P<0.05$) in smokers compared to non-smokers. There were no significant differences in total cholesterol (TC) levels between two groups ($P>0.05$). After 6-week of kefir consumption, PON1 and TAS values were significantly increased in smokers (both $P<0.05$) and non-smokers ($P<0.05$ and $P<0.01$, respectively). Kefir consumption did not have any significant effect on TOS, HDL-C, LDL-C, TC, and TG values both in smokers (all $P>0.05$) and non-smokers (all $P>0.05$). Regular consumption of kefir increases the PON1 activity and TAS value in both smokers and non-smokers. It can be concluded that kefir plays an important role in favor of antioxidants in the formation of antioxidant/oxidant balance in both smokers and non-smokers.

Keywords: kefir; PON1; smokers; oxidant; antioxidant.

Practical Application: Negative impact of smoking may be reduced by regular consumption of kefir.

1 Introduction

It is well known that smoking is one of the basic causes of several chronic and fatal diseases such as cardivascular disease, cancer, and respiratory diseases (Aksoy et al., 2012; WHO, 2008; Peto & Lopez, 2001). Cigarette smoke contains a large amount of free radicals and other oxidants that may enhance the production of reactive oxygen radicals (ROS), resulting in oxidative demage. ROS show their harmful effects mostly on the cell parts, including the DNA, enzyme inactivation, membrane lipids, and proteins (Kopani et al., 2006; Pryor & Stone, 1993). ROS also oxidize lipoproteins, particularly low-density lipoprotein (LDL) which is more atherogenic than native LDL (Bloomer, 2007).

The human body has several mechanisms to counteract the damage caused by ROS. Although the basic defense mechanism is mediated by the endogeneous antioxidant system (Halliwell, 2007; Sies, 1997), the exogeneous antioxidant defense system also plays an important role to avoid the oxidative damage caused by ROS (Charão et al., 2014). There is a balance between production rate of ROS and their destruction by antioxidant defence system. The imbalance associated with the increase in oxidative products or the decrease in antioxidant defence mechanisms is called oxidative stress (Sharifi-Rad et al., 2020; Aslan et al., 2014; Aksoy et al., 2012). The total effects of all antioxidants in plasma and in body fluid are measured by the total antioxidant status (TAS) and the total effects of oxidants are measured by total oxidant status (TOS) (Karademirci et al., 2018; Erel, 2005; Erel, 2004). Oxidative stress plays an important role in the pathogenesis of many diseases such as atherosclerosis, coronary artery disease, diabetes, and cancer (Karademirci et al.,2018; Onor et al., 2017; Eom et al., 2015; Aksoy et al., 2012; Nagamma et al., 2011; Ambrose & Barua, 2004). Smoking may enhance oxidative stress either increasing production of ROS or attenuating of antioxidant defense system (Karademirci et al., 2018; Jansen et al., 2014; Polidori et al., 2003).

The endogenous antioxidant paraoxanase-1 (PON1) is a polimorphic calcium-dependent serum enzyme with lipophilic antioxidant property (Çolak et al., 2020). PON1, which is associated with high-density lipoprotein cholesterol (HDL-C) hydrolysis of toxic metabolites found in some insecticides, nerve agents, and esters (Çolak et al., 2020; Draganov & La Du, 2004). PON1 also is involved in hydrolysis of lipid peroxidation. It protects low-density lipoprotein cholesterol (LDL-C) and HDL-C from oxidation and thus, prevents the occurence of atherosclerosis and cardiovascular diseases (Altınkaynak et al., 2018; Aslan et al., 2014). It has been also demonstrated that the reduced PON1 activity and concentration in smokers was associated with coronary heart disease (James et al., 2000). According to the literature knowledge, there is a corelation between smoking and lipid alterations (Majid et al., 2021; Sakila & Valarmathi, 2021).

In recent years, adding certain nutrients to diets for increasing and optimizing the physiological functions is an attractive option

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[1]*Department of Physiology, Dicle University Faculty of Medicine, Diyarbakır, Turkey*
[2]*Plant and Animal Production Department, Vocational School of Veterinary Medicine, İstanbul University-Cerahpaşa, İstanbul, Turkey*
*Corresponding author: berjan@iuc.edu.tr

(Rosa et al., 2017). Kefir, which is produced by fermenting milk with kefir grains, is an excellent source of probiotic with potential benefits for health. Kefir which contains a large diversity of microorganisms including bacterial species and yeasts is a good carrier for probiotics (Almeida Brasiel et al., 2021; Göktas et al., 2021). There are sme sensory differences among the different origins of kefir (Mitra & Ghosh, 2020). Sensory acceptance and health benefits of kefir are improved by adding different types of sugar in kefir (Larosa et al., 2021a; Larosa et al., 2021b). The results of many studies demonstrate that kefir possesses antioxidant activity and it may be considered among the most promising food in terms of preventing oxidative stress (Kumar et al., 2021; Larosa et al., 2021b; Ali et al., 2020; Barboza et al., 2018; Punaro et al., 2014; Liu et al., 2005; Güven et al., 2004). There are conflicting reports on the effect of kefir on serum lipids. Some previous studies report that kefir causes a decrease in lipid parameters (Ghizi et al., 2021; Huang et al., 2013), while others report that kefir has no effect on lipid profiles (Ostadrahimi et al., 2015; St-Onge et al., 2002).

To our knowledge, there is no study about the effect of kefir on PON1 activity, TAS, TOS levels, and serum lipids in smokers. Most of the studies on the protective role of kefir against oxidative stress were carried out in animal models or in vitro studies. Therefore, in this study we investigated the effect of kefir on PON1 activity, TAS, TOS, HDL-C, LDL-C, total cholesterol (TC), and triglyceride (TG) levels in smoker and non-smoker healthy volunteers.

2 Materials and methods

2.1 Study design and subjects

Experimental protocol is presented in Figure 1. A total of 30 healthy male volunteers (n=15 smokers and n=15 non-smokers) within the age range 25 to 55 years were included in the present study. Smokers consumed >1 pack of cigarette per day for more than 5 years whereas the non-smokers had no smoking history. The subjects were recruited from the staff of Dicle University School of Medicine. None of the subjects had any systemic diseases, nor signs or symptoms of infectious disease. Potential volunteers were excluded from study if they had lactose intolerance, took medication, took supplements, consumed kefir or any other probiotic-containing products in the last 2 months. This study was performed in accordance with the guidelines of good clinical practice and the Helsinki declaration, and the Clinical Research Ethics Committee of the Dicle University School of Medicine approved the study (118-22.04.11). All participants were informed about the study and signed the informed consents. At the begining of the study (baseline), biometric values and vital indications were measured and fasting venous blood samples were collected. Thereafter, each subject consumed 200 mL/day kefir (Altinkilic, Turkey) at lunch for 6 weeks. At the end of 6 weeks (endline), biometric values and vital indications were meausured (Table 1) and fasting blood samples were collected again. All blood samples at the beginning of study and after

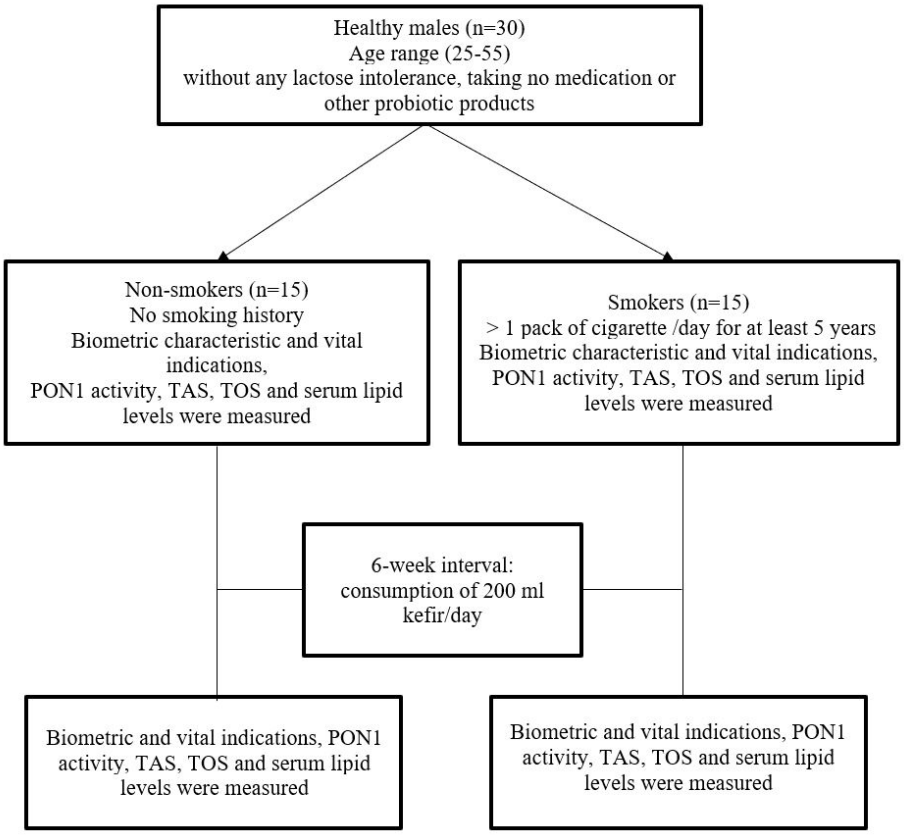

Figure 1. Flow chart for experimental protocol. PON1: paraxonase-1; TAS: Total antioxidant status; TOS: Total oxidant status.

Table 1. The biometric characteristics and vital indications of the subjects.

Parameters	Non-smokers n=15		Smokers n=15	
	Before Kefir (Baseline) Mean ± SD	After Kefir (Endline) Mean ± SD	Before Kefir (Baseline) Mean ± SD	After Kefir (Endline) Mean ± SD
Age (years)	34 ± 5		32 ± 5	
Height (meter)	1.71 ± 0.05		1.70 ± 0.04	
Weight (kg)	73.1 ± 7.6	73.9 ± 7.8	67.8 ± 9.9	68.1 ± 9.6
BMI (kg/m^2)	23.9 ± 2.5	24.7 ± 2.1	23.1 ± 3.1	23.6 ± 3.0
Sistolic Blood Pressure (mmHg)	117.4 ± 12.8	116.5 ± 5.9	114.4 ± 5.5	111.9 ± 4.9
Diastolic Blood Pressure (mmHg)	83.0 ± 12.9	78.6 ± 9.1	78.3 ± 7.4	74.6 ± 6.1
Heart Rate (BPM)	70.3 ± 7.4	71.4 ± 6.9	72.0 ± 7.6	74.0 ± 7.1

SD: Standard Deviation; BMI: Body Mass Index; BPM: Beat Per Minute. (all p>0.05).

6 week of kefir consumption were centrifuged at 6000×g for 10 min at 4 °C, and serum supernatants were separated and used immediately for the measurement of lipid parameters. A part of the supernatants were stored at -80 °C until the analyses of PON1 activity, TAS, and TOS.

2.2 Measurement of PON1 activity

PON1 activity was determined using paraoxon as a substrate and was measured by increases in the absorbance due to the formation of 4-nitrophenol as already described by Eckerson HW et al. (1983). Briefly, the PON1 activity was measured at 25 °C by adding 50 µL of serum to 1 mL Tris-HCl buffer (100 mM at (pH 8.0) containing 2 mM $CaCl_2$ and 5 mM of paraoxon. The rate of generation of 4-nitrophenol was determined at 412 nm by using Shimadzu UV 1280 spectrophotometer. Paraoxonase activity is expressed as U/L.

2.3 Measurement of TAS

Serum TAS levels of all samples were determined using a novel, automated method described by Erel (2004). Briefly, the rate of potent free-radical reactions initiated by hydroxyl radical was monitored by following the absorbance of colored dianisydl radicals. The antioxidative effect of samples was measured against the potent free radicals by supressing the color formation. TAS levels are expressed as mmol trolox equivalent per litre (mmol Trolox equiv/L). All measurements were performed using an automated analyzer (Abbott Architect C 16000, USA).

2.4 Measurement of TOS

Serum TOS levels of all samples were determined using the new automated colorimetric method decribed by Erel (2005). This method is based on spectrophotometric measurement of the colored complex formed by the reaction of ferric ions with xylenol orange in an acidic medium following the oxidation of ferrous ion-o-dianisidine complex to ferric ion. The assay was calibrated with hydrogen peroxide (H_2O_2) and the results are expressed in terms of micromolar hydrogen peroxide equivalent per litre (µmol H_2O_2 Eq/L). All measurements were performed using an automated analyzer (Abbott Architect C 16000, USA).

2.5 Measurement of lipid parameters

Serum HDL-C, LDL-C, TC, and TG levels were estimated by standard automated techniques (Abbott Architect C 16000, USA)

2.6 Kefir and its microbial composition

Commercial kefir (Altinkilic, Turkey) beverage, which is produced from cow milk with 3% fat content and stored in appropriate conditions, was used in this study. Microbial flora of the kefir was composed of bacteria (*Lactobacillus*, *Lactic acid Streptococcus*, *Acetic acid bacteria*) and yeasts (*Kluyveromyces marxianus*, *Torulaspora delbrueckii*, *Saccharomyces cerevisiae*, *Candida*). The concentration of bacteria was 7-10 million per 10 milliliter.

2.7 Statistical analysis

All statistical analyses were performed using the SPSS for Windows version 18.0 (SPSS Inc. Chicago, IL, USA). The results were expressed as mean ± SD. The normality of the distributed variables was assessed by the Kolmogorov-Smirnov test. The parameters were evaluated using the one-way analysis of variance (one-way ANOVA) followed by the Dunnett post-hoc test to correct for multiple comparision treatments. Statistical significance was set at the P<0.05 level.

3 Results

The biometric characteristic and vital indications of the subjects were summarized in Table 1. At baseline, there were no significant differences in age, weight, body mass index (BMI), sistolic - diastolic blood pressure, and heart rate values between smokers and non-smokers (all P>0.05). Following six weeks of kefir consumption, the baseline and endline values were compared in both smokers and non-smokers. Kefir consumption did not have significant effect on weight, BMI, sistolic - diastolic blood pressure, and heart rate in both groups (all P>0.05).

PON1 activity, TAS, TOS values, and lipid parameters (TC, LDL-C, HDL-C, TG) before (baseline) and after kefir consumption (endline) are presented in Table 2. In comparison of the baseline values of two groups, PON1 activity, TAS, and HDL-C levels were significantly lower (P<0.05, P<0.01 and P<0.05, respectively) while TOS, TG, and LDL-C levels were

Table 2. The effects of kefir on PON1 activity, total antioxidant status (TAS), total oxidant status (TOS), the levels of serum total cholestrol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels in smokers and non-smokers.

Parameters	Groups			
	Non-smokers (n=15)		Smokers (n=15)	
	Before Kefir (Baseline) Mean ± SD	After Kefir (Endline) Mean ± SD	Before Kefir (Baseline) Mean ± SD	After Kefir (Endline) Mean ± SD
PON1 (U/L)	50.20 ± 11.88	62.04 ± 19.75*	39.47 ± 12.19 ♣	53.39 ± 7.24 †
TAS (mmol Trolox equiv/L)	1.83 ± 0.13	2.19 ± 0.18**	1.67 ± 0.19 ♣♣	1.89 ± 0.12 †
TOS (μmol H_2O_2 equiv/L)	21.91 ± 3.51	21.47 ± 3.22	26.09 ± 5.92 ♣	24.61 ± 4.30
TC (mg/dL)	157.80 ± 22.19	171.13 ± 24.18	165.67 ± 30.49	163.87 ± 30.95
LDL-C (mg/dL)	103.00 ± 17.82	114.93 ± 22.41	120.04 ± 19.31♣	112.40 ± 28.35
HDL-C (mg/dL)	43.73 ± 4.14	44.66 ± 4.60	39.66 ± 3.81 ♣	42.20 ± 5.04
TG (mg/dL)	104.47 ± 40.90	113.53 ± 37.86	131.20 ± 41.94 ♣	127.47 ± 47.06

♣P<0.05; ♣♣P<0.01= smokers versus non-smokers at baseline; *P<0.05; **p<0.01= endline versus baseline in non-smokers; †P<0.05 = endline versus baseline in smokers. SD: Standard Deviation.

significantly higher (all P<0.05) in smokers than those of non-smokers. There was no significant differences in the baseline value of TC between two groups (P>0.05). In order to evaluate the effect of kefir consumption on PON1, TAS, TOS, and serum lipid parameters (TC, LDL-C, HDL-C, TG) in smokers and non-smokers, the baseline and endline values of each group were compared. At endline, kefir consumption increased the PON1 activity and TAS level significantly both in smokers (both P<0.05) and non-smokers (P<0.05 and P<0.01, respectively) compared to their each baseline values. The increases in PON1 activity and TAS values were 35% and 13% for smokers and 24% and 20% for non-smokers, respectively. TOS, TC, TG and LDL-C levels showed slight decreases and the HDL-C level showed a slight increase in smokers after kefir consumption, but these alterations were not statistically significant (all p>0.05).

4 Discussion

Cigarette smoking is one of the most harmful habits which causes many diseases and deaths all over the world. There are claims that kefir has health benefits. In this present study, the effects of kefir on PON1 activity, TAS, TOS, and some serum lipids between smokers and non-smokers were studied. Cigarette smoke contains many oxidants which are the causes of many diseases. Smoking initiates oxidative stress by impairing the antioxidant/oxidant balance. (Sharifi-Rad et al., 2020; Polidori et al., 2003). In our present study, smoking caused a significant decrease in TAS value, but a significant increase in TOS value. These results are consistent with the literature knowledge. Previous studies have shown that smoking reduces TAS values while increasing TOS values (Ahmadkhaniha et al., 2021; Karademirci et al., 2018; Jansen et al., 2014; Aksoy et al., 2012). In animals, rats and rat offsprings which were maternally exposed to smoke had lower TAS value and higher TOS value (Celik, 2020; Erdem Guzel et al., 2020). These results indicate that as a result of exposure to the smoke, the increase in oxygen radicals and the decrease in antioxidants impair the scavenging of the ROS and cause oxidative stress. Oxidative stress has been correlated with the pathogenesis of many diseases (Karademirci et al., 2018; Onor et al., 2017; Eom et al., 2015; Nagamma et al., 2011; Ambrose & Barua, 2004).

PON1 has an antioxidative property and protects lipids from oxidation (Ahmed et al., 2002). In our study, PON1 activity was significantly decreased in smokers compared to non-smokers. It has been shown that cigarette smoking and cigarette smoke extract reduced the PON1 activity significantly in vivo and in vitro (Ramanathan et al., 2014; Solak et al., 2005; Nishio & Watanabe, 1997). Nishio & Watanabe (1997) indicated that cigarette smoke extract inhibits PON1 activity in a dose- and time-dependent manner. Contrary to our results, Aslan et al. (2014) found that smoking did not affect the TOS, TAS values, and PON1 activity. This might be due these parameters being affected by many factors such as environmental factors, diet, mild viral infection, and smoking pattern.

Smoking alters the normal profile of serum lipids (Sakila & Valarmathi, 2021; Arslan et al., 2008). In our study, TG and LDL-C levels were significantly higher, whereas the HDL-C level was significantly lower in smokers. Previous studies demonstrate that cigarette smoking increases TC, TG, and LDL-C levels, but decreases HDL-C (Sakila & Valarmath, 2021¸ Whitehead et al., 1996). It has been also shown that the TC level is not affected in smokers (Majid et al., 2021). In our study, there was slight but not significant increase in TC level. This might be due to the fact that the higher HDL-C and the lower LDL-C levels compensate for each other, thus resulting in no statistically significant increase in TC level or the number of participants in our study was lower compared to previous studies.

Kefir has many nutraceutical effects such as being anti-inflammatory, anti-oxidative, anti-cancer, anti-microbial, anti-diabetic, anti-hypertensive, and anti-hypercholesterolemic (Azizi et al., 2021; Ghizi et al., 2021; Larosa et al., 2021b; Barboza et al., 2018; Rosa et al., 2017). Sensory acceptance of kefir has been associated with the emotion intensities of consumers (Larosa et al., 2021a). The plain kefir used in our study was highly appreciated by the participants in terms of taste, and texture and did not seem to affect the appetite of the consumers. It has been shown that kefir consumption has a beneficial effect on nicotine cessation-induced depression in rats (Noori et al., 2014). In our study, kefir consumption significantly increased the PON1 activity and TAS value in both smokers and non-smokers. In mice, it has been shown that kefir has gastroprotective effects by preventing the

oxidation of macro molecules (Barboza et al., 2018). An in vitro study indicates that kefir attenuates hydrogen peroxide-induced oxidative stress by up-regulating endogenous antioxidant levels in neuroblastoma cells (Kumar et al., 2021). A previous study also demonstrates that kefir increases TAS value in rats with the hepatic injury-induced oxidative stress. In the same study with rats, TG, TC, and LDL-C levels were decreased while HDL-C value was increased after kefir consumption (Ali et al., 2020). Kullisaar et al. (2011) has shown that kefir enriched with probiotic *Lactobacillus fermentum ME-3* reduces postprandial lipemia and oxidative stress (Kullisaar et al., 2011). Ghizi et al. (2021) demonstrated that, after kefir consumption, patients with metabolic syndrome have lower TG and LDL-C values and higher HDL-C values. On the contrary, it has been also shown that kefir has no effect on plasma lipid levels in hypercholesterolemic patients. Similar to that study, Ostadrahimi et al. (2015) reported that kefir has no effect on plasma lipids in type II diabetic patients. In our study, there were slight decreases in TOS, TG, TC, and LDL-C values and a slight increase in HDL-C value after kefir consumption in smokers. However, these values were not statistically significant. All the previous results about the effect of kefir on serum lipids were conducted with animal models or with patients of different illnesses. Our study was carried out with healthy people. Thus, this might be one of the reasons of no significant changes in these parameters. Moreover, the amount of kefir, and the type and concentration of bacteria in kefir were different in each study.

5 Conclusion

According to our knowledge, there is no study about the effects of kefir on PON1 activity, TOS, TAS, and serum lipids in smokers. We found that regular consumption of kefir increases the PON1 activity and TAS values, thus plays an important role on antioxidant/oxidant balance in the favor of antioxidants in smokers. However, further studies are needed to evaluate the effect of kefir on other endogenous antioxidants and lipid peroxidation products in smokers. Furthermore, sensory acceptance of kefir might be important for consumers to include kefir in their daily diet. The relationship between sensory acceptance and antioxidant property of kefir might be studied in humans in the future.

References

Ahmadkhaniha, R., Yousefian, F., & Rastkari, N. (2021). Impact of smoking on oxidant/antioxidant status and oxidative stress index levels in serum of the university students. *Journal of Environmental Health Science & Engineering*, 19(1), 1043-1046. http://dx.doi.org/10.1007/s40201-021-00669-y. PMid:34150292.

Ahmed, Z., Ravandi, A., Maguire, G. F., Emili, A., Draganov, D., La Du, B. N., Kuksis, A., & Connelly, P. W. (2002). Multiple substrates for paraoxonase-1 during oxidation of phosphatidylcholine by peroxynitrite. *Biochemical and Biophysical Research Communications*, 290(1), 391-396. http://dx.doi.org/10.1006/bbrc.2001.6150. PMid:11779181.

Aksoy, S., Cam, N., Gurkan, U., Oz, D., Özden, K., Altay, S., Durmus, G., & Agirbasli, M. (2012). Oxidative stress and severity of coronary artery disease in young smokers with acute myocardial infarction. *Cardiology Journal*, 19(4), 381-386. http://dx.doi.org/10.5603/CJ.2012.0069. PMid:22825899.

Ali, O. S. M., Amin, N. E., Abdel Fattah, S. M., & Abd El-Rahman, O. (2020). Ameliorative effect of kefir against γ-irradiation induced liver injury in male rats: impact on oxidative stress and inflammation. *Environmental Science and Pollution Research International*, 27(28), 35161-35173. http://dx.doi.org/10.1007/s11356-020-09833-7. PMid:32588307.

Almeida Brasiel, P. G., Dutra Medeiros, J., Barbosa Ferreira Machado, A., Schuchter Ferreira, M., Gouveia Peluzio, M. D. C., & Potente Dutra Luquetti, S. C. (2021). Microbial community dynamics of fermented kefir beverages changes over time. *International Journal of Dairy Technology*, 74(2), 324-331. http://dx.doi.org/10.1111/1471-0307.12759.

Altınkaynak, Y., Örem, A., Altınkaynak, B. A., Kural, B., Balaban, Y. F., & Örem, C. (2018). Investigation of Serum Paraoxonase 1 (PON1) Activity in Postprandial Lipemia. *Acta Medica Alanya*, 3(1), 3-11.

Ambrose, J. A., & Barua, R. S. (2004). The pathophysiology of cigarette smoking and cardiovascular disease: an update. *Journal of the American College of Cardiology*, 43(10), 1731-1737. http://dx.doi.org/10.1016/j.jacc.2003.12.047. PMid:15145091.

Arslan, E., Yakar, T., & Yavaşoğlu, I. (2008). The effect of smoking on mean platelet volume and lipid profile in young male subjects. *The Anatolian Journal of Cardiology*, 8(6), 422-425. PMid:19103537.

Aslan, R., Kutlu, R., Civi, S., & Tasyurek, E. (2014). The correlation of the total antioxidant status (TAS), total oxidant status (TOS) and paraoxonase activity (PON1) with smoking. *Clinical Biochemistry*, 47(6), 393-397. http://dx.doi.org/10.1016/j.clinbiochem.2013.10.002. PMid:24440837.

Azizi, N. F., Kumar, M. R., Yeap, S. K., Abdullah, J. O., Khalid, M., Omar, A. R., Osman, M. A., Mortadza, S. A. S., & Alitheen, N. B. (2021). Kefir and its biological activities. *Foods*, 10(6), 1210. http://dx.doi.org/10.3390/foods10061210. PMid:34071977.

Barboza, K. R. M., Coco, L. Z., Alves, G. M., Peters, B., Vasquez, E. C., Pereira, T. M. C., Meyrelles, S. S., & Campagnaro, B. P. (2018). Gastroprotective effect of oral kefir on indomethacin-induced acute gastric lesions in mice: Impact on oxidative stress. *Life Sciences*, 209, 370-376. http://dx.doi.org/10.1016/j.lfs.2018.08.035. PMid:30120965.

Bloomer, R. J. (2007). Decreased blood antioxidant capacity and increased lipid peroxidation in young cigarette smokers compared to nonsmokers: impact of dietary intake. *Nutrition Journal*, 6, 39. http://dx.doi.org/10.1186/1475-2891-6-39. PMid:17996062.

Celik, H. (2020). *Hayvan modelinde elektronik sigara buharı ve sigara dumanının pulmoner toksik etkilerinin değerlendirilmesi* (PhD thesis). Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi, Konya.

Charão, M. F., Moro, A. M., Valentini, J., Brucker, N., Bubols, G. B., Bulcão, R. P., Baierle, M., Freitas, F. A., Nascimento, S. N., Barth, A., Linden, R., Saldiva, P. H., & Garcia, S. C. (2014). Exogenous and endogenous antioxidants attenuate the lipid peroxidation in workers occupationally exposed to paints. *Drug and Chemical Toxicology*, 37(1), 69-75. http://dx.doi.org/10.3109/01480545.2013.806534. PMid:23841515.

Çolak, E., Cosan, D. T., Ak, G., Dal, A., Öner, Ç., Soyocak, A., Çolak, E., Güneş, H. V., & Metintaş, M. (2020). Evaluation of paraoxonase-1 enzyme activity and oxidative stress relations in malignant mesothelioma cases. *Eurasian Journal of Pulmonology*, 22(3), 153-157. http://dx.doi.org/10.4103/ejop.ejop_78_19.

Draganov, D. I., & La Du, B. N. (2004). Pharmacogenetics of paraoxonases: a brief review. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 369(1), 78-88. http://dx.doi.org/10.1007/s00210-003-0833-1. PMid:14579013.

Eckerson, H. W., Wyte, C. M., & La Du, B. N. (1983). The human serum paraoxonase/arylesterase polymorphism. *American Journal of Human Genetics*, 35(6), 1126-1138. PMid:6316781.

Eom, S. Y., Yim, D. H., Lee, C. H., Choe, K. H., An, J. Y., Lee, K. Y., Kim, Y. D., & Kim, H. (2015). Interactions between paraoxonase 1 genetic polymorphisms and smoking and their effects on oxidative stress and lung cancer risk in a Korean population. *PLoS One*, 10(3), e0119100. http://dx.doi.org/10.1371/journal.pone.0119100. PMid:25741997.

Erdem Guzel, E., Kaya, N., Tektemur, A., Ulker, N., Yardimci, A., Akkoc, R. F., Canpolat, S., & Ozan, I. E. (2020). Chronic effects of maternal tobacco-smoke exposure and/or α-lipoic acid treatment on reproductive parameters in female rat offspring. *Systems Biology in Reproductive Medicine*, 66(6), 387-399. http://dx.doi.org/10.1080/19396368.2020.1815248. PMid:32951465.

Erel, O. (2004). A novel automated method to measure total antioxidant response against potent free radical reactions. *Clinical Biochemistry*, 37(2), 112-119. http://dx.doi.org/10.1016/j.clinbiochem.2003.10.014. PMid:14725941.

Erel, O. (2005). A new automated colorimetric method for measuring total oxidant status. *Clinical Biochemistry*, 38(12), 1103-1111. http://dx.doi.org/10.1016/j.clinbiochem.2005.08.008. PMid:16214125.

Ghizi, A. C. S., Silva, M. A., Moraes, F. S. A., Silva, C., C. L., Endringer, D. C., Scherer, R., Lenz, D., Lima, E. M., Brasil, G. A., Maia, J. F., Bissoli, N. S., & de Andrade, T. U..(2021). Kefir improves blood parameters and reduces cardiovascular risks in patients with metabolic syndrome. *PharmaNutrition*, 16, 100266. http://dx.doi.org/10.1016/j.phanu.2021.100266.

Göktas, H., Dikmen, H., Demirbas, F., Sagdic, O., & Dertli, E. (2021). Characterisation of probiotic properties of yeast strains isolated from kefir samples. *International Journal of Dairy Technology*, 74(4), 715-722. http://dx.doi.org/10.1111/1471-0307.12802.

Güven, A., Güven, A., & Kamiloglu, N. N. (2004). Kefirin lipid peroksidasyonuna etkilerinin araştırılması. *Kafkas Üniversitesi Veteriner Fakültesi Dergisi*, 10(2), 165-169.

Halliwell, B. (2007). Biochemistry of oxidative stress. *Biochemical Society Transactions*, 35(5), 1147-1150. http://dx.doi.org/10.1042/BST0351147. PMid:17956298.

Huang, Y., Wu, F., Wang, X., Sui, Y., Yang, L., & Wang, J. (2013). Characterization of Lactobacillus plantarum Lp27 isolated from Tibetan kefir grains: a potential probiotic bacterium with cholesterol-lowering effects. *Journal of Dairy Science*, 96(5), 2816-2825. http://dx.doi.org/10.3168/jds.2012-6371. PMid:23498003.

James, R. W., Leviev, I., Ruiz, J., Passa, P., Froguel, P., & Garin, M. C. (2000). Promoter polymorphism T(-107)C of the paraoxonase PON1 gene is a risk factor for coronary heart disease in type 2 diabetic patients. *Diabetes*, 49(8), 1390-1393. http://dx.doi.org/10.2337/diabetes.49.8.1390. PMid:10923642.

Jansen, E., Beekhof, P., & Ruskovska, T. (2014). The effect of smoking on biomarkers of (anti) oxidant status. *Journal of Molecular Biomarkers & Diagnosis*, 5(6), 207.

Karademirci, M., Kutlu, R., & Kilinc, I. (2018). Relationship between smoking and total antioxidant status, total oxidant status, oxidative stress index, vit C, vit E. *The Clinical Respiratory Journal*, 12(6), 2006-2012. http://dx.doi.org/10.1111/crj.12757. PMid:29247592.

Kopani, M., Celec, P., Danisovic, L., Michalka, P., & Biro, C. (2006). Oxidative stress and electron spin resonance. *Clinica Chimica Acta*, 364(1–2), 61-66. http://dx.doi.org/10.1016/j.cca.2005.05.016. PMid:16125687.

Kullisaar, T., Shepetova, J., Zilmer, K., Songisepp, E., Rehema, A., Mikelsaar, M., & Zilmer, M. (2011). An antioxidant probiotic reduces postprandial lipemia and oxidative stress. *Central European Journal of Biology*, 6, 32-40.

Kumar, M. R., Yeap, S. K., Lee, H. C., Mohamad, N. E., Nazirul Mubin Aziz, M., Khalid, M., Masarudin, M. J., Leow, A. T. C., Abdullah, J. O., & Alitheen, N. B. (2021). Selected kefir water from malaysia attenuates hydrogen peroxide-induced oxidative stress by upregulating endogenous antioxidant levels in SH-SY5Y neuroblastoma cells. *Antioxidants*, 10(6), 940. http://dx.doi.org/10.3390/antiox10060940. PMid:34200854.

Larosa, C. P., Balthazar, C. F., Guimarães, J. T., Rocha, R. S., Silva, R., Pimentel, T. C., Granato, D., Duarte, M. C. K. H., Silva, M. C., Freitas, M. Q., Cruz, A. G., & Esmerino, E. A. (2021a). Sheep milk kefir sweetened with different sugars: Sensory acceptance and consumer emotion profiling. *Journal of Dairy Science*, 104(1), 295-300. http://dx.doi.org/10.3168/jds.2020-18702. PMid:33162085.

Larosa, C. P., Balthazar, C. F., Guimarães, J. T., Margalho, L. P., Lemos, F. S., Oliveira, F. L., Abud, Y. K. D., Sant'Anna, C., Duarte, M. C. K. H., Granato, D., Raices, R. S. L., Freitas, M. Q., Sant'Ana, A. S., Almeida Esmerino, E., Pimentel, T. C., Cristina Silva, M., & Cruz, A. G. (2021b). Can sucrose-substitutes increase the antagonistic activity against foodborne pathogens, and improve the technological and functional properties of sheep milk kefir? *Food Chemistry*, 351, 129290. http://dx.doi.org/10.1016/j.foodchem.2021.129290. PMid:33631613.

Liu, J. R., Chen, M. J., & Lin, C. W. (2005). Antimutagenic and antioxidant properties of milk-kefir and soymilk-kefir. *Journal of Agricultural and Food Chemistry*, 53(7), 2467-2474. http://dx.doi.org/10.1021/jf048934k. PMid:15796581.

Majid, S., Keith, R. J., Fetterman, J. L., Weisbrod, R. M., Nystoriak, J., Wilson, T., Stokes, A. C., Blaha, M. J., Srivastava, S., Robertson, R. M., Bhatnagar, A., & Hamburg, N. M. (2021). Lipid profiles in users of combustible and electronic cigarettes. *Vascular Medicine*, 26(5), 483-488. http://dx.doi.org/10.1177/1358863X211009313. PMid:34013801.

Mitra, S., & Ghosh, B. C. (2020). Quality characteristics of kefir as a carrier for probiotic *Lactobacillus rhamnosus GG*. *International Journal of Dairy Technology*, 73(2), 384-391. http://dx.doi.org/10.1111/1471-0307.12664.

Nagamma, T., Anjaneyulu, K., Baxi, J., Dayaram, P., & Singh, P. (2011). Effects of cigarette smoking on lipid peroxidation and antioxidant status in cancer patients from Western Nepal. *Asian Pacific Journal of Cancer Prevention*, 12(1), 313-316. PMid:21517278.

Nishio, E., & Watanabe, Y. (1997). Cigarette smoke extract inhibits plasma paraoxonase activity by modification of the enzyme's free thiols. *Biochemical and Biophysical Research Communications*, 236(2), 289-293. http://dx.doi.org/10.1006/bbrc.1997.6961. PMid:9240427.

Noori, N., Bangash, M. Y., Motaghinejad, M., Hosseini, P., & Noudoost, B. (2014). Kefir protective effects against nicotine cessation-induced anxiety and cognition impairments in rats. *Advanced Biomedical Research*, 3(1), 251. http://dx.doi.org/10.4103/2277-9175.146377. PMid:25590029.

Onor, I. O., Stirling, D. L., Williams, S. R., Bediako, D., Borghol, A., Harris, M. B., Darensburg, T. B., Clay, S. D., Okpechi, S. C., & Sarpong, D. F. (2017). Clinical effects of cigarette smoking: epidemiologic impact and review of pharmacotherapy options. *International Journal of Environmental Research and Public Health*, 14(10), 1147. http://dx.doi.org/10.3390/ijerph14101147. PMid:28956852.

Ostadrahimi, A., Taghizadeh, A., Mobasseri, M., Farrin, N., Payahoo, L., Beyramalipoor Gheshlaghi, Z., & Vahedjabbari, M. (2015). Effect of probiotic fermented milk (kefir) on glycemic control and lipid profile in type 2 diabetic patients: a randomized double-blind placebo-controlled clinical trial. *Iranian Journal of Public Health*, 44(2), 228-237. PMid:25905057.

Peto, R., & Lopez, A. D. (2001). Future worldwide health effects of current smoking patterns. In C. Everett Koop, C. E. Pearson & M. Rory Schwarz (Eds.), *Critical issues in global health*. San Francisco: Jossey-Bass.154-161.

Polidori, M. C., Mecocci, P., Stahl, W., & Sies, H. (2003). Cigarette smoking cessation increases plasma levels of several antioxidant micronutrients and improves resistance towards oxidative challenge. *British Journal of Nutrition*, 90(1), 147-150. http://dx.doi.org/10.1079/BJN2003890. PMid:12844386.

Pryor, W. A., & Stone, K. (1993). Oxidants in cigarette smoke: radicals, hydrogen peroxide, peroxynitrate, and peroxynitrite. *Annals of the New York Academy of Sciences*, 686, 12-27. http://dx.doi.org/10.1111/j.1749-6632.1993.tb39148.x. PMid:8512242.

Punaro, G. R., Maciel, F. R., Rodrigues, A. M., Rogero, M. M., Bogsan, C. S., Oliveira, M. N., Ihara, S. S., Araujo, S. R., Sanches, T. R., Andrade, L. C., & Higa, E. M. (2014). Kefir administration reduced progression of renal injury in STZ-diabetic rats by lowering oxidative stress. *Nitric Oxide*, 37, 53-60. http://dx.doi.org/10.1016/j.niox.2013.12.012. PMid:24406684.

Ramanathan, G., Araujo, J. A., Gornbein, J., Yin, F., & Middlekauff, H. R. (2014). Cigarette smoking is associated with dose-dependent adverse effects on paraoxonase activity and fibrinogen in young women. *Inhalation Toxicology*, 26(14), 861-865. http://dx.doi.org/10.3109/08958378.2014.965559. PMid:25472476.

Rosa, D. D., Dias, M. M. S., Grześkowiak, Ł. M., Reis, S. A., Conceição, L. L., & Peluzio, M. D. C. G. (2017). Milk kefir: Nutritional, microbiological and health benefits. *Nutrition Research Reviews*, 30(1), 82-96. http://dx.doi.org/10.1017/S0954422416000275. PMid:28222814.

Sakila, & Valarmathi. (2021). A comparative study of lipid profile among smokers and non-smokers. *International Archives of Integrated Medicine*, 8(3), 12-19.

Sharifi-Rad, M., Anil Kumar, N. V., Zucca, P., Varoni, E. M., Dini, L., Panzarini, E., Rajkovic, J., Tsouh Fokou, P. V., Azzini, E., Peluso, I., Prakash Mishra, A., Nigam, M., El Rayess, Y., Beyrouthy, M. E., Polito, L., Iriti, M., Martins, N., Martorell, M., Docea, A. O., Setzer, W. N., Calina, D., Cho, W. C., & Sharifi-Rad, J. (2020). Lifestyle, Oxidative Stress, and Antioxidants: Back and Forth in the Pathophysiology of Chronic Diseases. *Frontiers in Physiology*, 11, 694. http://dx.doi.org/10.3389/fphys.2020.00694. PMid:32714204.

Sies, H. (1997). Oxidative stress: oxidants and antioxidants. *Experimental Physiology*, 82(2), 291-295. http://dx.doi.org/10.1113/expphysiol.1997.sp004024. PMid:9129943.

Solak, Z. A., Kabaroğlu, C., Cok, G., Parildar, Z., Bayindir, U., Ozmen, D., & Bayindir, O. (2005). Effect of different levels of cigarette smoking on lipid peroxidation, glutathione enzymes and paraoxonase 1 activity in healthy people. *Clinical and Experimental Medicine*, 5(3), 99-105. http://dx.doi.org/10.1007/s10238-005-0072-5. PMid:16284731.

St-Onge, M. P., Farnworth, E. R., Savard, T., Chabot, D., Mafu, A., & Jones, P. J. (2002). Kefir consumption does not alter plasma lipid levels or cholesterol fractional synthesis rates relative to milk in hyperlipidemic men: a randomized controlled trial. *BMC Complementary and Alternative Medicine*, 2(1), 1. http://dx.doi.org/10.1186/1472-6882-2-1. PMid:11825344.

Whitehead, T. B., Robinson, D., & Allaway, S. L. (1996). The effects of cigarette smoking and alcohol consumption on blood lipids: a dose-related study on men. *Annals of Clinical Biochemistry*, 33(Pt 2), 99-106. http://dx.doi.org/10.1177/000456329603300201. PMid:8729716.

World Health Organization – WHO. (2008). *WHO report on the global tobacco epidemic, 2008: the MPOWER package*. Geneva: WHO. Retrieved from https://apps.who.int/iris/handle/10665/43818