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Research Article

Synergistic Effects of Microencapsulated Lipid Iron and Nutrient-Rich Botanical Extracts on Cellular Iron Absorption and Skin Health

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Abstract

Iron plays an essential role in oxygen transport, energy metabolism, and collagen biosynthesis, contributing to both systemic health and skin vitality. This study aimed to investigate the effects of the NYO3® Microencapsulated Lipid Iron Drink on iron absorption, collagen biosynthesis, and oxidative stress protection at the cellular level. Caco-2 intestinal epithelial cells and CCD-966SK human dermal fibroblasts were used as in vitro models. Iron absorption efficiency was assessed through intracellular ferritin quantification using an ELISA assay, collagen metabolism was analyzed by real-time PCR for collagen- and matrix-related genes, and antioxidative capacity was evaluated by measuring reactive oxygen species (ROS) under H_2O_2-induced stress. The results demonstrated that the microencapsulated lipid iron formulation significantly enhanced cellular ferritin accumulation compared with conventional ferrous sulfate, indicating improved bioavailability. In dermal fibroblasts, NYO3 upregulated type I (COL1A1, COL1A2) and type IV (COL4A1, COL4A4, COL4A5) collagen gene expression, suppressed MMP-1 expression, and increased fibrillin-1 (FBN1), suggesting strengthened dermal structural integrity. Additionally, NYO3 markedly reduced intracellular ROS levels, confirming its antioxidative protection. Overall, these findings indicated that microencapsulated lipid iron technology effectively improved iron utilization and supported skin health, providing mechanistic evidence for its application as a next-generation "beauty-from-within" functional beverage.

Keywords: Microencapsulated Iron; Ferritin; Collagen Biosynthesis; Oxidative Stress

Introduction

In recent years, the global health and nutrition market has increasingly emphasized the "inside-out" concept of beauty and wellness, where nutritional supplementation enhances skin health from within. Products that combine nutritional fortification with skin-conditioning benefits have gradually become mainstream. According to analyses by *Euromonitor* and the *Innova Database*, the global market for iron-fortified functional beverages has grown at an annual rate of approximately 6–8% [1]. Among these, formulations targeting women, individuals with suboptimal health, and those under chronic stress have gained significant attention due to their claims of improving complexion, reducing fatigue, and enhancing skin radiance. Iron is now recognized not only as an essential nutrient for hematopoiesis but also as a key element linked to energy metabolism, cognitive vitality, and skin health [2]. It plays a central role in the synthesis of hemoglobin and cytochromes, oxygen transport, cellular respiration, and enzymatic hydroxylation of collagen, making it indispensable for maintaining dermal structure and function [3].

Iron deficiency disrupts mitochondrial energy production and promotes the accumulation of reactive oxygen species (ROS), leading to skin dryness, dullness, and reduced elasticity [4]. Several studies have demonstrated that chronic iron deficiency correlates strongly with pale or uneven skin tone and premature aging [5]. Conversely, adequate iron levels enhance dermal fibroblast proliferation, collagen biosynthesis, and tissue repair capacity, thereby improving skin firmness, tone, and vitality [6]. These findings highlight the multifaceted role of iron in cellular metabolism and skin health.

However, conventional iron supplements such as ferrous sulfate and ferrous gluconate are readily oxidized to ferric iron (Fe^{3+}) in the gastrointestinal tract, resulting in poor absorption and frequent side effects such as constipation, bloating, and metallic taste, which reduce long-term compliance [7]. The development of microencapsulated lipid iron technology, which encapsulates ferrous ions (Fe^{2+}) within lipid bilayers, effectively protects the mineral from gastric oxidation and food interactions, enabling controlled release and improved intestinal absorption [8]. Clinical studies have reported that microencapsulated iron exhibits two- to three-fold higher bioavailability compared with traditional iron salts, significantly increases serum ferritin and hemoglobin concentrations, and greatly reduces gastrointestinal discomfort [9], establishing it as a next-generation platform for iron supplementation with superior efficacy and tolerability.

In addition, synergistic combinations of plant extracts and micronutrients can further enhance iron absorption and skin metabolism [10]. Purple carrot and pomegranate concentrates are rich in anthocyanins and polyphenols that stabilize ferrous ions and prevent oxidation [11]. Acerola berry extract provides abundant natural vitamin C, which promotes the absorption of non-heme iron [12]. Fish maw extract supplies bioactive peptides and amino acids that support dermal repair and hydration [13]. Furthermore, zinc, vitamins B2 and B6, folic acid, and biotin act as essential cofactors in heme synthesis and cellular energy metabolism, while contributing to keratin and collagen formation [14]. Collectively, these components exert complementary actions that improve iron bioavailability, stimulate skin cell renewal, and provide antioxidative protection.

The present study employed the NYO3® microencapsulated lipid iron beverage to conduct a preliminary *in vitro* investigation. The objective of this study was to verify whether microencapsulated lipid iron could effectively enhance cellular-level iron absorption and utilization, while promoting skin cell repair and metabolic activity, thereby providing mechanistic scientific evidence to support subsequent human clinical trials and formulation development.

Materials and Methods

Cell culture

Human colorectal adenocarcinoma cells (Caco-2, ATCC® HTB-37™) and human dermal fibroblasts (CCD-966SK, ATCC® CRL-1881™) were obtained from the American Type Culture Collection (ATCC, USA). Caco-2 cells were cultured in Dulbecco's Modified

Eagle's Medium (DMEM, high glucose, 4.5 g/L glucose; Gibco, USA) supplemented with 10% (v/v) fetal bovine serum (FBS; Gibco), 1% non-essential amino acids (NEAA), 100 U/mL penicillin, and 100 µg/mL streptomycin. CCD-966SK cells were maintained in Minimum Essential Medium (MEM; Gibco) containing 10% (v/v) FBS and 1% Penicillin–Streptomycin. All cells were incubated at 37 °C in a humidified atmosphere containing 5% CO_2, and the culture medium was replaced every 2–3 days. When the cells reached 80–90% confluence, they were detached using 0.25% trypsin–EDTA and subcultured at an appropriate split ratio. Cells between passages 5 and 20 were used for all experiments to ensure phenotypic stability and reproducibility.

Test sample

The test sample used in this study was NYO3® Microencapsulated Lipid Iron Drink (NYO3 INTERNATIONAL AS, China). Each serving (20 mL) contains 30 mg of microencapsulated lipid iron (as ferrous bisglycinate chelate) as the primary active ingredient. The product composition includes mixed purple carrot juice, pomegranate juice concentrate, acerola berry extract, fish maw extract, ascorbic acid, zinc, vitamin B2, vitamin B6, folic acid, and biotin. Other ingredients include water, isomalto-oligosaccharides, concentrated apple juice, lemon juice, trehalose, xanthan gum, arabic gum, sucralose, lecithin, and berry flavor.

Ferritin human detection

A sandwich enzyme-linked immunosorbent assay (ELISA) kit (Ferritin Human ELISA Kit, ab108837; Abcam, UK) was used to quantify intracellular human ferritin levels. Cells were washed twice with ice-cold phosphate-buffered saline (PBS) and then collected by scraping in ice-cold PBS containing 0.5 M EDTA. The cell suspension was centrifuged at 1,500 rpm for 10 min at 4 °C, and the supernatant was discarded. The cell pellet was resuspended in ice-cold lysis buffer and incubated on ice for 60 min to ensure complete lysis, followed by centrifugation at 13,000 rpm for 30 min at 4 °C. The resulting supernatant was collected for ferritin measurement. All samples were handled carefully to avoid repeated freeze–thaw cycles and stored at −80 °C when necessary. Before the assay, all reagents and samples were equilibrated to room temperature (18–25 °C). A total of 50 µL of standards or samples was added to the antibody-precoated 96-well plate and incubated for 2 h at room temperature, followed by five washing steps. Subsequently, 50 µL of biotinylated detection antibody was added and incubated for 1 h, washed, and then 50 µL of HRP-conjugated streptavidin solution was added and incubated for 30 min. After washing, 50 µL of TMB substrate solution was added for 12 min of color development, and the reaction was stopped with the stop solution. The absorbance was measured at 450 nm using a microplate reader, and ferritin concentrations were calculated from the standard curve.

Quantification of gene expressions by real-time PCR

The treated cells were harvested, and total RNA was isolated from cells using an RNA purification kit (Geneaid, Taiwan). DNA-free total RNA was reversely transcribed to cDNA using a SuperScript™ Reverse Transcriptase kit (Invitrogen, Life Technologies Co., CA, USA). Quantitative real-time PCR was conducted using an ABI StepOnePlus™ Real-Time PCR System (Thermo Fisher Scientific, Inc., CA, USA) and the SYBR Green Master Mix (KAPA Biosystems, MA, USA) for transcript measurements. The reaction mixture was cycled as follows: one cycle at 95 °C for 20 s, followed by 40 cycles of 95 °C (1 s), 60 °C (20 s), and a plate reading was conducted after each cycle. The melting curves of the PCR products were analyzed during the quantitative real-time PCR. The gene-specific primers used in this study are listed in Table 1. Real-time PCR reactions were performed using the ABI system. GAPDH was used as the reference gene to normalize relative expression. Data were analyzed using the ABI StepOne™ Software v2.2.3 (Thermo Fisher Scientific, Inc., Carlsbad, CA, USA). All PCR assays were performed in duplicate three times.

ROS analysis

Cells were seeded in 96-well plates and cultured to approximately 80% confluence. After washing with PBS, cells were incubated with 10 µM 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA) in serum-free medium for 30 min at 37 °C in the dark. The probe was removed, and cells were washed twice with PBS, followed by treatment with hydrogen peroxide (H_2O_2, 1 mM) for 30 min at 37 °C to induce intracellular ROS production. The fluorescence intensity was measured at excitation/emission wavelengths of 485/535 nm using a microplate reader.

Statistical analysis

The experimental data used paired t-tests and independent two-sample t-tests for statistical analysis, without applying a specific mean separation method for post-hoc multiple comparisons. A p-value of less than 0.05 was considered statistically significant.

Results

Evaluation of iron absorption efficiency of microencapsulated lipid iron drink

The study first aimed to evaluate the iron absorption efficiency of the NYO3 Microencapsulated Lipid Iron Drink and compare it with a conventional iron drink containing an equivalent iron content using ferrous sulfate ($FeSO_4$) as the iron source. The intracellular ferritin level in Caco-2 intestinal epithelial cells was used as a surrogate marker of iron uptake, as higher ferritin accumulation indicates greater iron absorption efficiency. The results showed that treatment with the $FeSO_4$-containing iron drink increased intracellular ferritin levels to 385.3% of the control (approximately 3.85-fold, $p < 0.01$), whereas the NYO3 Microencapsulated Lipid Iron Drink significantly elevated ferritin levels to 1973.6% of the control (approximately 19.7-fold, $p < 0.001$). Compared with the $FeSO_4$ iron drink, NYO3 exhibited approximately a 5-fold higher ferritin accumulation (###, $p < 0.001$) (Figure 1). These findings demonstrated that lipid microencapsulation markedly enhanced the iron absorption efficiency.

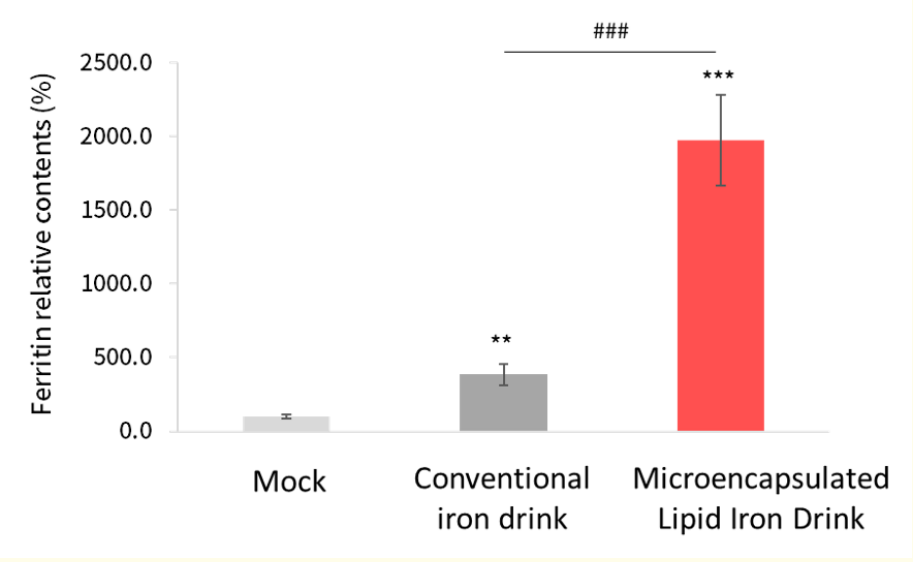

Figure 1: NYO3 Microencapsulated Lipid Iron Drink significantly enhanced cellular iron absorption. Cells were treated with either a conventional iron drink containing $FeSO_4$ or the NYO3 microencapsulated lipid iron formulation containing equivalent iron content. Intracellular ferritin levels were quantified using a human ferritin ELISA assay as an indicator of iron absorption efficiency. Significant differences compared with the mock group: **p < 0.01; ***p < 0.001; significant difference compared with the conventional iron drink group: ###p < 0.001.

Enhancement of collagen biosynthesis and dermal structural integrity by microencapsulated lipid iron drink

The study utilized CCD-966SK human dermal fibroblast cells (HDFs) to evaluate the effects of the NYO3 Microencapsulated Lipid Iron Drink on collagen biosynthesis and dermal structural stability. The results showed that NYO3 markedly promoted the expression of basement-membrane-related collagen genes COL4A1, COL4A4, and COL4A5, which increased by 38%, 36%, and nearly 5-fold, respectively ($p < 0.001$), indicating its potential to strengthen the basement membrane and enhance dermal repair capacity. In ad-

dition, the type I collagen synthesis genes COL1A1 and COL1A2 were upregulated by 51% and 86%, respectively ($p < 0.001$), while the collagen-degrading enzyme gene matrix metalloproteinase-1 (MMP-1) was suppressed by 89% ($p < 0.001$). Furthermore, the expression of fibrillin-1 (FBN1), a gene involved in maintaining dermal structural stability, increased by 34% ($p < 0.001$) (Figure 2). Collectively, these results demonstrated that the NYO3 Microencapsulated Lipid Iron Drink simultaneously enhanced type I and type IV collagen synthesis, inhibited collagen degradation, and improved dermal structural integrity, suggesting its potential to activate dermal repair and increase skin firmness and elasticity.

Reduction of ROS production by microencapsulated lipid iron drink

The antioxidant effect of the NYO3 Microencapsulated Lipid Iron Drink was evaluated in CCD-966SK exposed to oxidative stress induced by hydrogen peroxide (H_2O_2, 1 mM). Intracellular ROS levels were quantified using the DCFH-DA fluorescence assay. The results showed that NYO3 treatment markedly reduced ROS generation by 39.7% compared with the H_2O_2-induced group ($p < 0.001$), indicating a strong antioxidant protective effect (Figure 3). These findings suggested that the NYO3 formulation effectively scavenged free radicals and mitigated oxidative stress.

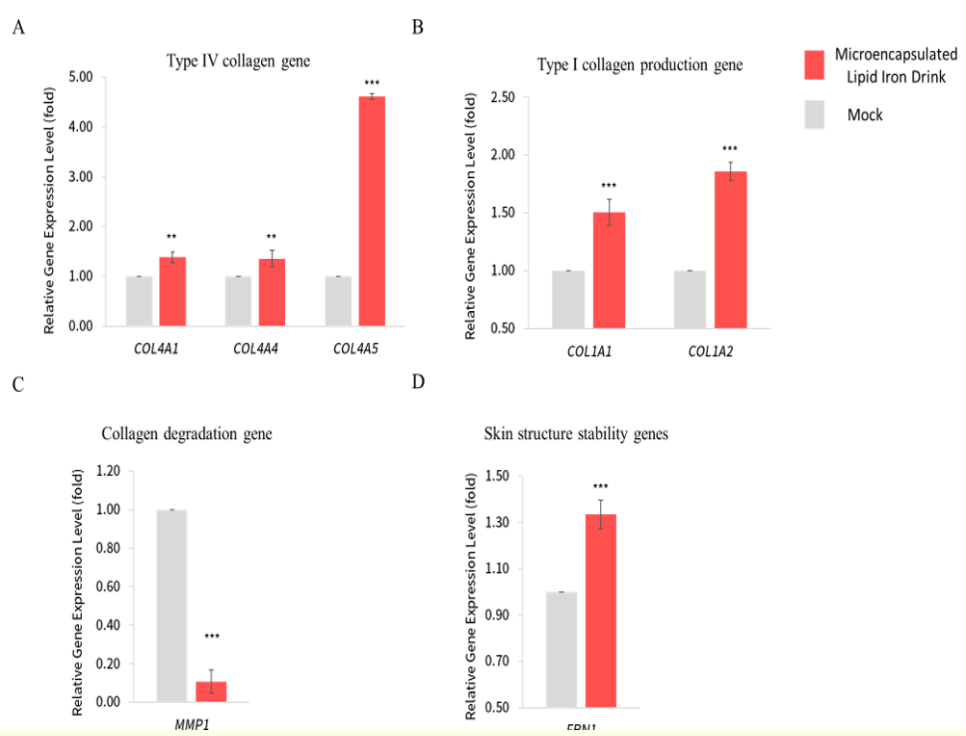

Figure 2: NYO3 Microencapsulated Lipid Iron Drink upregulated collagen biosynthesis–related genes and stabilized dermal structure. Cells were treated with the NYO3 Microencapsulated Lipid Iron Drink for 24 h, and mRNA expression levels of (A) COL4A1, COL4A4, COL4A5 (type IV collagen genes), (B) COL1A1 and COL1A2 (type I collagen genes), (C) MMP-1 (collagen-degrading enzyme), and (D) FBN1 (dermal structure stabilization gene) were quantified by real-time PCR. Significant differences compared with the mock group: **p < 0.01; ***p < 0.001.

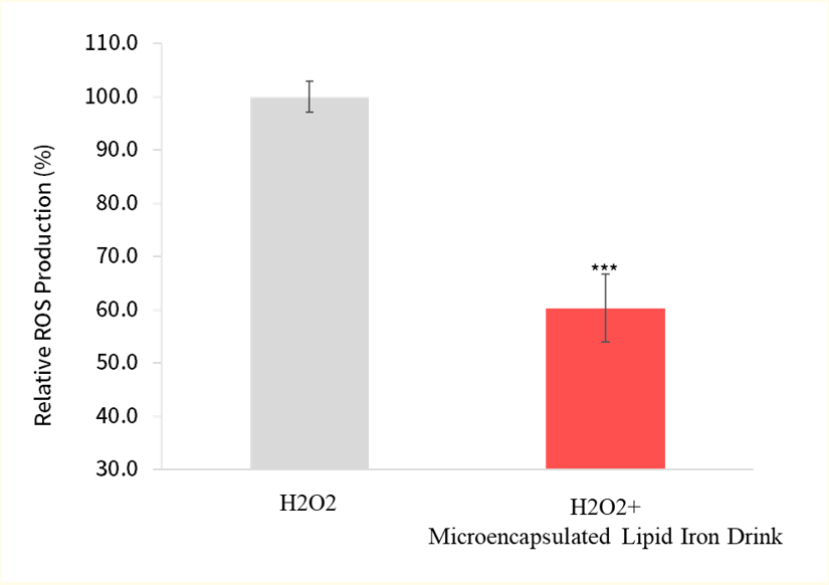

Figure 3: NYO3 Microencapsulated Lipid Iron Drink reduced intracellular ROS generation. Cells were exposed to hydrogen peroxide (H_2O_2, 1 mM) to induce oxidative stress, with or without NYO3 treatment. Intracellular reactive oxygen species (ROS) levels were quantified using the DCFH-DA fluorescence assay. Significant difference compared with H_2O_2 group: ***$p < 0.001$.

Discussion

This study demonstrated that the NYO3 microencapsulated lipid iron drink effectively enhanced cellular iron absorption, promoted collagen biosynthesis, and reduced oxidative stress in both intestinal epithelial and dermal fibroblast models. Overall, the findings indicate that microencapsulated lipid iron not only improves iron bioavailability but also supports dermal structural stability and cellular antioxidant defense, aligning with the emerging inside-out concept of nutritional beauty.

The superior absorption efficiency of NYO3 primarily resulted from its lipid microencapsulation technology. The phospholipid bilayer coating stabilized ferrous ions (Fe^{2+}), protecting them from oxidation to ferric ions (Fe^{3+}) in the stomach and minimizing interactions with dietary inhibitors such as phytates, polyphenols, and calcium [15]. Within the small intestine, the encapsulated particles were likely dispersed into micelles under the action of bile salts, facilitating controlled release and enhanced absorption through the intestinal epithelium [16]. This system may also promote endocytosis through lipid raft domains and uptake via divalent metal transporter 1 (DMT1), or mimic chylomicron-mediated lymphatic transport, collectively improving systemic iron utilization and stability [17]. In dermal fibroblasts, iron serves as an essential cofactor for prolyl and lysyl hydroxylases, enzymes responsible for the hydroxylation of proline and lysine residues during collagen biosynthesis [18]. Increased intracellular iron availability enhanced hydroxylase activity and upregulated collagen-related genes (COL1A1, COL1A2, COL4A1–A5), indicating activation of collagen formation pathways. The concurrent downregulation of MMP-1 and upregulation of FBN1 further reflected a shift from matrix degradation to matrix synthesis, suggesting strengthened dermal architecture and improved repair capacity [19].

NYO3 also exhibited significant antioxidant effects. Microencapsulation prevented the release of free iron that could catalyze Fenton reactions and generate hydroxyl radicals, thereby maintaining intracellular redox balance [20]. Moreover, its formulation contained multiple synergistic components. Mixed purple carrot

juice and pomegranate juice concentrate provide anthocyanins and polyphenols that stabilize Fe^{2+} and scavenge free radicals [21]; acerola berry extract supplies natural vitamin C to enhance non-heme iron absorption and regenerate ferrous ions [12]; fish maw extract contributes bioactive peptides and amino acids that support collagen formation and tissue repair [22]; while zinc, vitamins B2 and B6, folic acid, and biotin act as cofactors in heme synthesis, cellular metabolism, and keratin formation [23]. Together, these ingredients and the microencapsulated iron work synergistically to enhance absorption, antioxidant capacity, and dermal renewal. Collectively, NYO3 demonstrated an integrated mechanism of enhanced absorption, collagen promotion, and antioxidative protection, suggesting comprehensive benefits for both nutritional supplementation and skin health. Adequate iron absorption can improve oxygen transport and microcirculation, promoting skin brightness and elasticity. The synergistic effects of plant polyphenols and vitamins further reinforce antioxidative protection, potentially delaying skin aging and dullness, positioning NYO3 as a promising nutricosmetic formulation.

Nevertheless, this study had several limitations. First, it was conducted using in vitro cell models, which, although useful for mechanistic exploration, could not fully represent the complexity of iron absorption, distribution, and metabolism in vivo. Second, the study focused on short-term cellular responses and did not evaluate long-term exposure, bioavailability kinetics, or systemic safety. Third, parameters such as Fe^{2+} transmembrane transport rates, DMT1 expression, and mitochondrial metabolic flux were not directly measured. Future studies using animal models and human clinical trials, combined with fluorescent tracing and metabolic analyses, were needed to further elucidate absorption dynamics and confirm functional efficacy.

Conclusion

This study provided mechanistic evidence that microencapsulated lipid iron technology effectively enhanced iron absorption, stimulated collagen biosynthesis, and mitigated oxidative stress. Through the synergistic actions of iron, plant extracts, and micronutrients, NYO3 demonstrated strong potential as a next-generation functional beverage for efficient iron supplementation and beauty-from-within applications.

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