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Enhancing Lipid-Lowering Effects with DMN-Fucoidan: A New Approach to Hyperlipidemia Treatment

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Abstract. Hyperlipidemia is a common condition associated with increased cardiovascular risk, and novel therapies are needed to effectively manage lipid levels. This study investigates the efficacy of fucoidan-loaded dissolving microneedles (DMNs) as a transdermal therapy for hyperlipidemia in Wistar rats induced by a high-fat diet. Methods, wistar rats were divided into four groups and treated for 14 days with normal, DMN-fucoidan, placebo microneedles, and simvastatin. Lipid profiles, including total cholesterol, low-density lipoprotein (LDL), triglycerides, and high-density lipoprotein (HDL), were measured to evaluate treatment effects. Results, the DMN-fucoidan group showed a significant reduction in total cholesterol and LDL levels compared to the control and placebo groups. However, no significant changes were observed in triglyceride and HDL levels. These results suggest that DMN-fucoidan is effective in lowering total cholesterol and LDL levels, but further optimization is needed to address its effects on other lipid parameters. Conclusion, DMN-fucoidan demonstrates potential as an alternative lipid-lowering therapy, offering advantages in bioavailability and fewer side effects than conventional oral treatments. Further studies are needed to optimize treatment protocols, investigate combination therapies, and assess the long-term efficacy of DMN-based drug delivery systems for hyperlipidemia management.

Keywords: Fucoidan, Microneedles, Hyperlipidemia, Lipid profiles, Transdermal therapy

INTRODUCTION

Atherosclerosis is one of the most common cardiovascular diseases and a leading cause of death worldwide. This disease is primarily characterized by the accumulation of fatty plaques in the walls of the arteries, causing narrowing and hardening, which increases the risk of coronary artery disease, stroke, and other cardiovascular complications. The onset and development of atherosclerosis are closely related to hyperlipidemia, a condition characterized by elevated levels of cholesterol and triglycerides in the blood. Chronic inflammation of the arterial walls, often exacerbated by a high-fat diet, further contributes to the development of atherosclerosis. An imbalance in lipid levels, particularly an increase in low-density lipoprotein cholesterol (LDL-C) and a decrease in high-density lipoprotein cholesterol (HDL-C), plays a central role in the initiation and progression of this condition.

Current therapeutic strategies for managing hyperlipidemia primarily involve the use of statins, fibrates, and other lipid-lowering agents. Although these drugs are effective in reducing LDL-C and triglyceride levels, they are often associated with significant side effects, including myopathy, liver dysfunction, and gastrointestinal issues.[1,2] Furthermore, these treatments may not fully address the underlying causes of atherosclerosis or prevent its progression. Consequently, there is an urgent need for alternative therapeutic approaches that can more effectively manage lipid levels while minimizing side effects. Recent research has focused on the potential of natural compounds, such as fucoidan, a sulfate polysaccharide extracted from brown seaweeds, to provide lipid-lowering and anti-inflammatory benefits without the side effects associated with conventional therapies.[3,4] However, the bioavailability of fucoidan when administered orally remains a significant challenge, limiting its therapeutic potential.

To address these issues, novel drug delivery technologies, such as microneedles, have emerged as a promising alternative. Microneedles are small, minimally invasive devices that can deliver drugs through the skin, bypassing the gastrointestinal tract and first-pass metabolism, which often reduces the bioavailability of orally administered drugs. Among the various types of microneedles, dissolving microneedles (DMNs) are particularly promising for delivering bioactive compounds like fucoidan. These DMNs dissolve after insertion into the skin, providing a controlled and efficient release of active drugs directly into the bloodstream, thereby enhancing bioavailability and therapeutic efficacy. The combination of fucoidan with DMN technology holds particular promise for improving hyperlipidemia management and preventing atherosclerosis by increasing the absorption and effectiveness of drugs. Fucoidan has demonstrated a variety of beneficial biological activities, including antioxidant, anti-inflammatory, and anticoagulant effects, all of which are important for reducing the inflammatory processes associated with atherosclerosis. Studies have shown that fucoidan can effectively reduce total cholesterol and LDL-C levels while promoting reduced inflammation in the arterial walls.[5,6] However, the clinical application of fucoidan has been hampered by its low oral bioavailability. Studies have found that oral administration of fucoidan results in poor absorption, limiting its potential as an effective therapeutic agent[7]. These limitations necessitate the development of alternative delivery methods to optimize the therapeutic effects of fucoidan.

Microneedles, especially dissolving microneedles, offer a novel approach to drug delivery. By creating microchannels in the outer layer of the skin, microneedles allow direct drug absorption into the bloodstream without the

need for injections or oral administration. This method not only improves the bioavailability of drugs such as fucoidan but also offers a less invasive and more patient-friendly alternative to traditional drug delivery systems. Several studies have demonstrated the efficacy of microneedles in delivering a variety of therapeutics, including both lipophilic and hydrophilic molecules, through the skin.[7,8] However, the use of soluble microneedles for transdermal delivery of fucoidan remains largely unexplored. This study aims to fill this gap by evaluating the potential of DMN-loaded fucoidan to reduce lipid levels in an animal model of hyperlipidemia.

The main research question addressed in this study is whether dissolving microneedles containing fucoidan can effectively lower total cholesterol, triglycerides, and increase HDL-C levels in mice with diet-induced hyperlipidemia. This study aims to compare the effects of DMN-fucoidan treatment with the established lipid-lowering agent, simvastatin, providing a direct comparison of the two approaches. By focusing on changes in lipid profiles—total cholesterol, triglycerides, and HDL-C—this study seeks to clarify the effectiveness of DMN-fucoidan in modulating lipid metabolism and preventing atherosclerosis in the context of hyperlipidemia. Hyperlipidemia continues to be a significant public health concern, with conventional therapies such as statins often associated with side effects that can reduce patient adherence to treatment regimens. The need for safer and more effective lipid-lowering therapies is urgent, especially for patients who cannot tolerate statins or other traditional treatments. This study proposes that dissolving microneedles loaded with fucoidan may offer an innovative solution to this problem. By bypassing first-pass metabolism and increasing bioavailability, this novel delivery system may provide an effective and minimally invasive alternative therapeutic option.

The urgency of this research lies in its potential to offer safer and more effective treatments for hyperlipidemia, which can significantly reduce the incidence of atherosclerosis and related cardiovascular diseases. Fucoidan, when delivered via DMN, may represent a new frontier in the treatment of lipid disorders, offering a means to improve lipid management without the common side effects associated with oral medications. The results of this study will contribute to the growing body of evidence supporting the use of transdermal drug delivery systems, particularly DMN, for the treatment of hyperlipidemia and prevention of atherosclerosis. This research aligns with the strategic research objectives of the University of Palangka Raya (UPR), which aims to address national health priorities, particularly in the context of tropical peatland ecosystems and watershed environments. By exploring the potential of fucoidan as a treatment alternative for hyperlipidemia, this research also contributes to the broader research objectives of UPR, which focuses on developing innovative healthcare solutions to address local and global health challenges. Furthermore, this research is expected to produce new insights that can lead to publications in nationally accredited scientific journals, contributing to the advancement of medical science in Indonesia and beyond.

METHODS

This study was designed as an experimental laboratory investigation aimed to evaluate the effectiveness of fucoidan-loaded dissolvable microneedles (DMNs) as a transdermal therapy for hyperlipidemia. The main objective was to assess whether fucoidan administration via DMN could reduce lipid levels, particularly total cholesterol, triglycerides, and low-density lipoprotein cholesterol (LDL-C), while increasing high-density lipoprotein cholesterol (HDL-C) in rats with hyperlipidemia. This methodology section describes the study design, materials, procedures, and data analysis techniques.

Animal model

This study was conducted using Wistar rats, which were selected as an experimental model for hyperlipidemia induction and treatment evaluation. This animal model was chosen due to its documented use in lipid metabolism studies and its responses to diet-induced hyperlipidemia. [9,10] The rats were acclimatized to the laboratory environment for 7-14 days before the experiment began, allowing them to adapt to the conditions and reduce stress that could affect the results of the study. [11]

The rats were randomly divided into four groups, each containing three animals:

a. Normal: This group received a standard diet without high-fat supplementation or medication.
b. Positive Control (PC): Mice in this group were given simvastatin, a standard lipid-lowering agent, orally at a dose of 0.36 mg per 200 grams of body weight per day.
c. Negative Control (NC): These mice were fed a high-fat diet (HFD) but did not receive any treatment or microneedling, serving as the hyperlipidemic group without treatment.
d. Fucoidan DMN (F DMN): Rats in this group were given fucoidan-containing DMN once daily for 14 days after being induced with a high-fat diet, which is the test condition for evaluating the transdermal delivery system.

The experimental design aimed to compare the lipid-lowering effects of DMN-fucoidan with those of oral simvastatin and assess the efficacy of DMN as a drug delivery system in improving lipid profiles.

Induction of hyperlipidemia

Hyperlipidemia was induced by feeding the rats a high-fat diet (HFD) consisting of 15.8% fat, 1.25% cholesterol, and other lipid-rich ingredients such as butter and milk, known to significantly increase blood lipid levels. The diet was supplemented with ethanol at a dose of 4.5 g/kg body weight in a 20% solution to enhance the atherogenic effect of the diet.[12,13] The high-fat diet was given for two weeks to induce significant changes in lipid metabolism, specifically increasing LDL-C and triglyceride levels while reducing HDL-C, which reflects the pathophysiological condition of hyperlipidemia and atherosclerosis.[14]

This induction method effectively mimics the metabolic abnormalities observed in humans with hyperlipidemia, making it an appropriate model for evaluating potential therapeutic interventions.[15] The rats in both experimental and control groups were provided with this diet throughout the study period to ensure consistent hyperlipidemia induction.

Preparation of soluble microneedles (DMN)

The main experimental approach in this study involved the development and application of fucoidan-containing DMN. The DMNs were formulated using a combination of Polyvinylpyrrolidone (PVP-K30), gelatin, and fucoidan as the active pharmaceutical ingredient. The formulation was based on previous studies that optimized the proportions of PVP-K30 (25%), gelatin (1%), and fucoidan (15%).[16,17] These components were mixed with distilled water to achieve a final weight of 1 g, then heated to approximately 80°C to ensure complete dissolution.

The preparation of DMNs follows a two-step process. In the first step, the ingredients were mixed and sonicated to achieve a homogeneous solution. In the second step, the formulation was poured into a specially designed mold for microneedles. The mold was then placed in a centrifuge and spun at 3000 rpm for 10 minutes to ensure even distribution of the mixture into the microneedle array. After centrifugation, the microneedles were dried at 37°C for four hours to ensure that the solvent completely evaporated, leaving solid microneedles ready for application. This process was repeated for both active and placebo microneedles, with active microneedles containing fucoidan and placebo microneedles containing only excipients (PVP-K30 and gelatin).

Microneedle applications

DMNs were applied to the dorsal skin of the rats once daily for 14 days. Prior to microneedle application, the rats were anesthetized using ether to minimize discomfort and stress during the procedure, as excessive stress could potentially distort the results. The microneedles were gently inserted into the skin, allowing for controlled release of fucoidan into the bloodstream through the dermal layer. The microneedles dissolved upon contact with body fluids, ensuring a sustained release of fucoidan throughout the duration of the treatment period.[18].

DMN application was performed in a controlled environment to ensure all groups received their respective treatments consistently, without interference from external factors. The treatment regimen was maintained for 14 consecutive days to evaluate the cumulative effects of DMN-fucoidan on lipid profiles and other metabolic parameters.

Blood sample collection and lipid profile

To evaluate the effect of DMN-fucoidan on lipid metabolism, blood samples were taken from the rats at three time points: Day 0 (before treatment), Day 14 (after high-fat diet induction), and Day 28 (14 days after treatment). Blood was drawn from the tail vein using a sterile syringe and transferred to a vacuum tube for serum separation. The serum was processed in a centrifuge at 2500 rpm for 15 minutes, after which the separated serum was stored in an Eppendorf tube for further analysis.[19] Lipid profiles, including total cholesterol, triglycerides, and HDL-C, were measured using standard biochemical tests according to protocols established at the Clinical Pathology Laboratory at Hasanuddin University Hospital. The test used an enzymatic method to measure serum lipid concentrations, providing accurate and reliable data for comparison of treatment effects across groups.

Data analysis

Data obtained from lipid profile measurements were analyzed using statistical methods to determine the significance of the results. Initially, a normality test (Kolmogorov-Smirnov) was performed to assess the distribution of the data. After confirming normal distribution, analysis of variance (ANOVA) was applied to compare the differences between treatment groups. A 95% confidence level ($p < 0.05$) was considered statistically significant. Post-hoc tests, specifically the Bonferroni multiple comparison test, were used to identify specific differences between groups. This test allowed for a detailed evaluation of the effects of DMN-fucoidan treatment compared to control groups, including positive control (simvastatin), negative control (high-fat diet only), and normal control (no treatment). Statistical analysis was performed using SPSS software to ensure the accuracy and reliability of the results.

RESULTS AND DISCUSSION

The results of this study are based on the analysis of lipid profiles and the dissolving effect of microneedles (DMN) containing fucoidan in mice with hyperlipidemia. Data collected from lipid profile measurements were analyzed using statistical methods to determine treatment efficacy. This section presents the findings related to total cholesterol,

low-density lipoprotein (LDL), triglycerides, and high-density lipoprotein (HDL) levels, and provides a discussion of their significance in the context of the study hypotheses.

On the baseline, before induction hyperlipidemia, rats were found to have normal lipid levels within the typical range for Wistar rats. LDL levels in normal rats were estimated to range from 11.24–77.46 mg/dL for 10-week-old rats, with slight variations depending on the age and health of the animal. In this study, the average LDL levels in rats before induction were within the normal range, confirming that they were normal. before induction hyperlipidemia.

Table 1. Levels of cholesterol, HDL, triglycerides and LDL in blood plasma of rats before and after fat induction

Fat Induction	Cholesterol levels (mg/Dl)	HDL Levels (mg/dL)	Triglyceride levels (mg/dl)	LDL levels (mg/dl)
Before	48,92	30,92	78,92	33,78
After	127,67	27,83	72,83	85,27

After the induction period, the mice were divided into four treatment groups: normal control group (Control), negative control group (Blank) receiving high-fat diet without treatment, Simvastatin group (SIMVASTATIN) receiving Simvastatin as a lipid-lowering agent, and experimental group (FC-DMN) receiving fucoidan containing DMN. Each group underwent daily treatment for 14 days, and their lipid profiles were measured at the end of the treatment period. Statistical analysis of the data was performed using the Shapiro-Wilk test, which confirmed that the data followed a normal distribution. Consequently, the data were analyzed using one ANOVA direction with a 95% confidence level, and the results were considered statistically significant if the p-value was less than 0.05. Post-hoc analysis using the Games-Howell test further examined differences between groups.

Total cholesterol

Analysis of total cholesterol levels revealed significant differences between the groups. As shown in Figure 1, the control group (Control) had the lowest total cholesterol levels, consistent with the normal lipid profile in normal rats. In contrast, the negative control group (Blank), which was fed a high-fat diet without treatment, exhibited a significant increase in total cholesterol levels (p=0.025 compared to Simvastatin), confirming the impact of the high-fat diet on lipid metabolism.

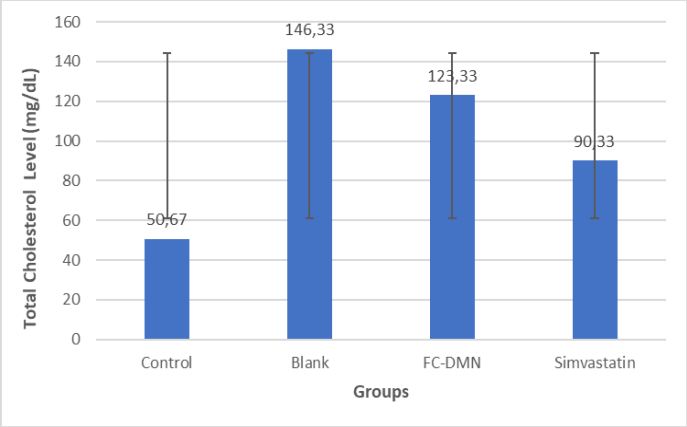

Figure 1. Average blood cholesterol levels in mice after 14 days of treatment

The DMN-fucoidan (FC-DMN) group demonstrated a significant reduction in total cholesterol levels compared to the negative control (Blank) group (p = 0.005), indicating the efficacy of DMN-fucoidan in lowering cholesterol. However, no significant difference was observed between the normal control (Control) group and the simvastatin (Simvastatin) group (p = 0.052), suggesting that simvastatin did not reduce total cholesterol levels as effectively as DMN-fucoidan. The significant reduction in total cholesterol levels in the DMN-fucoidan group supports its potential as an effective lipid-lowering therapy. Fucoidan, a natural compound with antioxidant and anti-inflammatory properties, may contribute to these effects by modulating lipid metabolism. This result is consistent with previous studies showing that fucoidan can reduce cholesterol levels.[5,6] The lack of significant difference between the normal control group and the simvastatin group suggests that DMN-fucoidan may be more effective than conventional statin therapy in lowering total cholesterol in this experimental model.

LDL levels

A similar trend was observed for LDL cholesterol levels. As shown in Figure 2, rats in the negative control (Blank) group exhibited the highest LDL levels, confirming the success of hyperlipidemia induction. The DMN-fucoidan (FC-DMN) group also demonstrated a significant decrease in LDL levels compared to the negative control

group (p = 0.012), which was consistent with the total cholesterol results. In contrast, the simvastatin (Simvastatin) group did not show a significant difference in LDL levels compared to the negative control group (p=0.240), indicating that simvastatin did not significantly lower LDL levels in this model.

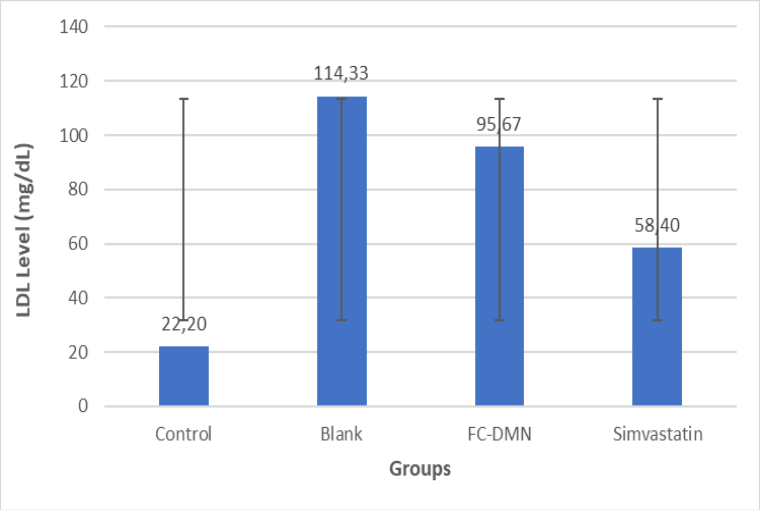

Figure 2. Average blood LDL levels in mice after 14 days of treatment

The reduction in LDL levels in the DMN-fucoidan group further reinforces the potential of DMN-fucoidan as a lipid-lowering agent. This result aligns with the findings on total cholesterol and suggests that DMN-fucoidan may be particularly effective in reducing atherogenic lipoproteins. Unlike simvastatin, which failed to significantly reduce LDL levels in this model, DMN-fucoidan may offer advantages in terms of bioavailability and therapeutic efficacy due to its transdermal delivery via microneedles.

In a clinical context, the ability to reduce total and LDL cholesterol is valuable, as these parameters are directly related to a reduced risk of atherosclerosis and coronary artery disease. While the lack of significant effects on triglycerides and HDL in this study may limit the therapeutic benefits of DMN-fucoidan in certain populations, the results still demonstrate the potential of this approach as a non-invasive and effective method for manage hyperlipidemia. By bypassing the gastrointestinal tract and avoiding the degradation associated with oral administration, DMN may enhance the bioavailability and therapeutic efficacy of fucoidan, providing a more effective means of lipid modulation. Efficient.[20] In addition, the minimally invasive nature of DMN technology, combined with its high bioavailability, offers a promising alternative to injected or oral lipid-lowering therapies, especially for patients experiencing side effects from traditional treatments.[21]

Triglyceride levels

The analysis of triglyceride levels (Figure 3) did not show significant differences across the treatment groups. While significant decreases in total cholesterol and LDL levels were observed, triglyceride levels in the DMN-fucoidan (FC-DMN) group were not significantly different from those in the negative control (Blank) group (p=0.883). This suggests that although DMN-fucoidan effectively lowers total cholesterol and LDL, it does not have the same impact on triglyceride levels.

The lack of significant effect on triglyceride levels indicates that DMN-fucoidan may be more effective at targeting specific lipid fractions, such as LDL and total cholesterol, rather than triglycerides. The differential effect on lipid fractions could be due to various factors, such as the specific mechanisms by which fucoidan modulates lipid metabolism. Further studies are needed to investigate the potential for optimizing DMN-fucoidan formulations to target triglyceride levels more effectively.

On the other hand, this study also found no significant reduction in triglycerides and no increase in HDL levels, indicating that although DMN-fucoidan shows promising results in some areas, DMN-fucoidan may require further optimization or combination with other therapies to achieve a broader spectrum of lipid-lowering effects. Findings This consistent with study previously that has been report varying results in matter the effect of fucoidan on triglycerides, depending on the method administration and animal models used.[22,23]

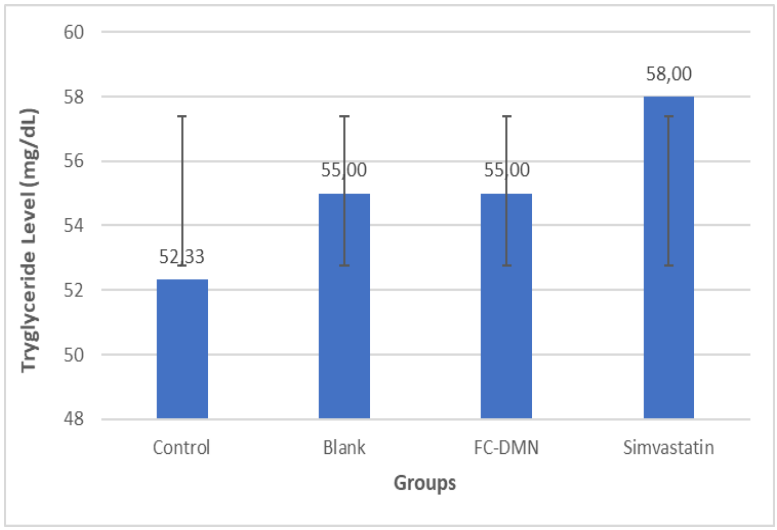

Figure 3. Average blood triglyceride levels in mice after 14 days of treatment

HDL levels

The effect of DMN-fucoidan on HDL cholesterol levels was also assessed. As shown in Figure 4, no significant difference in HDL levels was observed between the treatment groups. The DMN-fucoidan (FC-DMN) group did not show a significant increase in HDL levels compared to the negative control group (p=0.217), indicating that while DMN-fucoidan was effective in lowering total and LDL cholesterol levels, it did not significantly increase HDL levels in this study.

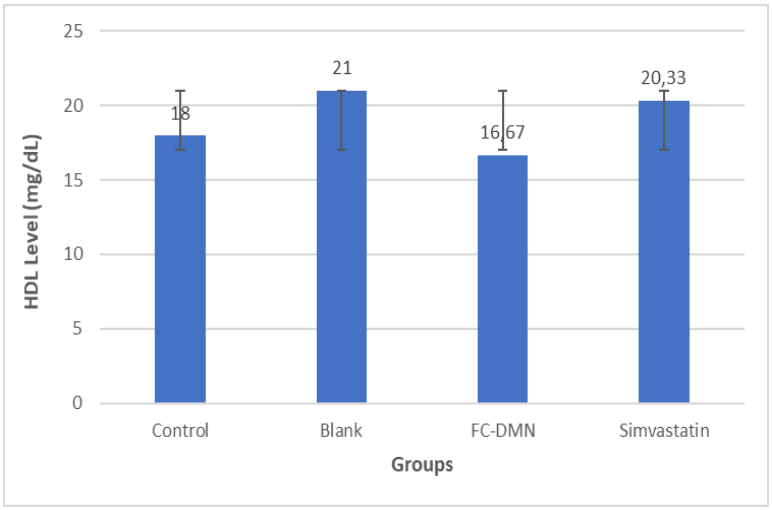

Figure 4. Average blood HDL levels in mice after 14 days of treatment

Despite the effectiveness of DMN-fucoidan in lowering total cholesterol and LDL, its lack of significant impact on HDL levels suggests that additional strategies may be needed to increase HDL-C. Fucoidan's effects on HDL may be more complex and may require dose optimization or combination therapies to achieve the desired effects on HDL metabolism. Similar findings have been reported in other studies, where fucoidan was found to primarily affect LDL and total cholesterol, with limited effects on HDL.[4] Future studies could explore ways to enhance fucoidan's impact on HDL through formulation adjustments or synergistic treatments.

CONCLUSION

This study demonstrates the potential of DMN-fucoidan as an effective lipid-lowering therapy, particularly for reducing total cholesterol and LDL levels. Although DMN-fucoidan showed limited effects on triglycerides and HDL, it offers a promising alternative to conventional lipid-lowering agents, such as simvastatin, with the added benefit of enhanced bioavailability through transdermal delivery. Further research is needed to optimize the formulation of DMN-fucoidan and explore its effects on other lipid fractions and long-term outcomes in the management of hyperlipidemia and atherosclerosis.

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