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ATTENUATION OF CIGARETTE-SMOKE-INDUCED OXIDATIVE STRESS BY OAT DIET

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ABSTRAK

Abstract:
Even after cessation of cigarette smoke exposure, long-term exposure leads to lung fibrous tissue growth characteristically by oxidative stress. Oat, an inexpensive dietary source with antioxidant characteristics, is expected to alleviate oxidative stress in the lung tissue after exposure to cigarette smoke has ceased. This research aims to evaluate the effect of an oat diet in alleviating oxidative stress in the lung tissue of BALB/c mice after cessation of cigarette smoke exposure. A randomized post-test-only control group design was used for this research. The sample used in this experiment is male BALB/c mice (n = 33). Mice with BALB/c strain were separated into two groups: (1) control and (2) treatment. SOD, GSH, and MDA were the variables of the study. Cigarette smoke exposure decreases the activity of SOD and GSH and increases the concentration of MDA. After cigarette smoke exposure had been stopped in the oat-treated mice group, SOD and GSH activities were enhanced, and the MDA content dropped. This research's variable outcomes were statistically significant (P<0.05) from the standard feed alone-treated BALB/c mice group. Thus, consuming oats may alleviate oxidative stress implicated in lung fibrogenesis following cessation of tobacco smoke exposure.

***Abstrak*:**
Setelah penghentian paparan asap rokok, paparan jangka panjang tetap menyebabkan terbentuknya jaringan fibrosa paru yang ditandai dengan stres oksidatif. Gandum, sumber makanan murah dengan karakteristik antioksidan, diharapkan dapat mengurangi stres oksidatif pada jaringan paru-paru tikus setelah penghentian paparan asap rokok. Tujuan penelitian ini adalah untuk mengetahui efek pemberian gandum terhadap penanda stres oksidatif tikus pasca penghentian pajanan asap rokok. Jenis penelitian yang digunakan adalah randomized post-test only control group design. Penelitian ini menggunakan sampel mencit jantan dengan galur BALB/c (n = 33). Secara acak, tikus BALB/c dipisahkan menjadi dua kelompok: kontrol dan perlakuan. SOD, GSH, dan MDA merupakan variabel penelitian. Setelah penghentian paparan asap rokok pada mencit BALB/c yang diberi gandum secara oral, aktivitas SOD dan GSH meningkat, dan konsentrasi MDA menurun. Hasil variabel penelitian ini bermakna secara statistik (P<0,05) dari kelompok mencit BALB/c yang tidak mendapatkan terapi gandum. Dengan demikian, mengonsumsi gandum dapat mengurangi stres oksidatif, yang terlibat dalam fibrogenesis paru setelah penghentian paparan rokok.

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INTRODUCTION

Pulmonary fibrosis is a lung condition that is chronic, progressive, and irreversible [1]. Among other environmental exposures, tobacco smoke, metals, dust, medicines, and infectious agents have been linked to an increased risk of pulmonary fibrosis [2], [3]. However, it is widely considered that cigarette smoke exposure is a significant risk factor for producing fibrotic tissue, primarily in the lower lobe of the lung [4]. Due to the presence of reactive oxygen species and reactive nitrogen species, cigarette smoke causes Alveolar Epithelial Cell (AEC) oxidative damage, which is essential for the onset of fibrogenesis [5]–[7]. Furthermore, the epithelium damage may continue after cigarette smoke exposure has ceased. The current therapy options for idiopathic pulmonary fibrosis have exhibited limited clinical improvement; thus, there is a continuing need for more therapeutic choices [3].

Oatmeal is an inexpensive source of soluble dietary fiber. In recent years, oat consumption has increased due to the health benefits associated with the dietary fiber β-glucan, functional protein, lipid and starch components, and phytochemicals [8], [9]. It has been demonstrated that β-glucan, a polysaccharide, has cholesterol-lowering and anti-diabetic effects, making it the most crucial active component of oat. Along with these advantageous effects, those compounds exhibit antioxidant activity, anti-inflammatory, as well as antiatherogenic properties [10].

Considering oat beneficial properties, it is expected that consuming oats will enhance the recovery of cigarette-smoke-induced lung injury and oxidative stress. This research aims to examine the impact of an oat-based diet on oxidative stress-induced fibrogenesis in the lungs of male BALB/c mice.

RESEARCH METHOD

Thirty-three male BALB/c mice weighing 25 – 35 g (12 – 14 weeks) were obtained and received standard feed once daily. Drinking water was available ad libitum via a hung bottle. Thirty-three mice were randomly divided into two groups: (1) control (CON, n = 5) and (2) treatment (SF+CSE, n = 28).

The CON group was treated with Standard Feed (SF) for two weeks without Cigarette Smoke Exposure (CSE). The SF+CSE group was fed a standard diet and exposed to cigarette smoke for six weeks. Mice were positioned in a smoke chamber mimicking passive smokers; the dose was one cigarette (Djie Sam Soe, PT Gudang Garam Tbk., Indonesia) per two mice, two times per day, and seven days per week. Following four weeks of treatment for cigarette smoke exposure, four mice died. After six weeks, eight mice were sacrificed.

For the second four-week treatment phase, the surviving animal in SF+CSE group were divided into two groups (SF and SF+O). There was no longer any cigarette smoke exposure. The SF group received regular feed, while the SF+O group received standard feed plus 3.5 grams of instant oatmeal daily.

Ketamine 10% was used to anesthetize animals in each group at the end of the treatment period (0.4 mg/10 g BW; intraperitoneally). For enzyme-linked immunosorbent assay (ELISA) measurements of superoxide dismutase (SOD), malondialdehyde (MDA), and glutathione (GSH), the right lung was homogenized. All samples were kept at -20 °C until further analysis.

Data analysis was carried out using SPSS V25 and presented as median with inter-quartile range. Kruskall-Wallis H test and pairwise comparisons were performed. P value < 0.05 was chosen as statistically significant.

RESULTS AND ANALYSIS

Cigarette smoke exposure and an oat-based diet significantly impact SOD, GSH, and MDA concentrations. The levels of SOD and GSH in the group treated with standard feed and cigarette smoke exposure (SF+CSE) were significantly lower and ($P<0.05$) than in the CON group, whereas the MDA concentration was significantly higher ($P <0.05$). The difference of the levels of SOD, GSH, and MDA between animal in the SF+CSE group and SF treatment alone were not statistically significant, implying that standard feed alone is ineffective at reducing oxidative stress caused by cigarette smoke exposure. Meanwhile, treatment with an oat-based diet (SF+O) increased SOD activity ($P<0.05$), with values comparable to the CON group. Similarly, after oat intervention (SF+O), GSH concentration increased ($P<0.05$). Furthermore, MDA levels in the SF+CSE group were significantly lower ($P<0.05$). These findings indicated that oat might help with oxidative stress.

Table 1.
SOD, GSH, and MDA Levels in Each Group

Parameters	CON (n = 5)	SF+CSE (n = 8)	SF (Post-CSE) (n = 8)	SF+ O (Post-CSE) (n = 8)
	median (IQR)	median (IQR)	median (IQR)	median (IQR)
SOD (U/mL)	0.177 (0.027)	0.108 (0.014)	0.123 (0.010)	0.169 (0.026)
GSH (µM)	12.090 (0.211)	7.760 (0.068)	8.794 (0.491)	11.430 (1.063)
MDA (µM)	3.196 (0.097)	9.158 (0.293)	7.172 (0.318)	4.897 (0.388)

Environmental tobacco smoke (ETS) or secondhand smoke is the byproduct of the combustion of tobacco products and is composed of both mainstream smoke (smoke emitted by active smokers) and sidestream smoke (burning cigarette ends) [11]. ETS is a ubiquitous pollutant that is extremely hazardous to human health due to the presence of millions of free radicals in the form of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which induce oxidative stress in bronchial epithelial cells, bronchioli, and alveoli.

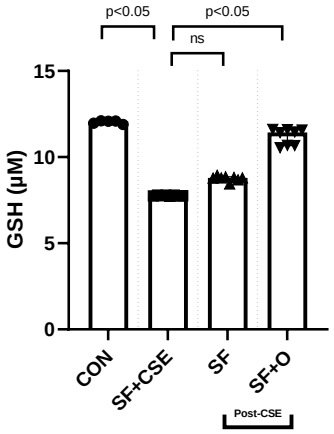

Figure 1. GSH concentration in each group

Cigarette smoke contains reactive compounds such as superoxide, hydrogen peroxide, hydroxyl radicals, and nitric oxide. Oxidative stress is caused by an imbalance between ROS/RNS production and the antioxidant defense system, resulting in dysfunctional cells and tissue damage [12], [13]. ROS/RNS produced by cigarette smoke directly damage alveolar epithelial cells (AEC) and promote lung fibrogenesis by increasing the secretion of the pro-fibrotic growth factor transforming growth factor-β (TGF-β) from the epithelium; TGF-β then stimulates fibroblast proliferation and differentiation into myofibroblasts [14], [15].

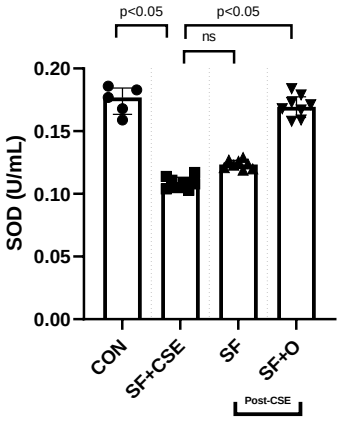

Figure 2. SOD activity in each group.

Cigarette smoke containing free radicals alters the homeostasis of oxidants and antioxidants by reducing antioxidant mechanisms found in intracellular, resulting in oxidative stress in mice lung tissue. GSH is an antioxidant with a low molecular weight produced by bronchial epithelial cells and alveolar macrophages [16]. GSH can react with a wide range of molecules and electrophilic reactive components in cigarette smoke, making it an effective antioxidant and detoxifying agent [17]. Recent research indicates that GSH protects against oxidative stress in cells caused by cigarette smoke exposure [18]. Bazzini et al. (2013) discovered that exposure to cigarette smoke for three hours decreased GSH levels [17]. Our study implies that six weeks of cigarette smoke exposure reduces GSH levels; however, oat intervention could increase the GSH level, thereby increasing the antioxidant and cytoprotective mechanisms.

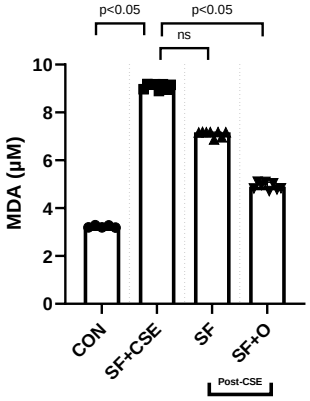

Figure 3. MDA content in each group.

SOD decomposes superoxide radicals to H_2O_2 and thus plays an essential part in the respiratory system's antioxidant defense. Lung cells contain all three isoforms of mammalian SOD (intracellular copper-zinc SOD, mitochondrial manganese SOD, and extracellular SOD [EC-SOD]). EC-SOD is abundant in the lung and has been linked to the pathophysiology of ROS-induced pulmonary illnesses such as pulmonary fibrosis [19], [20]. Cigarette smoke exposure promoted a decrease in SOD activity in the SF+CSE group, suggesting that the enzymatic antioxidant mechanism was reduced, contributing to oxidative damage. Treatment with an oat-based diet was able to neutralize the oxidative molecules generated in response to cigarette smoke exposure by increasing the antioxidant activities of SOD.

Malondialdehyde (MDA) is the main product of lipid peroxidation and is used as a marker of oxidative stress. Our results indicate that oat is capable of reducing lipid peroxidation that occurs in the presence of ROS, as indicated by reduced MDA levels in treated animals (SF+O). Overall, our data clearly imply that an oat-based diet is an efficient antioxidant by increasing the activity of enzymatic and non-enzymatic antioxidants (SOD and GSH, respectively) while lowering the levels of MDA in lung tissue homogenate after cigarette smoke exposure had been stopped.

CONCLUSION

After cessation of exposure to cigarette smoke, oat-based diet enhanced enzymatic and non-enzymatic antioxidants (SOD and GSH) and reduced the product of lipid peroxidation (MDA). Treatment with oat effectively attenuates cigarette smoke-induced oxidative damage; thus, an oat-based diet may alleviate pulmonary fibrosis through the oxidation pathway by scavenging and neutralizing oxidative molecules triggered by cigarette smoke.

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