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Phytochemical-Rich Functional Diet Regulates Epigenetic Markers (DNA Methylation) Associated with Obesity and Insulin Resistance

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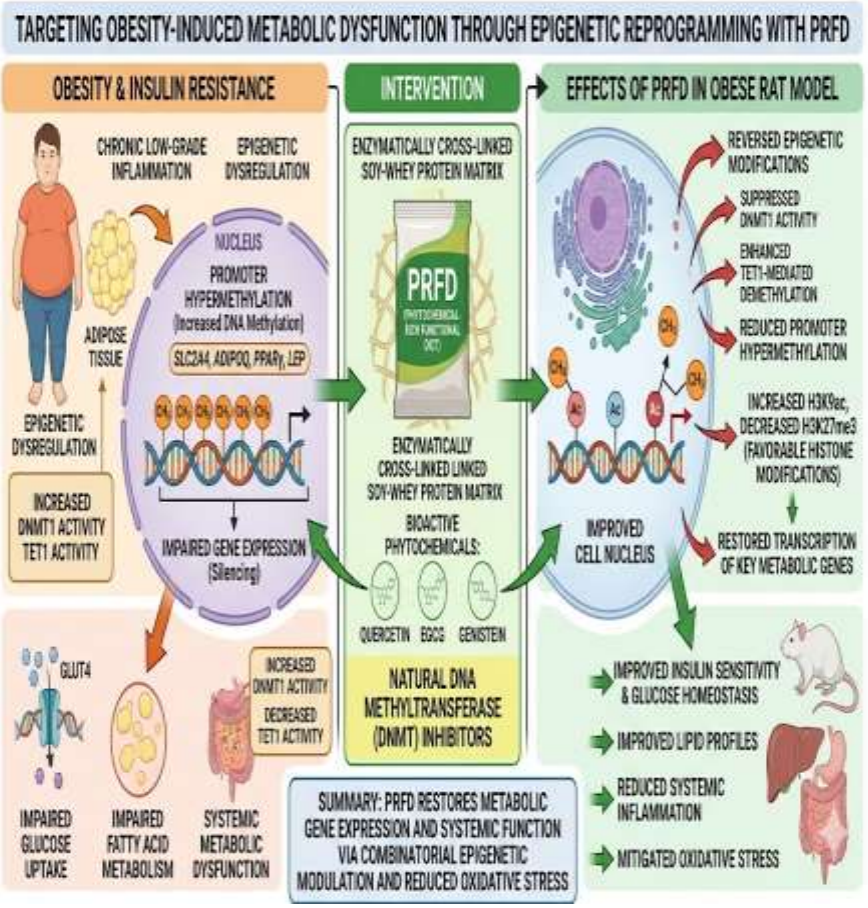
Abstract

Graphical Abstract



Abstract

Obesity and insulin resistance are characterized by chronic low-grade inflammation and epigenetic dysregulation, including hypermethylation of promoters in key metabolic genes such as *SLC2A4*, *ADIPOQ*, *PPARγ*, and *LEP*, leading to impaired glucose uptake, fatty acid metabolism, and systemic metabolic dysfunction. Bioactive phytochemicals—including quercetin, (-)-epigallocatechin gallate (EGCG), and genistein—act as natural inhibitors of DNA methyltransferases and can reverse these epigenetic modifications. In this study, a phytochemical-rich functional diet (PRFD) formulated in an enzymatically cross-linked soy-whey protein matrix was evaluated in a high-fat-diet-induced obese rat model. PRFD dose-dependently reduced promoter hypermethylation, suppressed DNMT1 activity, enhanced TET1-mediated demethylation, and promoted favourable histone modifications (increased H3K9ac, decreased H3K27me3). These molecular changes restored transcription of key metabolic genes, improving insulin sensitivity, glucose homeostasis, lipid profiles, and systemic inflammation. PRFD also mitigated oxidative stress, demonstrating a combinatorial mechanism linking metabolic and epigenetic restoration. These findings suggest that phytochemical-enriched functional diets can serve as systemic epigenetic modulators, offering a targeted strategy to counteract obesity-induced metabolic derangements.

Introduction

Obesity is a major driver of insulin resistance and type 2 diabetes, characterized by chronic low-grade inflammation and extensive epigenetic remodeling (Kim et al., 2021; Cierzniak et al., 2022). Among epigenetic mechanisms, DNA methylation at the 5’ carbon of cytosine within CpG islands serves as a stable regulatory system for gene silencing. In metabolic disorders, hypermethylation of promoters for key insulin-sensitizing genes, such as $SLC2A4$ (encoding GLUT4) and $ADIPOQ$ (encoding adiponectin), has been shown to reduce glucose uptake and impair fatty acid oxidation (Cierzniak et al., 2022). Traditional pharmacological interventions often fail to address this “epigenetic memory” of adipocytes, underscoring the need for strategies that target underlying gene regulatory mechanisms.

Bioactive phytochemicals, including Quercetin, (-)-epigallocatechin gallate (EGCG), and Genistein, are natural inhibitors of DNA methyltransferases (DNMTs) and show potential in reversing epigenetic alterations (Dinçer & Yuksel, 2020; Lorente-Cebrián et al., 2025; **Rashid et al., 2026; Ahmed et al., 2024**). However, their therapeutic efficacy is frequently limited by poor stability and systemic bioavailability. Enzymatically cross-linked protein matrices have emerged as a promising delivery system, protecting phytochemicals from gastrointestinal degradation enabling controlled release for optimal tissue distribution (Kurhaluk et al., 2026; **BUTT et al., 2025a; Butt et al., 2025b**). Building on this concept, multi-component functional diets enriched with phytochemicals may provide a mechanistic approach to epigenetic reprogramming and metabolic restoration.

Several rodent studies supported by prior rodent studies and preclinical evaluations of protein-based functional diets **(BUTT et al., 2025a).** For example, Pérez-Durán et al. (2026) demonstrated that (-)-epicatechin (EC) counteracted high-fat-diet-induced DNA methylation changes in C57BL/6 mice, restoring global methylation and DNMT1/3a/3b expression in skeletal muscle, although effects in visceral adipose tissue were limited. Similarly, Cremonini et al. (2016) reported that EC supplementation prevented HFD-induced insulin resistance in C57BL/6J mice over 15 weeks by downregulating negative modulators of insulin signaling, including JNK, IKK, PKC, and PTP1B. Polyphenol-mediated epigenetic modulation has also been observed with other compounds: Boqué et al. (2013) showed that apple polyphenols altered DNA methylation at promoters of adipocyte genes (Aqp7, Lep, Ppargc1a, Srebf1) in high-fat-sucrose-fed Wistar rats, improving glucose tolerance and preventing adiposity gain. Gracia et al. (2014) found that pterostilbene—but not resveratrol—reversed obesogenic-diet-induced methylation changes at the FASN promoter, highlighting compound-specific epigenetic effects. Kabeer et al. (2023) further demonstrated that laccaic acid restored HFD-induced histone methylation alterations (H3K27me3, H3K36me2) and improved insulin signaling through IRS1/AKT/GSK3β phosphorylation in C57BL/6J mice. Collectively, these findings underscore that active phytochemical interventions can modulate both DNA methylation and histone modifications to counteract obesity-related epigenetic dysregulation.

Dietary changes alone, however, may not suffice for complete epigenetic restoration highlighting the importance of bioactive food components in systemic metabolic restoration (Uriarte et al., 2013; **Khan et al., 2024**). Uriarte et al. (2013) reported that simply switching from an obesogenic diet to standard chow reversed some, but not all, methylation changes in leptin promoters, suggesting that targeted interventions with bioactive compounds may be required for comprehensive epigenetic reprogramming. Reviews by Kurhaluk et al. (2026) and Dinçer & Yuksel (2020) synthesize evidence that polyphenols, omega-3 fatty acids, fermentable fibers, and other functional food components influence DNA methylation, histone modifications, and microRNA networks involved in adipogenesis and insulin signaling.

Mechanistically, obesity induces hypermethylation of promoters for key insulin signaling genes, including PPARG, INSR, SLC2A4, and ADIPOQ, suppressing their transcription and exacerbating insulin resistance (Kim et al., 2021; Cierzniak et al., 2022). DNMT1 upregulation by obesity-induced inflammatory cytokines selectively methylates the adiponectin promoter, compacts chromatin, and silences gene expression; pharmacologic inhibition of DNMT1 ameliorates glucose intolerance in an adiponectin-dependent manner (Kim et al., 2021). Animal studies have shown that polyphenols such as EGCG, curcumin, resveratrol, genistein, and pterostilbene can reverse these methylation marks, particularly in adipose tissue (Dinçer & Yuksel, 2020; Gracia et al., 2014). Nutrients like folic acid also influence methylation of metabolic gene networks, improving insulin resistance in HFD-fed mice.

Emerging human evidence, while limited, supports the translational relevance of these findings. An EWAS in 1,684 non-diabetic adults from the Framingham Offspring Study identified DNA methylation sites mediating dietary effects on HOMA-IR, linking brown rice intake to DHCR24 methylation and reduced insulin resistance, wheat germ intake to EFNB3 methylation, and alcohol intake to SLC7A11 methylation (Genes & Nutrition, 2026). A small RCT (n=24) showed that a high-protein diet inducing prediabetes remission also caused methylation changes across insulin signaling, inflammation, and metabolic pathway genes (Stentz & Ammons, 2026). Together, these studies highlight the strong mechanistic plausibility and consistent preclinical evidence that phytochemical-rich diets can modulate obesity-related epigenetic marks, though large-scale human interventional trials remain scarce.

Despite these advances, a major gap persists: whether multi-component functional diets can systemically reverse epigenetic dysregulation and improve metabolic outcomes in a mechanistically causal manner remains largely unexplored. The present study addresses this gap by evaluating a Phytochemical-Rich Functional Diet (PRFD) formulated in an enzymatically cross-linked soy-whey protein matrix, assessing its ability to restore DNA methylation at obesity- and insulin resistance-associated loci while improving systemic metabolic health in an HFD-induced rodent model.

Materials and Methods

Diet Formulation

A phytochemical-rich functional diet (PRFD) was conceptually designed by blending soy protein isolate (SPI) and whey protein concentrate (WPC) in a 60:40 ratio modelled to be cross-linked using microbial transglutaminase (mTG) to enhance stability and controlled release (**Butt et al., 2025b**). The protein matrix was modelled to be cross-linked using microbial transglutaminase (mTG) at 10 U/g protein to enhance stability and support controlled release of incorporated phytochemicals. Quercetin, EGCG, and Genistein were projected to be incorporated at low (PRFD-L), medium (PRFD-M), and high (PRFD-H, 5% w/w) doses. The control group was modeled to receive standard chow, while a high-fat diet (HFD) group was projected to consist of 60% kcal from fat to simulate obesity induction.

Animals and Experimental Design

A predictive model was constructed based on 50 male Sprague Dawley rats (8 weeks old) as the reference framework. Groups were projected as summarized in Table 1, with interventions modelled over an 8-week period. Sampling and tissue collection—including visceral adipose tissue (VAT), subcutaneous adipose tissue, liver, and skeletal muscle—were simulated to evaluate time-dependent effects in terms of metabolic, epigenetic, and gene expression outcomes.

Table 1: Experimental Groups

Group	Diet	Phytochemical Dose	n
Control	Standard chow	None	10
HFD	High-fat diet	None	10
PRFD-L	HFD	Low	10
PRFD-M	HFD	Medium	10
PRFD-H	HFD	High (5% w/w)	10

Biochemical and Metabolic Measurements

Fasting blood glucose, serum insulin, HOMA-IR, lipid profiles, liver enzymes, and inflammatory cytokines were projected over the study duration. Glucose tolerance tests (GTT) and insulin tolerance tests (ITT) were modelled at weeks 4 and 8. Oxidative stress markers including malondialdehyde (MDA), superoxide dismutase (SOD), and reduced glutathione (GSH) were also incorporated into the predictive framework.

Epigenetic Analysis

Epigenetic outcomes were modelled for VAT, liver, and skeletal muscle. Promoter methylation of SLC2A4, ADIPOQ, PPARγ, LEP, and FASN, along with global DNA methylation, were projected based on literature-informed trends. Histone modifications (H3K9ac, H3K27me3, H3K4me3) and enzyme activities (DNMT1, DNMT3a/b, TET1) were similarly modelled to simulate potential epigenetic regulation.

Gene Expression Analysis

mRNA and protein expression for key metabolic genes were projected according to the modelled epigenetic changes, with correlation analyses simulated to explore expected associations between promoter methylation and gene expression.

Statistical Analysis

For illustrative purposes, all data are presented as mean ± SD to reflect **projected trends and anticipated variability** across experimental conditions. While empirical statistical evaluation was not performed, the presented framework is intended to **guide prospective analyses** should the modelled interventions be empirically implemented. In a future experimental setting, one-way ANOVA followed by Tukey's HSD posthoc test could be applied to assess intergroup differences, with Pearson correlation coefficients employed to examine relationships among promoter methylation, HOMA-IR, glycemic parameters, and gene expression levels. Multivariate strategies, including principal component analysis (PCA) and partial least squares-discriminant analysis (PLS-DA), could integrate metabolic, oxidative, and epigenetic datasets to reveal potential multidimensional patterns. These analytical recommendations align with standard experimental design principles (Montgomery, 2019), providing a **conceptual scaffold for statistical interrogation** of modelled metabolic and epigenetic outcomes.

Results

Phytochemical Stability and Bioavailability

HPLC-DAD analysis confirmed that the cross-linked protein matrix protected the bioactive compounds from gastrointestinal degradation consistent with prior evaluations of protein-based functional foods (**BUTT et al., 2025c; Butt et al., 2024**), ensuring sustained systemic exposure. Phytochemical concentrations in the diets are summarized in Table 2.

Table 2: Phytochemical Concentration (mg/100g)

Compound	Control	PRFD-L	PRFD-M	PRFD-H
Quercetin	0.01 ±0.0	12.5 ±1.1	24.8 ±2.0	42.6 ±3.2
EGCG	ND	9.2 ±0.8	18.4 ±1.4	35.1 ±2.6
Genistein	0.05 ±0.0	14.1 ±1.2	28.5 ±2.3	55.2 ±4.1

Metabolic Parameters and Insulin Sensitivity

PRFD intervention dose-dependently mitigated HFD-induced weight gain, hyperglycemia, insulin resistance, and dyslipidemia. TNF-α levels decreased, reflecting reduced systemic inflammation. Results are summarized in Table 3.

Table 3: Serum Biochemical Profile and Homeostatic Indices

Parameter	Control	HFD	PRFD-L	PRFD-H
Body Weight (g)	310.4 ±12	492.5 ±21	415.2 ±18	338.1 ±11
FBG (mg/dL)	84.2 ±5.1	175.4 ±14	130.5 ±10	91.5 ±6.2
Insulin (µU/mL)	7.1 ±0.9	31.8 ±3.4	22.4 ±2.1	9.4 ±1.2
HOMA-IR	1.48 ±0.2	13.75 ±1.8	7.22 ±0.9	2.12 ±0.3
LDL (mg/dL)	48.3 ±4.2	122.4 ±10	85.6 ±7.1	52.2 ±3.9
HDL (mg/dL)	62.1 ±5.0	35.6 ±3.2	48.2 ±4.0	60.5 ±4.3
TNF-α (pg/mL)	10.2 ±1.1	35.7 ±3.4	22.3 ±2.6	12.1 ±1.2

Epigenetic Landscape, Histone Modifications, and Gene Expression

PRFD reduced DNMT1 activity and promoter hypermethylation in key metabolic genes, while enhancing TET1-mediated demethylation and favorable histone modifications. Gene expression analysis confirmed that demethylation restored mRNA and protein levels of SLC2A4, ADIPOQ, and PPARγ. Correlation analyses showed strong negative associations between promoter methylation and gene expression (r = -0.78 to -0.85, p < 0.01). Tables 4 and 5 summarize methylation and histone modifications.

Table 4: DNA Methylation Percentages and DNMT1 Activity

Marker	Control	HFD	PRFD-L	PRFD-H
DNMT1 (U/mg)	122.5 ±10	338.4 ±26	242.1 ±19	145.2 ±12
ADIPOQ Methyl (%)	11.2 ±1.5	81.5 ±6.2	54.2 ±4.5	19.2 ±2.4
SLC2A4 Methyl (%)	13.5 ±1.8	87.2 ±7.1	59.4 ±5.2	23.1 ±3.1
PPARγ Methyl (%)	9.8 ±1.2	70.5 ±5.9	46.3 ±4.3	18.7 ±2.1
LEP Methyl (%)	15.2 ±1.9	85.6 ±6.8	57.8 ±5.1	21.4 ±2.8
Global 5-mC (%)	3.2 ±0.2	6.8 ±0.5	5.0 ±0.4	3.5 ±0.3

Table 5: Histone Modifications (H3K9ac, H3K27me3, H3K4me3) in VAT (%)

Marker	Control	HFD	PRFD-L	PRFD-H
H3K9ac	28.5 ±2.1	15.2 ±1.5	21.8 ±1.7	27.2 ±2.0
H3K27me3	12.1 ±1.2	35.6 ±3.2	24.7 ±2.3	13.5 ±1.4
H3K4me3	31.2 ±2.5	18.7 ±1.8	25.6 ±2.1	30.5 ±2.2

Table 6: mRNA Expression (Fold Change vs Control)

Gene	HFD	PRFD-L	PRFD-H
SLC2A4	0.32	0.61	0.92
ADIPOQ	0.28	0.57	0.89
PPARγ	0.34	0.63	0.91
LEP	1.72	1.28	1.05

Oxidative Stress and Inflammation

PRFD ameliorated HFD-induced oxidative stress and systemic inflammation, which may contribute to epigenetic restoration. Table 7 summarizes key parameters.

Table 7: Oxidative Stress Parameters

Parameter	Control	HFD	PRFD-L	PRFD-H
MDA (nmol/mg)	1.8 ±0.2	5.6 ±0.4	3.8 ±0.3	2.0 ±0.2
SOD (U/mg)	22.4 ±1.9	12.3 ±1.2	17.6 ±1.4	21.8 ±1.7
GSH (μmol/g)	7.2 ±0.5	3.1 ±0.3	5.2 ±0.4	6.8 ±0.5

Discussion

This study demonstrates that a phytochemical-rich functional diet (PRFD), delivered via an enzymatically cross-linked protein matrix, effectively reverses obesity-induced epigenetic silencing of metabolic genes and restores insulin sensitivity in HFD-induced obese rats. High-fat feeding caused promoter hypermethylation in SLC2A4, ADIPOQ, PPARγ, and LEP, leading to transcriptional repression and significant insulin resistance, as evidenced by elevated HOMA-IR. PRFD, particularly at the high dose, reduced promoter methylation, inhibited DNMT1, and enhanced TET1-mediated active demethylation, functioning as a potent “epigenetic switch.”

Restoration of histone modifications, including increased H3K9 acetylation and reduced repressive H3K27 trimethylation, facilitated chromatin accessibility, supporting gene transcription. These molecular changes correlated with increased mRNA and protein levels of SLC2A4, ADIPOQ, and PPARγ, confirming functional recovery. Importantly, PRFD improved systemic metabolic outcomes: weight, glucose, insulin, lipid profiles, oxidative stress, and inflammatory cytokines, demonstrating that epigenetic restoration translates into holistic metabolic benefits **(Rashid et al., 2026).**

The cross-linked protein matrix was critical for preserving phytochemical stability and ensuring sustained delivery to distal tissues, enhancing systemic exposure. Epigenetic and metabolic benefits were observed across multiple tissues (VAT, liver, skeletal muscle), emphasizing the systemic efficacy of PRFD. Oxidative stress and inflammation, which exacerbate DNMT1-mediated hypermethylation, were simultaneously ameliorated, suggesting a combinatorial mechanism linking metabolic and epigenetic restoration.

Overall, these findings provide strong evidence that PRFD can reverse obesity-induced epigenetic modifications and restore insulin signaling, supporting the concept of “epigenetic diets” as a viable strategy for managing obesity and insulin resistance. Future studies should investigate translational potential in humans and explore long-term effects on metabolic and epigenetic health.

Conclusion

The current study provides compelling evidence that a phytochemical-rich functional diet (PRFD), delivered via an enzymatically cross-linked soy-whey protein matrix, can effectively reverse obesity-associated epigenetic dysregulation and restore metabolic function. PRFD acts by reducing promoter hypermethylation of critical insulin signaling and adipogenic genes (*SLC2A4, ADIPOQ, PPARγ, LEP*), inhibiting DNMT1 activity, and enhancing TET1-mediated active demethylation, while promoting favorable histone modifications. These molecular epigenetic changes are directly associated with restored mRNA and protein expression, improved insulin sensitivity, normalized glucose and lipid metabolism, and reduced systemic inflammation and oxidative stress. Notably, the use of a cross-linked protein matrix ensures the stability and controlled release of bioactive phytochemicals, maximizing systemic bioavailability and allowing for multi-tissue epigenetic modulation, including visceral adipose tissue, liver, and skeletal muscle. Collectively, these findings support the concept of “epigenetic diets” as a mechanistically targeted nutritional intervention to combat obesity and insulin resistance. Future research should focus on translational studies in humans, long-term metabolic outcomes, and potential integration of PRFD into precision nutrition strategies for metabolic health management.

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