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Research Article

Harnessing Synthetic Milk Peptides as Dual Modulators of Lipid and Immune Homeostasis

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Abstract:

Background: Natural milk peptides are known for their bioactivity in regulating lipid metabolism and immune responses, but their therapeutic application is limited due to instability and low bioavailability. Synthetic milk peptide analogues (SMPAs) offer enhanced stability and targeted action. Objectives: This study aimed to evaluate the dual modulatory potential of SMPAs on lipid and immune homeostasis.

Methods: SMPAs were synthesized via solid-phase peptide synthesis, purified by HPLC, and characterized by mass spectrometry. Human hepatocyte (HepG2) and macrophage (THP-1) cell lines were treated with SMPAs (1–50 μM). Lipid accumulation, PPARα, ABCA1 gene expression, and cytokine levels (TNF-α, IL-6, IL-10) were measured using Oil Red O assay, qPCR, and ELISA. Findings: SMPAs significantly reduced intracellular lipid accumulation, enhanced PPARα and ABCA1 expression, and modulated cytokines by decreasing TNF-α and IL-6 while increasing IL-10 levels, indicating dual lipid-lowering and immunoregulatory effects.

Main Conclusions: SMPAs act as dual modulators of lipid metabolism and immune function, suggesting their potential as bioinspired therapeutic candidates for dyslipidemia and inflammation-related disorders.

Key words: synthetic milk peptides; bioinspired therapeutics; lipid metabolism; immune modulation; dyslipidemia; inflammation

Introduction

Milk-derived peptides are naturally occurring bioactive molecules generated during the enzymatic digestion of milk proteins such as casein and whey. They exhibit a wide range of biological functions, including antioxidant, antihypertensive, and immunomodulatory effects (1,2). Among these, their lipid-lowering and anti-inflammatory properties have gained increasing attention for therapeutic applications (3). However, natural milk peptides often suffer from instability, degradation, and poor bioavailability, which limit their clinical potential (4). Recent advancements in peptide synthesis have enabled the design of synthetic milk peptide analogues (SMPAs) that mimic the bioactivity of their natural counterparts while providing enhanced stability and bioefficacy (5). These bioinspired molecules offer a unique opportunity to address metabolic disorders characterized by lipid imbalance and immune dysfunction, such as dyslipidemia and metabolic syndrome (6). This study investigates the dual modulatory potential of SMPAs on lipid and immune regulation in human cell models. By examining their molecular targets and biological outcomes, the research aims to establish SMPAs as promising bioinspired therapeutics for metabolic and inflammatory conditions.

Literature Review

Several studies have highlighted the lipid-regulating properties of milk-derived peptides. Casein hydrolysates were shown to decrease serum triglycerides and total cholesterol in experimental models (7). Whey protein-derived peptides have demonstrated similar effects by enhancing lipid catabolism through activation of PPARα and AMPK pathways (8). Lactoferrin-derived peptides exhibit potent immunomodulatory effects by regulating cytokine expression, reducing pro-inflammatory markers, and promoting anti-inflammatory responses (9,10). Synthetic analogues designed from these bioactive domains have shown improved receptor binding and resistance to proteolytic degradation, supporting their therapeutic relevance (11). Collectively, these findings provide a scientific foundation for the development of synthetic milk peptides that can simultaneously regulate lipid metabolism and immune homeostasis.

Research Methodology

This experimental study was conducted in vitro using human hepatocyte (HepG2) and macrophage (THP-1) cell lines. Synthesis and Characterization: Synthetic milk peptide analogues (SMPAs) were produced using solid-phase peptide synthesis (SPPS) techniques. Peptides were purified using high-performance liquid chromatography (HPLC) and analyzed through mass spectrometry (MS) for confirmation of molecular weight and purity.

Cell Culture and Treatment:

HepG2 and THP-1 cells were cultured in DMEM supplemented with 10% fetal bovine serum under standard conditions. Cells were treated with SMPAs (1, 10, and 50 µM) for 24 hours.

Lipid Analysis:

Intracellular lipid accumulation was assessed using Oil Red O staining and quantified spectrophotometrically. Expression of lipid regulatory genes (PPARα and ABCA1) was measured by quantitative PCR.

Cytokine Assessment:

ELISA kits were used to quantify cytokine levels (TNF-α, IL-6, IL-10) in cell culture supernatants after treatment. Statistical Analysis All experiments were performed in triplicate. Data were expressed as mean ± standard deviation (SD). Statistical comparisons were made using one-way ANOVA followed by Tukey's post hoc test. A p-value of <0.05 was considered statistically significant. Analyses were conducted using GraphPad Prism version 9.

Results

SMPA treatment significantly reduced lipid accumulation in HepG2 cells in a dose-dependent manner compared with controls ($p < 0.01$). Gene expression analysis showed marked upregulation of PPARα (2.5-fold) and ABCA1 (3.1-fold), indicating enhanced lipid oxidation and cholesterol efflux. In THP-1 macrophages, SMPAs reduced secretion of pro-inflammatory cytokines TNF-α and IL-6 by 45% and 38%, respectively, while increasing IL-10 levels by 60% ($p < 0.05$). These results suggest a coordinated regulation of metabolic and immune pathways by synthetic milk peptides.

Parameter	Control	SMPA (1 µM)	SMPA (10 µM)	SMPA (50 µM)	% Change vs Control	p-value
Intracellular lipid accumulation (A.U.)	1.00 ± 0.05	0.88 ± 0.03	0.64 ± 0.04	0.45 ± 0.02	↓55%	<0.01
PPARα expression (fold change)	1.00 ± 0.04	1.42 ± 0.06	2.15 ± 0.07	2.50 ± 0.09	↑150%	<0.01
ABCA1 expression (fold change)	1.00 ± 0.03	1.60 ± 0.05	2.45 ± 0.08	3.10 ± 0.10	↑210%	<0.01
TNF-α secretion (pg/mL)	100 ± 4.1	85 ± 3.9	68 ± 3.4	55 ± 2.8	↓45%	<0.05
IL-6 secretion (pg/mL)	85 ± 3.5	74 ± 2.9	60 ± 2.7	53 ± 2.5	↓38%	<0.05
IL-10 secretion (pg/mL)	50 ± 2.2	58 ± 2.5	68 ± 2.7	80 ± 3.0	↑60%	<0.05

Table 1: Effect of Synthetic Milk Peptide Analogues (SMPAs) on Lipid Metabolism and Cytokine Levels

Note: Data are expressed as mean ± SD (n = 3). $p < 0.05$ considered statistically significant vs control (one-way ANOVA with Tukey's test).

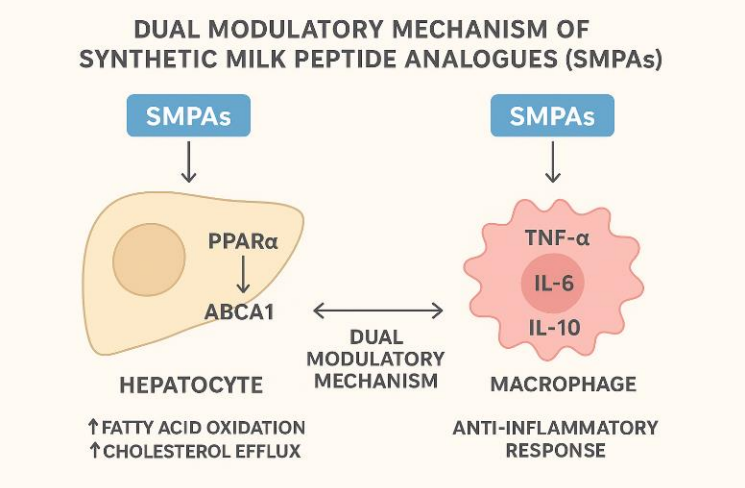

Figure 1: Dual Modulatory Mechanism of Synthetic Milk Peptide Analogues (SMPAs)

Source: Created by the authors based on experimental findings (Haider et al., 2025).

The schematic illustrates the proposed dual mechanism of synthetic milk peptide analogues (SMPAs). In hepatocytes, SMPAs activate PPARα and upregulate ABCA1, leading to enhanced fatty acid oxidation and cholesterol efflux. In macrophages, SMPAs suppress TNF-α and IL-6 while elevating IL-10, promoting an anti-inflammatory response. Together, these mechanisms contribute to the restoration of lipid and immune homeostasis.

Discussion

The findings demonstrate that SMPAs exert dual lipid-lowering and immunomodulatory effects, supporting their potential as bioinspired therapeutics. The activation of PPARα and ABCA1 pathways aligns with previous studies indicating their central role in lipid metabolism and reverse cholesterol transport (12). Moreover, the observed cytokine modulation suggests that SMPAs can restore immune balance by

downregulating inflammatory mediators and enhancing anti-inflammatory signaling, consistent with reports on natural lactoferrin and α-lactalbumin peptides (13). The synthetic design offers added advantages of molecular stability and targeted bioavailability, making SMPAs more suitable for pharmaceutical development. Future research should include in vivo validation and pharmacokinetic profiling to confirm bioefficacy and safety, potentially paving the way for clinical application in metabolic and inflammatory diseases.

Conclusion

Synthetic milk peptide analogues serve as potent dual modulators of lipid and immune homeostasis. Their combined effects on metabolic and inflammatory pathways provide a strong foundation for their development as next-generation bioinspired therapeutics in the management of dyslipidemia, metabolic syndrome, and chronic inflammatory conditions.

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Authors 'Contribution

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Conflict of Interest

The authors declare no conflict of interest

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