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Effects of DNA demethylation with rich intake of CYP2E1, glutathione and decarboxylase enzymes on cholesterol of smokers in the printing industry in Surabaya

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ABSTRACT

Introduction: Toluene is a chemical solvent widely used in the printing industry that can generate reactive oxygen species (ROS) and induce oxidative stress, leading to lipid peroxidation.

Aims: This study investigates the effect of toluene exposure on malondialdehyde (MDA) and cholesterol levels and evaluates the potential protective role of a dietary enzyme-enriched beverage.

Methods: This research employed a pre-experimental design without a control group. The study population included all workers at Airlangga University Press and PT. Graha Cipta Pustaka in Surabaya, totaling 26 individuals. A sample of 15 workers was selected for analysis. Participants consumed a powdered beverage enriched with CYP2E1 and decarboxylase enzymes (10 g/day dissolved in 200 mL water, administered once daily for 14 days). Blood samples were collected before and after the intervention to measure MDA and cholesterol. Data were analyzed using a paired sample t-test. Dropout handling was performed by oversampling beyond the minimum required sample size.

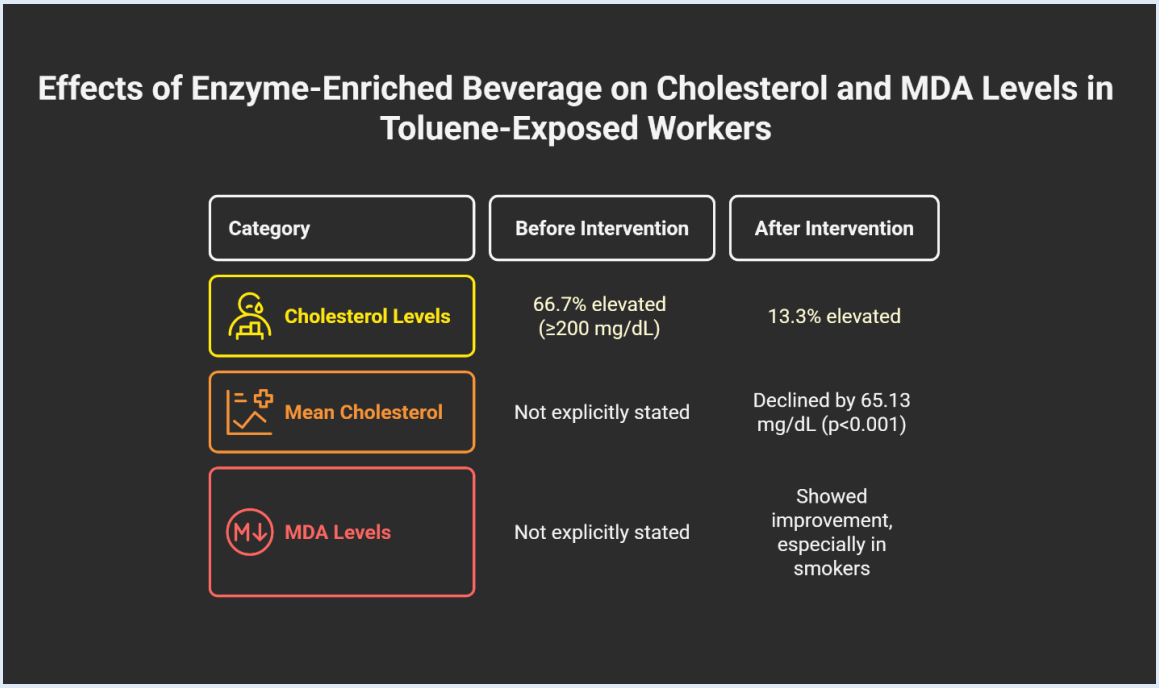
Results: Before intervention, 66.7% of participants had elevated cholesterol levels (≥200 mg/dL). After the intervention, this proportion decreased to 13.3%. Mean cholesterol levels declined significantly (65.13 mg/dL reduction, $p<0.001$). MDA levels also showed improvement, particularly among smokers.

Conclusion: Consumption of a CYP2E1 and decarboxylase-enriched beverage significantly reduced cholesterol and MDA levels in toluene-exposed workers. The absence of a control group is acknowledged as a limitation, and future studies should adopt randomized controlled designs.

Novelty: This study is among the first to explore enzyme-based dietary intervention for mitigating oxidative stress biomarkers in toluene-exposed workers. It highlights a practical approach for occupational health management in industries with solvent exposure.

Keywords: Toluene exposure; DNA demethylation; CYP2E1 enzyme; Cholesterol; Oxidative stress; Printing industry workers

Graphical Abstract: Effects of DNA demethylation with rich intake of CYP2E1, glutathione and decarboxylase enzymes on cholesterol of smokers in the printing industry in Surabaya.



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INTRODUCTION

In Indonesia, various industrial sectors exist including the printing industry. In printing processes, whether conducted manually or with machines, the primary raw materials used include paper, ink, and solvents that contain hazardous chemicals (1–3). In the printing industry, toluene is involved in approximately 75% of all work activities (4,5), with the highest usage for automatic cleaning (6,7). It is also used as a lubricant for printing machines and in printing ink (7,8). Toluene is a chemical that behaves as a free radical upon entering the body, capable of triggering oxidative stress. Oxidative stress occurs when there is an imbalance between free radical production and antioxidant defenses, where free radicals dominate over antioxidants (9–11). This condition is indicated by elevated levels of malondialdehyde (MDA), a biomarker of increased oxidative stress (12,13).

Cytochrome P450 2E1 (CYP2E1) is known to be the primary enzyme responsible for metabolizing toluene. This enzyme is abundantly found in liver tissue (14–16). In the human body, the Phase I biotransformation of toluene is predominantly carried out by CYP2E1 (17,18). Cytochrome P450 (CYP) enzymes play a crucial role in metabolizing various drugs, carcinogens, alkaloids, pesticides, and other xenobiotics (19–21). Toluene can be metabolized into several compounds in the human body. One of the main metabolic pathways involves oxidation into benzoic acid via alcohol dehydrogenase in the liver (22–24). Toluene can also be converted into benzoyl-coenzyme A (benzoyl-CoA), which may enter the citric acid cycle or be further transformed into more easily excreted compounds (25,26). The accumulation of toxic metabolites can lead to an increase in reactive oxygen species (ROS) (27,28). ROS are normal byproducts produced by mitochondria that function in maintaining physiological processes such as cell proliferation, host defense, signal transduction, and gene expression (29,30).

Several studies have examined toluene toxicity and its health risks, but only limited research has focused on nutritional or enzymatic interventions to counteract these effects. In particular, the use of dietary intake enriched with CYP2E1 and decarboxylase enzymes as a

preventive approach for occupationally exposed workers has not been widely reported. This positions the current study as a novel contribution to occupational health research. According to the Indonesian Ministry of Health, normal cholesterol is defined as <200 mg/dL, while levels ≥200 mg/dL indicate elevated cardiovascular risk (31). Strategies to mitigate oxidative stress and lipid abnormalities in solvent-exposed workers are therefore essential.

Based on the explanation above, it is important to conduct a study analyzing changes in malondialdehyde and cholesterol levels before and after the administration of dietary intake rich in CYP2E1 and decarboxylase enzymes among printing industry workers in Surabaya. This study is the first to investigate whether an enzyme-enriched beverage can reduce MDA and cholesterol levels in printing industry workers exposed to toluene. By linking occupational exposure with a dietary enzymatic intervention, this research provides a new perspective on preventive measures for solvent-related health risks.

METHODS

This study used a pre-experimental design without a control group. In this design, the intervention is applied to research subjects, and outcomes are compared before and after treatment. The absence of a control group is recognized as a limitation of this design, and results should therefore be interpreted with caution regarding causality. The study was conducted at Airlangga University Press and PT. Graha Cipta Pustaka printing companies in Surabaya, from November to December 2024.

The study population included all workers who met the following inclusion criteria: signing informed consent, being in good health without coronary heart disease, chronic hypercholesterolemia, stroke, or arterial disease, and not previously exposed to similar enzyme-enriched beverages. A simple random sampling method was employed. Based on the minimum sample size calculation, 11 participants were required. To anticipate potential dropout, 15 participants were recruited, and all completed the study.

Participants received a powdered beverage enriched with CYP2E1 and decarboxylase enzymes. Each sachet contained 10 g of powder standardized to approximately 150 mg of active enzymatic protein. The powder was dissolved in 200 mL of water and consumed once daily after lunch for 14 consecutive days. The enzymes were derived from food-based extracts, with salmon and fish oil as the primary sources of CYP2E1, and fermented plant-based protein as the main source of decarboxylase. Compliance was monitored through daily logs and direct interviews.

Data collection included questionnaire-based assessment of demographic and occupational characteristics, measurement of toluene concentrations in workplace air using personal sampling devices, and venous blood collection. Five milliliters of blood were obtained from each participant by trained medical staff using sterile vacutainer tubes. Samples were processed at the Tropical Disease Diagnostic Laboratory, Universitas Airlangga. Malondialdehyde (MDA) levels were measured using the spectrophotometric thiobarbituric acid reactive substances (TBARS) assay, while cholesterol levels were determined using enzymatic colorimetric methods. Data were analyzed both descriptively and analytically. Descriptive analysis was used to characterize demographic variables, toluene exposure levels, and changes in MDA and cholesterol concentrations. A normality test was performed for all continuous variables, followed by a paired sample t-test to evaluate differences in pre- and post-intervention measurements.

RESULTS

The results of this study are presented in descriptive and analytical form, including participants' smoking habits, cholesterol profiles, and changes in malondialdehyde

(MDA) levels. Tables 1–8 illustrate these findings in detail. To improve clarity, two visual aids are presented in addition to the tables. Figure 1 provides a flowchart summarizing the study design, including participant recruitment, intervention, and outcome measurement. Figure 2 illustrates the proposed biological mechanism, in which toluene exposure generates reactive oxygen species (ROS) that induce oxidative stress, leading to elevated MDA and cholesterol levels, while the enzyme-enriched beverage (CYP2E1 and decarboxylase) supports detoxification pathways and reduces oxidative damage.

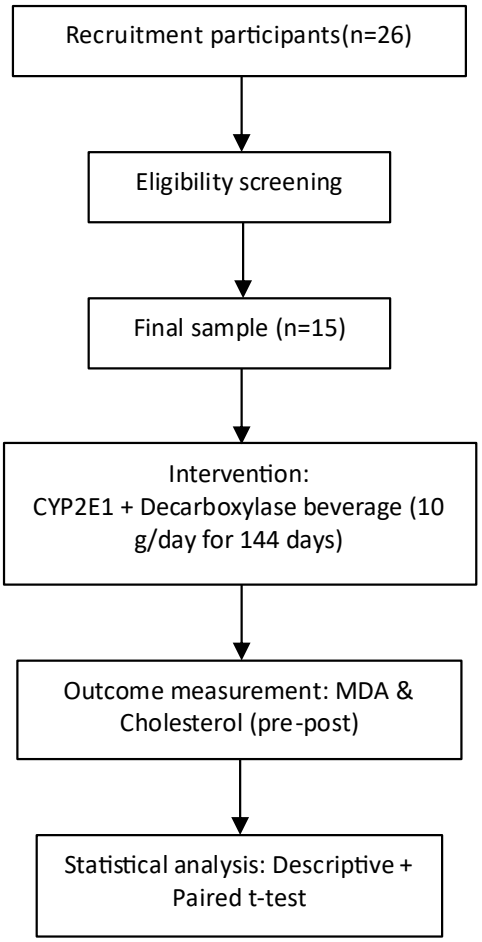

Figure 1. Flowchart of Study Design.

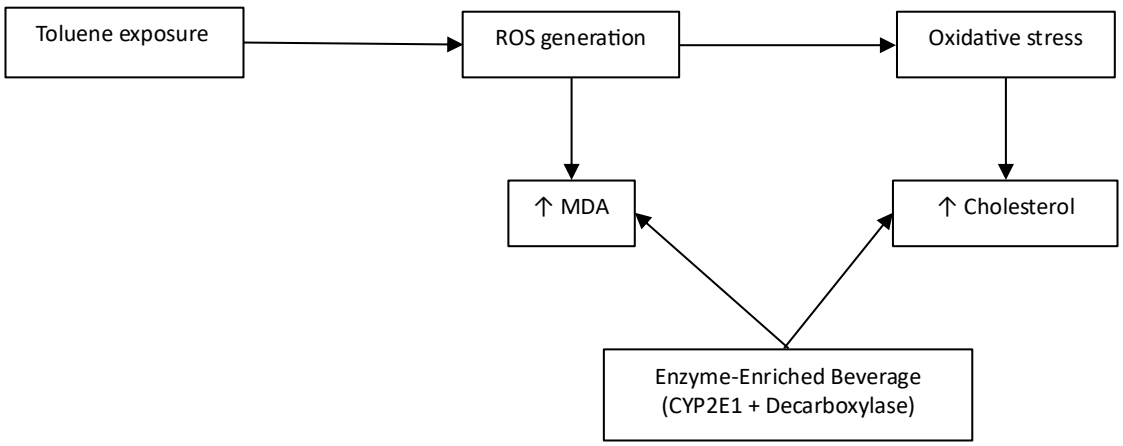

Figure 2. Mechanistic Pathway of Toluene-Induced Oxidative Stress and Enzymatic Mitigation.

Smoking Habits: In this study, smoking habits were classified into two categories: smokers and non-smokers. Table 1 displays the distribution of smoking habits among workers in the printing industry in Surabaya. Based on Table 1, the majority of workers do not smoke, with 8 workers (53.3%) identified as non-smokers, while 7 workers (46.7%) are smokers. The data was analyzed using the paired t-test with an alpha of 0.05.

Table 1. Distribution of Smoking Habits Among Printing Industry Workers in Surabaya, 2024.

Smoking habit	Frequency	
	f	Percentage (%)
Non-smoker	8	53.3
Smoker	7	46.7
Total	15	100.0

Analysis of Cholesterol Levels in the Blood of Printing Industry Workers in Surabaya Before and After Administration of CYP2E1 and Decarboxylase-Rich Supplement: According to the Indonesian Ministry of Health (2019), cholesterol levels are considered good if <200 mg/dL and not good if ≥200 mg/dL. The results of cholesterol measurements in the blood of workers at Surabaya's printing industry before and after receiving the CYP2E1 and decarboxylase-enriched powdered drink are shown in Table 2. Based on Table 2, it can be observed that the cholesterol measurements in the blood of workers before receiving the CYP2E1 and decarboxylase-enriched powdered drink showed that the majority of printing industry workers in Surabaya had elevated cholesterol levels (≥200 mg/dL), accounting for 66.7% or 10 workers. In contrast, 33.3% (5 workers) had normal cholesterol levels (<200 mg/dL).

Table 2. Cholesterol Distribution Among Printing Industry Workers in Surabaya, 2024.

Cholesterol Levels (mg/dL)	Before		After	
	f	%	f	%
Good (<200 mg/dL)	5	33.3	13	86.7
Not good (≤200 mg/dL)	10	66.7	2	13.3
Jumlah	15	100.0	15	100.0

Table 3. Cholesterol Level Measurements Among Printing Industry Workers in Surabaya, 2024.

	Cholesterol Level (mg/dL) After Intervention	Cholesterol Level (mg/dL) After Intervention	Difference (mg/dL)
Mean	213.93	148.80	65.13
Standard Deviation	26.532	36.462	-
Minimum	182	102	80
Maximum	277	226	51

Based on Table 3, the average difference in cholesterol levels before and after the administration of the CYP2E1 and decarboxylase-enriched powdered drink was 65.13 mg/dL, with a minimum difference of 80 mg/dL and a maximum difference of 51 mg/dL. Based on the normality test results, the p-value for cholesterol levels before and after the intervention was 0.200.

The difference in cholesterol levels before and after the intervention among printing industry workers in Surabaya is shown in Table 4. Based on Table 4, the p-value was 0.000. Since the p-value < alpha (0.05), this indicates a statistically significant difference in the mean

cholesterol levels of printing industry workers in Surabaya before and after the intervention with the CYP2E1 and decarboxylase-enriched supplement. The average cholesterol level decreased by 65.13 mg/dL, from 213.93 mg/dL before the intervention to 148.80 mg/dL after the intervention.

Table 4. Difference in Cholesterol Levels Before and After Intervention Among Printing Industry Workers in Surabaya, 2024.

	Average cholesterol levels (±SD) (mg/dL)	P-value
Before	213.93 (±26.5)	0.000
After	148.80 (±36.4)	0.000
Difference	65.13 (±31.7)	-

Analysis of Changes in Malondialdehyde and Cholesterol Levels Before and After the Intervention Based on Individual Characteristics, Activity Patterns, and Toluene Exposure Among Printing Industry Workers in Surabaya: The analysis of malondialdehyde (MDA) and cholesterol levels before and after the administration of CYP2E1 and decarboxylase-enriched supplements was conducted using cross-tabulation, taking into account several factors. These factors include: (1) Individual characteristics: age, sex, and nutritional status (BMI); (2) Activity patterns: duration of daily work, length of employment, smoking habits, and physical exercise habits; and (3) Toluene exposure levels.

Smoking habits: The cross-tabulation results between smoking habits and MDA levels before and after the intervention are presented in Table 5. Based on Table 5, it can be observed that after administering the CYP2E1 and decarboxylase-enriched powder supplement, workers who smoked exhibited a greater reduction in MDA levels. Initially, all 8 smoking workers (100%) had abnormal MDA levels. After the intervention, only 1 worker (12.5%) still had abnormal MDA levels, indicating that 7 smoking workers experienced improvement in MDA concentrations following the supplement intervention.

Table 5. Cross-tabulation of Smoking Habits and Malondialdehyde Levels Before and After Intervention Among Printing Industry Workers in Surabaya, 2024.

Smoking Habit	MDA Before		MDA After		Total
	Normal (<3.5 nmol/ml)	Abnormal (>3.5 nmol/ml)	Normal (<3.5 nmol/ml)	Abnormal (>3.5 nmol/ml)	n
Smoking	0 (0%)	8 (100%)	7 (87.5%)	1 (12.5%)	8 (100%)
Not smoking	0 (0%)	7 (100%)	6 (87.7%)	1 (14.3%)	7 (100%)
Total	0 (0%)	15 (100%)	13 (86.7%)	2 (13.3%)	15 (100%)

Age: The cross-tabulation results between age and cholesterol levels before and after the intervention are presented in Table 6. Based on Table 6, the adult age group (19–44 years) showed a more significant reduction in cholesterol levels after consuming the powdered drink enriched with CYP2E1 and decarboxylase enzymes. Initially, 7 workers (70%) in this age group had elevated cholesterol levels. After the intervention, only 1 worker (10%) remained with high cholesterol, indicating that 6 workers in this group experienced improvement.

Table 6. Cross-tabulation of Age and Cholesterol Levels Before and After Intervention Among Printing Industry Workers in Surabaya, 2024.

Age	Cholesterol Level – Before Intervention		Cholesterol Level – After Intervention		Total
	Good (<200 mg/dL)	Not good (>200 mg/dL)	Good (<200 mg/dL)	Not good (>200 mg/dL)	n
Adult (19-44 years)	3 (30%)	7 (70%)	9 (90%)	1 (10%)	10 (100%)
Pre-elderly (45-59 years)	2 (40%)	3 (60%)	4 (80%)	1 (20%)	5 (100%)
Total	5 (66,7%)				

Sex: The cross-tabulation between sex and cholesterol levels before and after the intervention is presented in Table 7. Based on Table 7, male workers showed a greater reduction in cholesterol levels after consuming the powder drink enriched with CYP2E1 and decarboxylase enzymes. Initially, 8 male workers (66.6%) had unfavorable cholesterol levels (≥200 mg/dL); after the intervention, only 1 worker (8.3%) remained in this category. This indicates that 7 male workers experienced improvement in cholesterol levels following the intervention.

Table 7. Cross-tabulation of Sex and Cholesterol Levels Before and After the Intervention among Printing Industry Workers in Surabaya, 2024.

Sex	Cholesterol Level – Before Intervention		Cholesterol Level – After Intervention		Total
	Good (<200 mg/dL)	Not good (>200 mg/dL)	Good (<200 mg/dL)	Not good (>200 mg/dL)	n
Female	1 (33.3%)	2 (66.6%)	2 (66.6%)	1 (33.3%)	3 (100%)
Male	4 (33.3%)	8 (66.6%)	11 (91.6%)	1 (8.3%)	12 (100%)
Total	5 (26.7%)	10 (66.7%)	13 (86.7%)	2 (13.3%)	15 (100%)

Table 8. Cross-tabulation of Smoking Habits and Cholesterol Levels Before and After the Intervention among Printing Industry Workers in Surabaya, 2024.

Smoking Habit	Cholesterol Level – Before Intervention		Cholesterol Level – After Intervention		Total
	Good (<200 mg/dL)	Not good (>200 mg/dL)	Good (<200 mg/dL)	Not good (>200 mg/dL)	n
No smoking	3 (37.5%)	5 (62.5%)	7 (87.5%)	1 (12.5%)	8 (100%)
Smoking	2 (28.6%)	5 (71.4%)	6 (85.7%)	1 (14.3%)	7 (100%)
Total	5 (33.3%)	10 (67.7%)	13 (86.7%)	2 (13.3%)	15 (100%)

Smoking Habits: The cross-tabulation of smoking habits and cholesterol levels before and after the intervention is presented in Table 8. Based on Table 8, it can be seen that after giving powder drinks rich in CYP2E1 and decarboxylase enzymes, workers who have a smoking habit experience a greater decrease in cholesterol levels than workers who do not smoke, namely from 5 workers (71.4%) who had bad cholesterol before treatment to 1 worker (14.3%) who had bad cholesterol after treatment.

DISCUSSION

Smoking Habits: The findings of this study revealed that workers who smoked experienced a greater reduction in malondialdehyde (MDA) levels after consuming the enzyme-enriched beverage compared to non-smokers. Before the intervention, all smoking workers showed

abnormal MDA levels, yet only one remained abnormal after the intervention. This suggests that enzymatic supplementation may have provided a stronger detoxification effect in individuals with higher oxidative stress burden. Smoking is well known to increase oxidative damage through the generation of free radicals and reactive oxygen species (ROS), which may explain why the intervention yielded more pronounced improvements in this group.

Previous studies have consistently shown that smoking contributes to lipid profile disturbances, including increased LDL and VLDL, as well as decreased HDL levels (32,33). These changes accelerate atherosclerotic processes and cardiovascular risk. The improvement seen in smoking workers in this study supports the idea that targeted enzymatic support can partially counteract these deleterious effects. However, it must be emphasized that dietary interventions cannot fully neutralize the harmful impact of smoking, and cessation remains the primary preventive measure.

Toluene Concentrations and Oxidative Stress: Although the measured toluene concentrations in the workplace were well below the national occupational exposure threshold (0.0265 ppm versus 20 ppm), significant differences in MDA and cholesterol levels were observed after intervention. This indicates that even low-level, chronic exposure may have biological consequences, particularly in susceptible populations such as smokers. The results are consistent with previous evidence suggesting that sub-threshold solvent exposure can still elevate oxidative stress biomarkers (34). Mechanistically, toluene metabolism occurs mainly via CYP2E1 in the liver, which produces ROS as byproducts (35). Accumulation of ROS contributes to oxidative stress, lipid peroxidation, and endothelial dysfunction. The observed improvements after the intervention highlight the potential role of nutritional strategies in enhancing detoxification and reducing oxidative damage. These findings add to the growing body of literature that solvent-induced health risks cannot be solely managed through regulatory threshold values but also require biological monitoring and preventive measures at the worker level.

Effect of Enzymatic Intervention: The intervention with CYP2E1 and decarboxylase-enriched beverages resulted in significant reductions in both cholesterol and MDA levels. On average, cholesterol levels decreased by more than 65 mg/dL, and the proportion of workers with normal cholesterol rose from 33.3% to 86.7%. Similarly, MDA levels improved markedly, especially among smokers. These results demonstrate the potential effectiveness of enzymatic supplementation in occupational health contexts. Biochemically, CYP2E1 facilitates toluene metabolism into less harmful metabolites, while decarboxylase enzymes support energy metabolism and the clearance of toxic intermediates (36). By enhancing these enzymatic pathways, the intervention may have reduced ROS production and lipid peroxidation (37). This mechanistic explanation is consistent with experimental studies linking enhanced biotransformation capacity to reduced oxidative burden. The study therefore provides empirical evidence that nutritional interventions targeting metabolic enzymes can complement conventional workplace safety measures.

Scientific Innovations & Practical Implications: This research presents a novel approach by linking nutritional biochemistry with occupational health. To our knowledge, it is one of the first studies to apply enzyme-based dietary interventions in workers exposed to toluene. The innovation lies not only in the type of intervention but also in the context of its application: occupational environments where solvent exposure is common. This positions the study as an important step in bridging laboratory findings with real-world industrial health strategies. From a practical perspective, the

intervention is low-cost, simple to administer, and potentially scalable to other industrial sectors where solvent exposure occurs. While engineering controls and personal protective equipment remain essential, dietary supplementation could serve as an additional layer of protection. Nevertheless, the study has limitations, including the absence of a control group, small sample size, and short intervention duration. Future research should adopt randomized controlled trial designs, include larger populations, and evaluate long-term outcomes to validate and expand upon these findings.

CONCLUSION

Based on the results and discussion, it can be concluded that printing industry workers in Surabaya are exposed to low but measurable levels of toluene, averaging 0.0265 ppm. Despite being below the national threshold, this exposure was associated with changes in oxidative stress biomarkers. Most workers had relatively stable occupational activity patterns, with working time ≤8 hours per day and employment duration ≤9 years, yet significant differences in cholesterol and malondialdehyde (MDA) levels were observed before and after intervention.

Administration of a CYP2E1- and decarboxylase-enriched beverage for 14 days resulted in a substantial reduction in both cholesterol and MDA levels, indicating that enzyme-based nutritional supplementation can mitigate solvent-related oxidative stress. Although the findings are promising, the absence of a control group, small sample size, and short intervention duration limit causal interpretation. Nevertheless, this study provides novel evidence supporting the role of dietary enzymatic interventions as complementary strategies in occupational health, particularly for workers exposed to toluene in the printing industry.

Competing interests: The authors declare that they have no competing interests.

Authors' contributions: PR and AT performed data analysis and reference analysis. GP, AR, and SS field data collection and respondent interviews. AS, AH, and EM are writing and reviewing the manuscript. KA, DM, and LH are reviewing the novelty of the manuscript. NM and DS data processing. AT the article submission. MA, SS, RM, and JF are reviewing relationships between items within the manuscript. BL, MN, RL, and ID provided feedback and comments on the manuscript.

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