Effect of Freeze-Dried Soyghurt on Malondialdehyde (MDA) Levels in Hypercholesterolemic Rats

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Abstract

The reduction of malondialdehyde (MDA) levels, a biomarker of lipid peroxidation holds clinical relevance in assessing oxidative stress associated with hypercholesterolemia. This study investigated the potential of freeze-dried soybean sourdough as a non-pharmacological intervention to lower cholesterol and mitigate oxidative stress in hypercholesterolemic rats. Thirty male Wistar rats were randomly assigned to 5 groups: negative control, positive control, Treatment 1 (high-fat diet containing 30% lard and simvastatin 5 mg/kg body weight), Treatment 2 (high-fat diet supplemented with soybean sourdough at 10 g/kg body weight), and Treatment 3 (high-fat diet combined with soybean sourdough and simvastatin). The intervention period lasted four weeks. Significant reductions in MDA levels were observed in Treatment Groups 1, 2, and 3, with the most pronounced decrease – 45% (($p < 0.01$) – recorded in Treatment Group 2. These findings suggest a possible interaction between soyghurt and simvastatin that may affect simvastatin's efficacy. Further research is needed to further explore this interaction and its underlying mechanisms.

Keywords: Hypercholesterolemia, Soyghurt, Simvastatin, Malondialdehyde

INTRODUCTION

Individuals who neglect their health may be at increased risk of developing hypercholesterolemia, a condition characterized by cholesterol levels in the blood exceeding normal thresholds. Contributing factors include genetic predisposition, age, gender, physical inactivity, and poor dietary habits (Berta et al., 2022). Hypercholesterolemia may reflect an accumulation of free radicals, highly reactive molecules with unpaired electrons, that contribute to oxidative stress, as indicated by elevated levels of malondialdehyde (MDA)(Vona et al., 2019). MDA, a byproduct of lipid peroxidation, is widely recognized as a biomarker of oxidative stress. Elevated MDA levels have been linked to dyslipidemia, a lipid imbalance in the blood that can heighten the risk of cellular and tissue damage, thereby exacerbating various health conditions(Klisic et al., 2018).

Soy isoflavones, particularly genistein, play a pivotal role in modulating the Nrf2/ARE signalling pathway, a key mechanism for reducing malondialdehyde (MDA) levels. Genistein activates the transcription factor Nrf2 (nuclear factor erythroid 2–related factor 2), which

subsequently binds to the antioxidant response element (ARE) on DNA. This interaction induces the expression of genes encoding critical antioxidant enzymes, including superoxide dismutase (SOD), catalase, and glutathione peroxidase. These enzymes work synergistically to neutralize free radicals and reactive oxygen species (ROS), thereby mitigating lipid peroxidation and ultimately lowering MDA production, the end product of this oxidative process. Recent research supports the mechanism by which genistein induces Nrf2 translocation from the cytoplasm to the nucleus through modification of cysteine residues in KEAP1 (Kelch-like ECH-associated protein 1), a natural inhibitor of Nrf2. Upon activation, Nrf2 promotes the synthesis of antioxidant proteins by regulating the transcription of its target genes. This protective effect is further amplified by genistein's role as an electron donor, enabling it to directly neutralize free radicals and thereby exert a dual action against oxidative stress. Under hypercholesterolemic conditions, characterized by elevated oxidative stress and increased malondialdehyde (MDA) production, genistein in soyghurt demonstrates notable protective effects. Beyond its role in activating the Nrf2/ARE pathway, genistein also engages multiple signalling cascades involved in redox homeostasis, including the PI3K/Akt and MAPK pathways, which collectively support the maintenance of cellular oxidant–antioxidant balance.

This dual mechanism, genetic modulation via Nrf2 and direct antioxidant activity, positions genistein in soyghurt as a promising agent for reducing MDA levels in hypercholesterolemic statesRecent research has increasingly focused on phytopharmaceutical treatments, including soyghurt—a yogurt product made from soy milk. Soyghurt is a probiotic beverage rich in isoflavones and recognized for its antioxidant properties(Rusmarilin & Silalahi, 2022). In this study, soyghurt is utilized in freeze-dried form, which offers greater probiotic viability compared to its wet counterpart (M. N. Handayani & Wulandari, 2016; Labiba et al., 2020).

Probiotics such as Lactobacillus acidophilus and Bifidobacterium bifidum are classified as lactic acid bacteria (LAB). Prebiotics can mitigate reactive oxygen species (ROS) by modulating immune responses, specifically, by inducing proinflammatory cytokines such as IFN-1 via the Toll-like receptor 4 (TLR-4) pathway and attenuating inflammatory mediators through the nuclear factor kappa B (NF-κB) pathway. Yogurt-derived probiotics, particularly Lactobacillus species, have been shown to lower cholesterol by inhibiting bile reabsorption and reducing intestinal cholesterol absorption(Markowiak & Śliżewska, 2017) (Abdi et al., 2022; Olas, 2020). Additionally, probiotics can reduce ROS by enhancing superoxide dismutase (SOD) activity, which neutralizes free radicals, a mechanism comparable to that of statins. The

fermentation process facilitated by these bacteria also promotes digestive health, further supporting cholesterol regulation(Corby-Edwards, 2013; Korcz et al., 2018; Voidarou et al., 2020). Overall, regular consumption of yogurt containing probiotic strains may offer a multifaceted strategy for lowering cholesterol and improving cardiovascular health.

Although statins remain the primary therapeutic option for hypercholesterolemia, patient intolerance to these drugs has highlighted the need for non-pharmacological adjuvants that can be used alongside conventional treatment. The fermentation process mediated by probiotic bacteria not only enhances digestive health but also contributes to the regulation of blood cholesterol levels. Accordingly, the consumption of yogurt containing probiotic strains may offer a complementary strategy for lowering cholesterol and promoting cardiovascular health through multiple interrelated mechanisms.

This study proposes two hypotheses:

H1: Soyghurt will reduce malondialdehyde (MDA) levels more effectively than simvastatin due to its combined antioxidant and probiotic effects.

H2: Combination therapy will exhibit antagonistic effects as a result of biotransformation.

Therefore, the aim of this study is to evaluate the impact of freeze-dried soyghurt on MDA levels in hypercholesterolemic rats.

METHODS

This study employed a pretest–posttest design to evaluate the effects of probiotic administration, using a laboratory experimental approach involving animal subjects. A total of 30 Wistar strain rats were randomly assigned to five groups: the negative control group (KN), positive control group (KP), simvastatin group (P1), soyghurt group (P2), and combination group (soyghurt + simvastatin) (P3). The experimental design followed a completely randomized method and was analyzed using a dependent-sample t-test and Tukey's one-way ANOVA post hoc analysis. The combined use of the t-test and ANOVA enabled a more comprehensive and nuanced examination of group differences. Prior to the study, ethical approval was obtained under permit number 025/UH1.09/2023, dated November 10, 2023.

RESULT

This study was conducted in the animal, biochemistry, and microbiology laboratories of Jenderal Achmad Yani University, using a total of 30 samples that met the established research criteria. Relevant subject data are presented in Table 1.

Table 1. Comparison of Cholesterol Levels Before and After Fat Induction

Group	Before (mg/dL)	After (mg/dL)	Difference (mg/dL)	Percentage
KN	72	73	-1	2%
KP	76	83	-7	14%
P1	67	88	14	28%
P2	65	91	19	38%
P3	66	81	9	18%

As shown in Table 1, all rat groups exhibited a percentage increase in cholesterol levels following induction with a high-fat diet composed of palm oil, egg yolk, and lard, indicating that such dietary intervention effectively induces hypercholesterolemic conditions (Anggraeni et al., 2021). Experimental models aiming to elevate cholesterol levels in rats commonly employ high-fat or high-cholesterol diets(Azemi et al., 2022; Magri-Tomaz et al., 2018; Sidorova et al., 2024). These diets typically include ingredients such as chicken feed, egg yolks, and lard. In addition, some studies utilize specific compounds or extracts to further modulate lipid metabolism in rats.

Table 2. Comparison of MDA Levels Before and After Treatment

Group	Before (mg/dL)	After (mg/dL)	Difference (mg/dL)	Percentage
KN	0.0043	0.0033	0.0010	6%
KP	0.0078	0.0047	0.0031	17%
P1	0.0065	0.0017	0.0048	27 %
P2	0.0074	0.0014	0.0060	33%
P3	0.0065	0.0035	0.0030	17%

Table 2 presents the pre- and post-treatment differences for each group, with the most pronounced reductions observed in Group P1 (27%) and Group P2 (32%). The substantial decrease in Group P2 is attributed to the antioxidant properties of soyghurt, which help mitigate oxidative stress. Although Group P3 also showed a reduction, it was less significant than those observed in P1 and P2.

Antioxidants play a critical role in cardiovascular health by inhibiting the oxidation of low-density lipoprotein (LDL) cholesterol—a process that contributes to arterial plaque formation(Malekmohammad et al., 2019; Poznyak et al., 2020). This relationship can be assessed by measuring total cholesterol, LDL cholesterol, and high-density lipoprotein (HDL) cholesterol levels in the blood, alongside serum antioxidant levels, which reflect the body's capacity to counteract oxidative stress.

Table 3. Test Results of Group Comparison Before and After Treatment

Group		N	MDA Average (*mg/dl)* ± SD	Difference	SE	p
Negative	Before	6	0.0043 ± 0.00066	0.0010	0.00038	0.364
	After	6	0.0033 ± 0.00095		0.00054	
Positive	Before	6	0.0078 ± 0.0001	0.0038	0.00006	0.074
	After	6	0.0040 ± 0.0020		0.00115	
Simvastatin	Before	6	0.0065 ± 0.0013	0.0046	0.00073	0.008
	After	6	0.0019 ± 0.0007		0.00040	
Soyghurt	Before	6	0.0074 ± 0.0023	0.0060	0.00131	0.056
	After	6	0.0014 ± 0.00067		0.00038	
Combination	Before	6	0.0067 ± 0.00026	0.0031	0.00015	0.097
	After	6	0.0035 ± 0.00169		0.00097	

As shown in Table 3, the simvastatin group yielded a statistically significant result ($p < 0.05$), indicating a measurable improvement before and after treatment. Although the soyghurt group did not reach statistical significance ($p > 0.05$), the mean difference in outcomes was greater than that observed in the simvastatin group. This suggests that both the soyghurt and simvastatin groups demonstrated improvements, with soyghurt showing a potentially stronger effect despite the lack of statistical significance.

Table 4. Comparison test of MDA Levels among Groups Using Post Hoc Tests

No	Variables		p-Value	Mean Difference
1.	Negative Group (KN)	KP	0. 002	- 0.0045
		P 1	0.303	0. 0017
		P 2	0.181	0. 0020
		P3	1,000	-0.0002
2.	Positive Group (KP)	P 1	0.000	0.0061
		P 2	0. 000	0.0064
		P3	0.002	0.0043
3.	Treatment 1 (P1)	P2	0.995	0.0003
		P3	0.216	- 0.0 019
4.	Treatment 2 (P 2)	P3	0.126	-0.0021

The results of the Tukey post hoc analysis revealed a significant difference ($p < 0.05$) between the KN and KP groups, indicating a marked increase in malondialdehyde (MDA) levels in rats subjected to fat induction compared to those in the negative control group. This finding confirms that a high-fat diet can induce oxidative stress.

Significant differences ($p < 0.05$) were also observed between the KP group and the treatment groups—P1 (simvastatin), P2 (soyghurt), and P3 (combination)—demonstrating that all three interventions effectively reduced MDA levels in hypercholesterolemic rats. However, the magnitude of reduction varied among the treatments. The soyghurt group (P2) exhibited the greatest mean decrease in MDA levels, followed by the simvastatin group (P1), while the combination group (P3) showed the least reduction. These results suggest that soyghurt may exert a stronger antioxidant effect than simvastatin or the combined treatment.

DISCUSSION

The results demonstrated that soyghurt administration significantly reduced malondialdehyde (MDA) levels in hypercholesterolemic rats. This reduction suggests a protective effect of soyghurt against oxidative stress, which is commonly associated with hypercholesterolemia, where cholesterol accumulation promotes lipid peroxidation and the generation of cell-damaging free radicals. The observed decrease in MDA may not solely reflect direct reactive oxygen species (ROS) scavenging by isoflavones, but may also result from indirect effects linked to improved lipid profiles (Kim, 2021). Although MDA is widely used as a biomarker of oxidative stress, its interpretation can be complex due to the multifactorial nature of lipid peroxidation.

Freeze-dried soyghurt generally exhibits enhanced stability, contributing to an extended shelf life. However, a reduction in probiotic colony counts may occur during the drying process, which warrants consideration prior to initiating human trials. While the stability of freeze-dried soyghurt presents promising potential for clinical application, it is essential to ensure that probiotic viability remains within safe and therapeutically effective thresholds. These findings are consistent with the study by Verma et al. (2022), which reported that simvastatin reduces malondialdehyde (MDA) levels through inhibition of the HMG-CoA reductase enzyme, suppression of reactive oxygen species (ROS) production, and attenuation of inflammation. This parallel strengthens the evidence that both soyghurt and simvastatin possess antioxidant potential, albeit via distinct mechanisms of action.

The beneficial effects of soyghurt are further supported by findings from Ruscica et al. (2022), Choi et al., (2022) and Riasatian et al. (2023) who reported that its probiotic and isoflavone components act synergistically to reduce oxidative stress. Probiotics stimulate the production of anti-inflammatory cytokines such as IFN-1, which inhibit the NF-κB signaling pathway, while isoflavones function as hydrogen ion donors, neutralizing free radicals. This

dual mechanism may account for the superior efficacy of soyghurt compared to simvastatin alone in suppressing malondialdehyde (MDA) levels.

The soyghurt–simvastatin combination group exhibited a less pronounced reduction in malondialdehyde (MDA) levels. This outcome is likely attributable to the biotransformation of simvastatin into its M1 metabolite by probiotic bacteria, as described byĐanić et al. (2023). The lactone ring structure of simvastatin is particularly susceptible to enzymatic metabolism by bacterial esterases—such as those produced by Lactobacillus species—which may diminish its bioavailability and therapeutic efficacy.

According to Pazra et al. (2023) and Handayani et al. (2022), the biotransformation mechanism of simvastatin by probiotic bacteria is a critical factor in the development of combination therapies. The interaction between probiotics and simvastatin warrants further investigation, particularly in relation to dosage, bacterial strain specificity, and formulation strategies, in order to minimize drug metabolism while preserving antioxidant efficacy (Cai et al., 2020; Shanu-Wilson et al., 2020; Vander Schaaf et al., 2024).

Although this study found that the combination of soyghurt and simvastatin was less effective in reducing malondialdehyde (MDA) levels than soyghurt alone, several other studies have reported contrasting outcomes. For instance,Tian et al., (2024) demonstrated that co-administration of probiotics with statins enhanced the statin's efficacy in lowering total cholesterol and low-density lipoprotein (LDL) cholesterol levels in patients with hypercholesterolemia. Their findings suggest that probiotics may modulate lipid metabolism and improve statin bioavailability, resulting in a synergistic effect. Similarly, Yilmaz et al. (2024) reported that combining probiotic yogurt with statins not only reduced cholesterol levels but also improved overall lipid profiles. These results indicate that the interaction between probiotics and statins may vary depending on the probiotic strain used and individual patient characteristics. Such discrepancies underscore the need for further research to elucidate the mechanisms underlying probiotic–statin interactions and to identify the factors that influence the therapeutic efficacy of this combination.

The practical implications of these findings suggest that soyghurt may serve as an effective non-pharmacological adjuvant therapy for hypercholesterolemia, particularly in patients with statin intolerance. Its clinical application as an adjunct treatment could help mitigate cardiovascular risk by improving lipid profiles and reducing oxidative stress. In practice, soyghurt may be recommended as part of a comprehensive dietary strategy for managing hypercholesterolemia, encouraging the adoption of a nutrient-rich diet that includes fibre, healthy fats, and probiotics.

Moreover, patient education on the potential benefits and appropriate consumption of soyghurt is essential for achieving optimal therapeutic outcomes. However, when soyghurt is combined with simvastatin, specific formulation strategies must be considered to prevent adverse interactions. Further research is warranted to determine the optimal dosage and most effective formulation for this combination therapy his study demonstrates strength through its controlled experimental design; however, several limitations should be acknowledged. The reliance on a single biomarker (MDA) and the use of a mouse model limit the generalizability of the findings to the complex pathophysiology of human hypercholesterolemia. Additionally, the relatively short study duration may have been insufficient to capture long-term therapeutic effects.

Despite these limitations, the findings support the potential of soyghurt as a non-pharmacological adjuvant therapy for hypercholesterolemia. Its pronounced antioxidant properties present a promising alternative for reducing the risk of cardiovascular complications. Nevertheless, specific formulation strategies are required when soyghurt is co-administered with simvastatin to prevent adverse interactions.

Further research is warranted, including dose–response analyses of soyghurt, evaluation of long-term outcomes, multi-biomarker assessments (e.g., SOD, glutathione), and molecular investigations into simvastatin–probiotic interactions. Human clinical trials are essential to validate these preclinical findings and establish translational relevance.

CONCLUSION

This study aimed to evaluate the efficacy of soy yogurt as a non-pharmacological intervention for reducing malondialdehyde (MDA) levels in hypercholesterolemic rats. The results demonstrated a 33% reduction in MDA levels in the soy yogurt treatment group, compared to a 17% reduction in the group receiving simvastatin. These findings suggest that soy yogurt may be a promising option for mitigating oxidative stress in individuals with hypercholesterolemia. However, the co-administration of soy yogurt with simvastatin may lead to adverse interactions that diminish the drug’s therapeutic efficacy. Further investigation is warranted to elucidate these interactions and inform the development of optimized formulations.

Recommended follow-up studies include human clinical trials to validate these preclinical findings, as well as microbiome analyses to explore the influence of probiotics on lipid metabolism. Additionally, research should focus on enhancing freeze-dried soy yogurt formulations by incorporating protective elements such as prebiotic matrices and

microencapsulation technologies to preserve probiotic viability during storage and gastrointestinal transit.

Suggestions for Clinical Practice and Public Health Interventions include implementing resistance training programs and promoting education on balanced, protein-rich diets to support muscle protein synthesis and reduce fat accumulation. Utilizing anatomically based assessment tools, such as Bioelectrical Impedance Analysis (BIA) or Dual-Energy X-ray Absorptiometry (DXA), to monitor changes in body composition over time can provide valuable insights for both patients and healthcare professionals. These tools can aid in tailoring intervention programs to meet individual needs effectively.

Future directions for this research could include longitudinal studies utilizing imaging techniques such as Dual-Energy X-ray Absorptiometry (DXA) or Magnetic Resonance Imaging (MRI) to gain deeper insights into changes in body composition over time. Emphasizing the use of anatomically based assessment tools is essential, as they offer more precise information on the distribution of fat and muscle mass. This, in turn, can support the development of more targeted and effective interventions aimed at improving the health outcomes of obese women in this age group.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest related to the content of this scientific article.

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