Journal of Medicinal and Chemical Sciences 6 (2023) 2785-2792

Journal of Medicinal and Chemical Sciences

Journal homepage: http://www.jmchemsci.com/

Original Article

Curcuma Longa May Prevent Endothelial Dysfunction in *Rattus Norvegicus* Exposed by Soot Particulate through Changes of OxLDL and eNOS Levels

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ARTICLE INFO

Article history

Receive: 2023-06-09
Received in revised: 2023-07-11
Accepted: 2023-07-12
Manuscript ID: JMCS-2306-2097
Checked for Plagiarism: **Yes**
Language Editor:
Dr. Fatima Ramezani
Editor who approved publication:
Dr. Yasser Fakri Mustafa

DOI:10.26655/JMCHEMSCI.2023.11.23

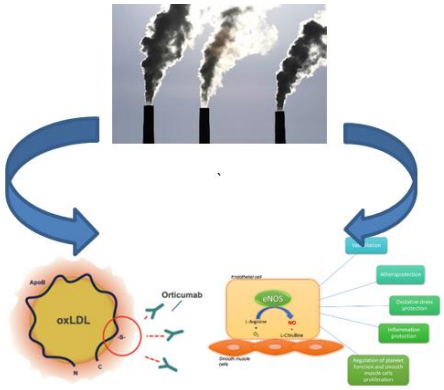
KEYWORDS

Carbon black
Curcumin
Health care
Oxidative stress
Rat

ABSTRACT

The purpose of this study is to prove the efficacy of *Curcuma longa* (turmeric) extracts against soot (carbon black)-exposed rats with Ox-LDL and eNOS levels. A total of 30 rats were divided into 5 groups with 6 rats in each group. Negative control group (C-) received no treatment. The positive control group (C+) exposed to soot at a concentration of 1064 mg/m3 for 8 hours. Treatment group T1 was exposed to soot at 1064 mg/m^3 for 8 hours + *Curcuma longa* at 1 mg/kg body weight. T2 group was exposed to soot at 1064 mg/m^3 for 8 hours + 2 mg curcuma longa mg/kg body weight, and T3 group were exposed to soot at of 1064 mg/m^3 for 8 hours + curcuma longa 3 mg/kg body weight. The result of T3 group had lower Ox-LDL levels and higher eNOS levels, and also the difference was significant ($p>0.05$) than the C+ group. We conclude that the treatment of rats exposed to 1064 mg/m^3 soot particles for 8 hours with *Curcuma longa* extract at a dose of 3 mg/kg body weight reduced Ox-LDL levels and increased eNOS levels because curcumin from *Curcuma longa* extract effective to break the chain reaction from lipid peroxidation, inhibit LOX-1 expression, prevent LDL modification into ox-LDL, and decrease coupled eNOS levels that prevent NO and GSH degradation.

GRAPHICAL ABSTRACT



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Introduction

Air pollution impairs endothelial function by various mechanisms that are still not fully understood. Fine particulate matter ($PM_{2.5}$) in air pollution was the fifth leading risk factor for death in 2015 [1].

PM2.5 particulates in air pollution can initiate and influence the body to cause acute cardiovascular disease. The disease onset begins with vascular dysfunction that results in multiple systemic disorders, such as dysregulation of lipid metabolism, inflammation, and thrombus formation and arterosclerosis [2].

At the cellular level, particulate carbon black damages cell membranes through lipid peroxidation, generating hydroxyl radicals and leading to the formation of malondialdehyde (MDA). This process is commonly referred to as reactive oxygen species (ROS). These compounds can cause cell damage and are indicators of increased oxidative stress in blood plasma. Oxidative stress due to the increased levels of MDA will induce cell degeneration and then result in endothelial cell dysfunction [3, 4].

Some of the antioxidants include the antioxidant enzyme Superoxide Dismutase (SOD). This SOD enzyme acts as a frontline protective enzyme against superoxide anions. The SOD enzyme works by catalyzing and breaking down superoxide into hydrogen peroxide and oxygen. The O_2 molecule will be reduced to H_2O to form superoxide anion radicals which are then converted by the SOD enzyme into H_2O_2. In the process of formation of soot particles, incomplete phosphorylation occurs because the number of electrons that reduce the molecule is less so that the soot particles can enter the blood vessels. In the blood vessels, the body performs the body's defense mechanisms by increasing pro-inflammatory cytokines by macrophage cells. Increased pro-inflammatory cytokines by inflammatory cells will activate Nuclear Factor Kappa B (NF-kB) causing endothelial cell dysfunction. Endothelial cell dysfunction occurs due to a barrier formed by monocyte cells that gather and adhere to each other to form a thrombus in the subendothelial layer, causing increased vascular permeability and leukocyte adhesion. The thrombus that forms and differentiates into macrophages in the subendothelial layer will bind to OxLDL which causes activation of the inflammatory process, and macrophage polarization, as well as promotes platelet aggregation and activation [5-11].

OxLDL inhibits eNOS and increases iNOS, thereby increasing NO production and protein S-nitrosylation in human endothelial cells, and then iNOS-mediated S-nitrosylation is becoming important in cardiovascular disease [12].

Curcuma longa, or commonly called turmeric, is a plant of the Zingiberaceae family. This rhizomatous plant is a native plant species in Southeast Asia and has spread to India and Malaysia. Curcuma longa is a herbal medicine and natural alternative medicine. Herbal medicines are believed to have beneficial effects on the body without side effects. Curcuma itself is known to be widely used by people all over the world as a consumer and medicinal ingredient. This genus currently includes 133 species worldwide. The researchers chose Curcuma longa over other plants because it is a rhizomatous plant that grows abundantly and is readily available in the tropics. Curcuma longa, which belongs to the ginger family (Zingiberaceae), is widely used in Asian countries and India as a spice, food preservative, and coloring agent. According to various literature, this plant is rich in polyphenols. Polyphenols contained in this plant are known to have antioxidant, anti-inflammatory, antibacterial, and anticancer effects [13, 14].

Curcuma longa, which contains polyphenols, is known to act as an antioxidant because it contains phenolic and ketone groups. The polyphenol in these plants is known to be biologically capable of protecting cell membranes from damage due to lipid peroxidation and actively scavenging free radicals [15].

One of the polyphenols is curcumin, which is a polyphenolic curcuminoid from the roots and rhizomes of Curcuma longa which is known to have a positive effect on cardiovascular disease. Therefore, curcumin supplementation is suggested to be given in cases of endothelial

dysfunction as an alternative to prevent cardiovascular disease [16].

Accordingly, based on this description, the researchers used rats as laboratory experiments and experimental animals to study the effects of curcuma longa as an anti-inflammatory and antioxidant agent on vascular damage from exposure to soot particles. This study was conducted to demonstrate that Curcuma Longa can suppressed eNOS and oxLDL levels in rats exposed to soot particles.

Material and Methods

This study complies with the Code of Ethics and has been approved by the Ethics Committee of Airlangga University College of Veterinary Medicine under no. 3.KE.043.03.2021.

The study subjects were 30 male rats divided into 5 treatment groups [17-20].

C-: Group of rats that received no treatment (negative control).

C+: Group of rats that were exposed by soot particulate with concentration of 1064 mg/m^3 for 8 hours (positive control).

T1: Group of rats exposed by soot particulate with concentration of 1064 mg/m^3 for 8 hours + *Curcuma Longa* 1 mg/kg bw dose.

T2: Group of rats exposed by soot particulate concentration 1064 mg/m^3 for 8 hours + *Curcuma Longa* 2 mg/kg bw.

T3: Group of rats exposed by soot particulate concentration 1064 mg/m^3 for 8 hours + *Curcuma Longa* dose 3 mg/kg bw.

All the five groups of rats were treated simultaneously and the oxLDL and eNOS levels were measured on day 30 of treatment.

Procedure of soot particulate powder exposure

All experimental rats were housed in maintenance cages until the start of treatment. Prior to treatment, an acclimation process was performed in an exposure box to acclimatize the test animals to the exposure treatment. Rats were exposed to soot particles at 1064 mg/m^3 for 8 hours each day for 30 days [19, 20].

Negative control rats, on the other hand, received no treatment and remained in maintenance cages.

The soot particle powder (carbon, mesoporous <100 µm) used for treatment was pre-calculated according to the dose at 1064 mg/m^3. Each group of rats was then placed in an exposure box, and soot particle powder was sprayed into the box through a blowpipe that operated continuously for 8 hours. During treatment, the temperature, airflow, and humidity were controlled, and feeding and drinking were provided ad libitum.

Curcuma longa extract administration procedure

Curcuma Longa powder extract (*Curcumin, (Curcuma Longa) Turmeric, C1385-Sigma-Aldrich*) made into solution for each treatment group. The T1 group was administered at dose of 1 mg/kg bw, T2 group at dose of 2 mg/kg bw, and the T3 groups at 3 mg/kg bw, respectively. Oral administration of the extract with sonde everyday for 30 days after soot exposure treatment [17, 18].

Measurement of oxLDL levels

Measurement of oxLDL levels using a TBA (thiobarbituric acid) measured spectrophotometrically. The oxLDL ELISA kit is used for this test (oxLDL Assay Kit competitive ELISA, MBS262297). Supernatant absorbance observed by spectrophotometer at 450 nm.

Measurement of eNOS levels

Measurements of eNOS levels were performed in TBA and read with a spectrophotometer to quantify MDA compounds produced by lipid peroxidation. The eNOS measurement used ELISA Kit (eNOS Assay Kit competitive ELISA, MBS721860). Supernatant absorbance observed by spectrophotometry at 450 nm.

Data analysis

The metrics data obtained at the oxLDL and eNOS levels were summarized in distribution tables and frequencies for each variable and tabulated. Data were analyzed with the ANOVA method. The analysis was performed with assuming the tested population was normally distributed, homogenous, and the samples, were not related to each other. Differences between treatments

were further analyzed using the LSD (Least Significant Difference) test.

Results and Discussion

Effect of treatment on OxLDL levels

An ANOVA study of OxLDL values from the five treatment groups resulted in a calculated F-value of 172.677 with a significance value (p-value) of 0.000 ($p<0.05$). Therefore, there were significant differences in OxLDL levels among the five treatment groups.

The results showing the highest OxLDL level in the C+ treatment group with a mean of 51.583 ± 4.019 and the lowest level were obtained in the T3 group with a mean of 3.487 ± 0.110. Hypothesis test results indicate that administration of curcuma longa may lower his OxLDL levels (Table 1).

Effect of treatment on ENOS levels

The five treatment group results for ENOS levels showed that a calculated F-value of 70,084 was achieved a significance (p-value) of 0.000 ($p<0.05$). Significant differences in ENOS scores were found among the five treatment groups.

The results showing the highest ENOS levels were found in the C- group with an average of 30.349 ± 6.182. The lowest ENOS levels were in the T1 group, with a mean of 7.459 ± 0.949. Although listed as containing Curcuma Longa may increase ENOS levels (Table 2).

Exposure from inhaled soot particulate can cause damage and dysfunctioin of blood vessels due to an increase ROS production and attack cell membranes of the endothelium [21].

Increase in ROS levels that exceed the normal level causes oxidative stress in the blood vessels known as vascular oxidative stress and it is predisposition to atherosclerosis [22].

ROS production is mediated by several enzymes, such as NADPH oxidase, Xanthine oxidase, electron transport system 2, and uncoupled endothelial in endhothelial nitric oxide synthase (eNOS) on the vascular wall [23].

Increased ROS improves expression of eNos through the mechanism of post transcription and postranslation [24].

During vascular oxidative stress, the endothelium also undergoes and activation and changes the shape from coupled eNOS and uncoupling eNOS along with an increase in ROS. Furthermore, the enzyme produces superoxide, and then degrades NO into another form i.e. peroxynitrite form [25].

Table 1: Analysis result of OxLDL levels

Treatment	N	Sig. S-W	M ± SD	Sig. LSD Test				
				C-	C+	T1	T2	T3
C-	6	0.389	3.478 ± 0.152	-	0.000	0.000	0.000	0.997
C+	6	0.053	51.583 ± 4.019	0.000	-	0.716	0.199	0.000
T1	6	0.159	50.572 ± 6.483	0.000	0.716	-	0.351	0.000
T2	6	0.711	47.958 ± 7.420	0.000	0.199	0.351	-	0.000
T3	6	0.733	3.487 ± 0.110	0.997	0.000	0.000	0.000	-
Sig. Levene		0.175						

Table 2: Analysis result of eNOS levels data

Treatments	N	Sig. S-W	M ± SD	Sig. LSD Test				
				C-	C+	T1	T2	T3
C-	6	0.552	30.349 ± 6.182	-	0.000	0.000	0.000	0.000
C+	6	0.158	8.494 ± 1.157	0.000	-	0.541	0.613	0.435
T1	6	0.610	7.459 ± 0.949	0.000	0.541	-	0.914	0.170
T2	6	0.735	7.640 ± 0.844	0.000	0.613	0.914	-	0.204
T3	6	0.157	9.818 ± 0.788	0.000	0.435	0.170	0.204	-
Sig. Levene		0.060						

This is proven by the decrease of coupled eNOS levels in the C+ group that received exposure to soot particulates and the highest eNOS levels in the C- group who did not get soot particulate matter exposure.

Superoxide produced by eNOS feeds on NO so that the NO levels are significantly reduced [25]. Peroxynitrite that produced further reduced glutathione (GSH) levels which will increase the sensitivity of cells to ROS. Peroxynitrite also inactivates the enzyme Superoxide Dismutase (SOD) thereby reducing the capacity of cells in facing excessive ROS production and increasing superoxide levels, and also the cycle continues and initiates each other [22, 23].

The increased of superoxide and peroxynitrite caused by carbon black oxidized LDL into oxidize LDL (ox-LDL). Ox-LDL activating endothelial with increasing the monosit adhesion that will differentiate into macrophage.

The activation from macrophage will increasing the expression from toll-like receptor (TLR) and scavenger receptor (SR) that trigger enhancement lipid accumulation and foam cell forming at tunica intima [26].

In this study, ox-LDL levels in C group increased significantly because of the effect of giving soot particulate compared with the C- group.

Ox-LDL will bond with SR and lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) [26]. On the other hand, proinflammation cytokines as the ROS enhancement respond such as tumor necrosis factor alpha (TNF-*α*), *interleukin-1* (IL-1), and *interleukin-6* (IL-6) also increasing the LOX-1 expression [27].

The expression enhancement from LOX-1 receptor has a role in inflammatory respond, endothelial dysfunction, and lipid desposition in blood vessels [28].

The result of this research showing that the administration of soot particulate induce endothelial dysfunction through oxidative stress mechanism with the decrease coupled eNOS levels that prevent NO and GSH degradation also increase ox-LDL levels that bond with LOX-1 which is predisposition of lipid desposition in blood vessels.

Active ingredients from *Curcuma longa* extract i.e. curcumin has high antioxidant activity as reported from previous study includes Fleenor [29] who reported that the administration of curcumin extract normalize superoxide production and oxidative stress also restore the NO bioavailability.

Curcumin also reported by Lukitaningsih [30] increasing antioxidant especially GSH so that can prevent oxidative stress that occurs in endothelial. By *in vitro*, curcumin was reported by Nurseta [31] can increasing eNOS levels in trophoblast cell. That result in line with this study which eNOS levels in T3 with the highest *Curcuma longa* dose has eNOS levels that higher compared to C group, T1, and T2 groups.

Moreover, curcumin has a role in decreasing ox-LDL levels as reported by Mahfouz and Funamoto [32, 33].

Curcumin mechanism, as *chain breaking antioxidant*, is effective to break the chain reaction from lipid peroxidation and prevent LDL modification into ox-LDL [32].

Curcumin also reported inhibit LOX-1 expression with signal wnt disturbance and stimulating activation PPARγ [33].

This study showed that the administration of *Curcuma longa* extract can decreasing ox-LDL levels with effective dose in T3 group compared with another groups.

In the T3 group, *Curcuma longa* administration showed a pattern of eNOS increase, although it was not as high as eNOS levels in the negative control group. This is probably because the measured eNOS levels are eNOS in serum, not functional eNOS levels in vascular endothelial cells. In addition, the dose of Curcuma longa 1, 2, and 3 mg/kg BW and the administration duration for 30 days has not been able to increase eNOS levels optimally, but needs to be evaluated to get the optimum dose. The eNOS enzyme is constitutively expressed by endothelial cells in modulating endothelial function and has the main responsibility for producing nitric oxide (NO) in the vascular endothelium. NO produced by eNOS in the vascular endothelium plays an important role in regulating vascular tone, cellular proliferation, leukocyte adhesion, and platelet aggregation. In the soot-exposed group, blood vessel stiffness occurred, causing NO to be produced more to maintain blood vessels. This

increase in NO levels is a compensatory process. When given exposure to *Curcuma longa*, blood vessel dilatation occurs so there is no need for high NO production anymore. The results of this study showed that soot particulate matter induced endothelial dysfunction through oxidative stress mechanisms with decreased levels of coupled eNOS which prevents the degradation of NO, GSH, and increased levels of Ox-LDL which will bind to LOX-1 which predisposes to lipid deposition in blood vessels [32, 33].

Conclusion

Treatment of rats exposed to 1064 mg/m^3 soot particles for 8 hours with *Curcuma longa* extract at a dose of 3 mg/kg body weight reduced Ox-LDL levels and increased eNOS levels because curcumin from *Curcuma longa* extract effective to break the chain reaction from lipid peroxidation, inhibit LOX-1 expression, prevent LDL modification into ox-LDL, and decrease coupled eNOS levels that prevent NO and GSH degradation.

Acknowledgments

The authors thank the authorities of Universitas Airlangga, Surabaya, East Java, Indonesia and Faculty of Veterinary Medicine.

Conflict of Interest

All authors have declared no conflicts of interest.

Funding

The author received no financial support for the research, writing, and/or publication of this article.

Authors' Contribution

MA, JS, TWS, and WW organized this study. MA, JS, TWS, and WW conducted surveys and took samples from sample fields. All authors tested samples in the laboratory. All authors edited, read, revised and approved the final manuscript.

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HOW TO CITE THIS ARTICLE

Muhammad Aminuddin, Djanggan Sargowo, Teguh Wahju Sardjono, Widjiati Widjiati*. *Curcuma longa* May Prevent Endothelial Dysfunction in *Rattus Norvegicus* Exposed by Soot Particulate through Changes of OxLDL and eNOS Levels. *J. Med. Chem. Sci*., 2023, 6(11) 2785-2792.
DOI: https://doi.org/10.26655/JMCHEMSCI.2023.11.23
URL: https://www.jmchemsci.com/article_175740.html