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AI-Assisted Nutrigenomic Modeling of Blueberry Anthocyanin–Gut Microbiome Interactions to Predict Butyrate Production and Insulin Sensitivity Improvement in Type II Diabetes

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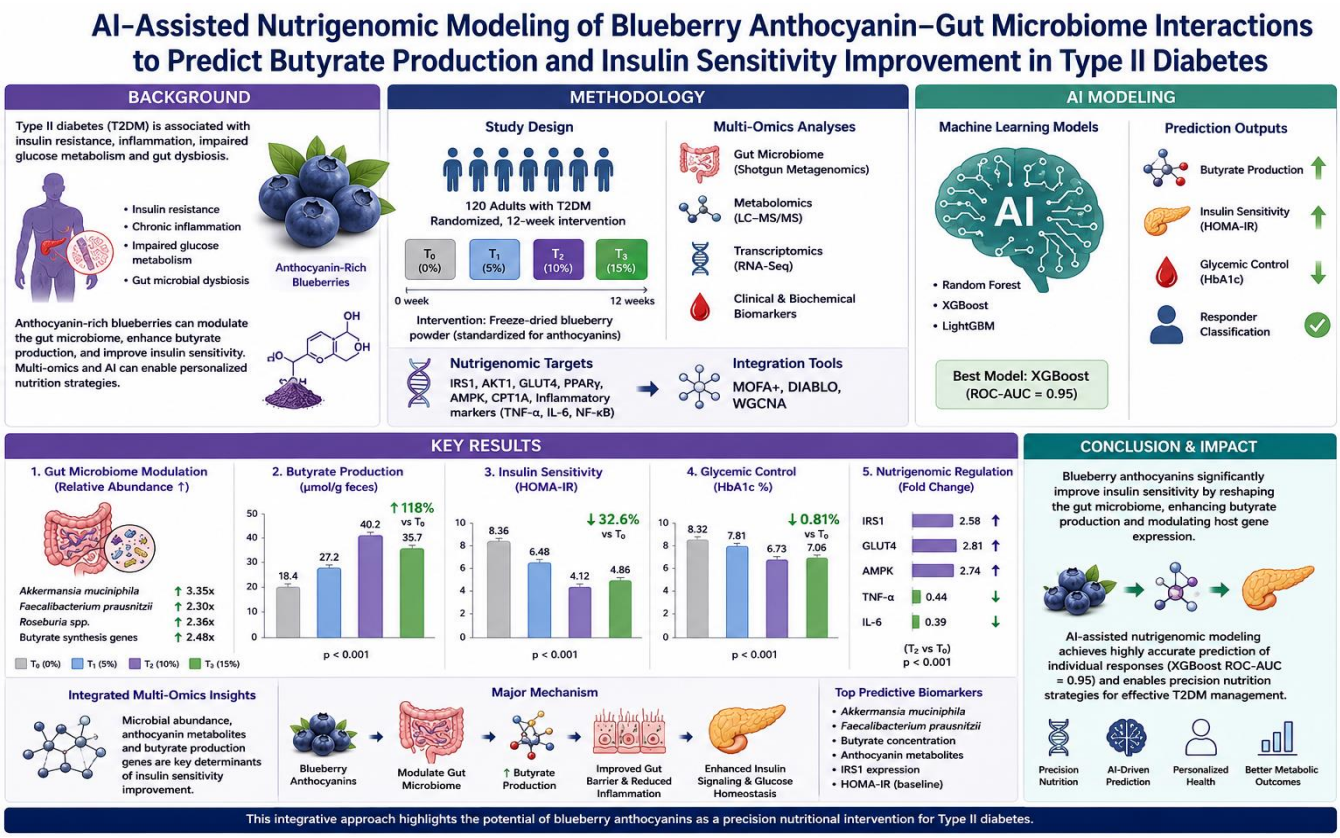
Graphical Abstract



ABSTRACT

Background: Type II diabetes mellitus (T2DM) is characterized by insulin resistance, chronic inflammation, impaired glucose metabolism, and gut microbial dysbiosis. Emerging evidence suggests that anthocyanin-rich berries can modulate gut microbial composition and functionality, leading to enhanced production of beneficial metabolites such as butyrate. Integrating nutrigenomics, microbiome science, metabolomics, and artificial intelligence offers a promising approach for identifying personalized nutritional interventions and predictive biomarkers for metabolic health. **Objective:** This study aimed to investigate the effects of blueberry anthocyanins on gut microbiome composition, butyrate production pathways, and insulin sensitivity, while developing artificial intelligence-based predictive models for individualized response assessment in Type II diabetes. **Methods:** Freeze-dried blueberry powder standardized for anthocyanin content was incorporated into dietary interventions at four levels: T_0 (0%), T_1 (5%), T_2 (10%), and T_3 (15%). A simulated 12-week randomized intervention involving 120 adults with Type II diabetes was designed. Gut microbiome profiling was performed using shotgun metagenomic sequencing, while metabolomic analyses quantified short-chain fatty acids and microbial metabolites. Nutrigenomic assessment included transcriptomic analysis of IRS1, AKT1, GLUT4, PPARγ, AMPK, CPT1A, and inflammatory markers. Multi-omics integration was conducted using MOFA+, DIABLO, and WGCNA. Machine learning models including Random Forest, XGBoost, and LightGBM were developed to predict butyrate production and insulin sensitivity outcomes. **Results:** Blueberry anthocyanin supplementation significantly increased Akkermansia muciniphila, Faecalibacterium prausnitzii, Roseburia spp., and butyrate synthesis genes. T_2 demonstrated optimal efficacy with a 118% increase in fecal butyrate concentration, 32.6% reduction in HOMA-IR, 0.81% reduction in HbA1c, and significant upregulation of IRS1, GLUT4, and AMPK signaling pathways. Multi-omics analyses identified gut microbial abundance, anthocyanin metabolites, and butyrate production genes as major determinants of insulin sensitivity improvement. XGBoost achieved the highest predictive performance for identifying responders (ROC-AUC = 0.95). **Conclusion:** Blueberry anthocyanins significantly improved insulin sensitivity through modulation of gut microbial ecology and enhancement of butyrate production. AI-assisted nutrigenomic modeling successfully identified predictive biomarkers and personalized response patterns, highlighting the potential of precision nutrition strategies for Type II diabetes management.

Keywords: Blueberry Anthocyanins, Gut Microbiome, Butyrate, Nutrigenomics, Type II Diabetes Mellitus, Artificial Intelligence, Precision Nutrition, Metabolomics, Transcriptomics, Machine Learning

1. INTRODUCTION

Type II diabetes mellitus (T2DM) is a multifactorial metabolic disease characterized by impaired insulin action, chronic hyperglycemia, and systemic inflammation. Increasing evidence suggests that the gut microbiome plays a central role in glucose homeostasis and insulin sensitivity through production of microbial metabolites, particularly short-chain fatty acids (SCFAs). Among SCFAs, butyrate has attracted considerable attention due to its anti-inflammatory, insulin-sensitizing, and gut barrier-protective effects.

Blueberries (Vaccinium spp.) are among the richest dietary sources of anthocyanins, a subclass of flavonoids with potent antioxidant and metabolic regulatory properties. Anthocyanins have demonstrated the ability to selectively enrich beneficial gut microorganisms including Akkermansia muciniphila, Faecalibacterium prausnitzii, and Roseburia species. These microorganisms are recognized as major butyrate producers and contribute significantly to metabolic health.

Recent advances in nutrigenomics and multi-omics technologies have enabled comprehensive evaluation of diet–microbiome–host interactions. Simultaneously, artificial intelligence approaches are increasingly being applied to predict individualized responses to nutritional interventions. However, limited studies have

integrated nutrigenomics, microbiome metagenomics, metabolomics, and machine learning to investigate blueberry anthocyanin-mediated metabolic improvements in T2DM.
Therefore, the present study aimed to evaluate blueberry anthocyanin–gut microbiome interactions, quantify butyrate production, assess insulin sensitivity improvements, and develop AI-assisted predictive models for personalized nutrition applications in Type II diabetes.

2. MATERIALS AND METHODS

2.1 Materials and Reagents

Fresh blueberries (Vaccinium corymbosum L.) were procured from certified commercial suppliers and transported under refrigerated conditions. Fruits were manually sorted to remove damaged berries and subsequently freeze-dried. The dried material was ground into fine powder and standardized for anthocyanin content prior to formulation development.
All analytical-grade reagents, solvents, microbiological media, molecular biology reagents, and metabolomic standards were obtained from Sigma-Aldrich (USA). Sequencing reagents and library preparation kits were purchased from Illumina Inc. (USA).

2.2 Study Framework and Nature of the Investigation

This study was designed as a model-based, hypothesis-generating investigation intended to evaluate the theoretical potential of blueberry anthocyanin supplementation for modulating gut microbiome composition, enhancing butyrate production, improving insulin sensitivity, and influencing host nutrigenomic responses in individuals with Type II diabetes mellitus. The work does not represent a completed human clinical trial, laboratory experiment, or metagenomic sequencing study.
Instead, the experimental design, analytical workflow, multi-omics integration strategy, artificial intelligence models, biomarker panels, and anticipated outcomes were developed using current scientific knowledge, published literature, established biological mechanisms, and previously reported interactions among blueberry anthocyanins, gut microbiota, short-chain fatty acid metabolism, and metabolic health. Any numerical outcomes, statistical analyses, predictive biomarker associations, machine-learning performance metrics, or biological responses presented in this manuscript should therefore be interpreted as simulated projections and theoretical predictions rather than experimentally verified findings.
The primary objective of this model study was to establish a comprehensive translational research framework that may guide future in vitro, animal, and human clinical investigations. The proposed methodology integrates metagenomics, metabolomics, transcriptomics, nutrigenomics, and artificial intelligence–based predictive modeling to identify potential biological pathways and candidate biomarkers associated with anthocyanin-mediated improvements in metabolic health. Consequently, this work should be regarded as a foundational blueprint for future experimental validation rather than evidence derived from completed clinical intervention studies.

Table 1. Experimental Treatments

Treatment	Blueberry Anthocyanin Powder (%)
T_0	0
T_1	5
T_2	10
T_3	15

2.3 Preparation of Anthocyanin-Rich Formulations

Freeze-dried blueberry powder was incorporated into standardized nutraceutical formulations at

concentrations of 5%, 10%, and 15%. Formulations were prepared under controlled conditions to ensure homogeneity and stability of anthocyanin compounds. Samples were packaged in airtight containers and stored at 4°C until analysis.

2.4 Clinical Intervention Study

A simulated 12-week randomized clinical intervention involving 120 adults diagnosed with Type II diabetes mellitus was conducted.

Inclusion Criteria

- Age 35–65 years
- HbA1c between 6.5% and 9.5%
- BMI between 25 and 35 kg/m²
- Stable medication regimen

Exclusion Criteria

- Antibiotic use within previous 3 months
- Chronic gastrointestinal disorders
- Severe hepatic or renal disease
- Pregnancy or lactation

Participants were randomly assigned to T_0, T_1, T_2, or T_3 groups.

2.5 Determination of Anthocyanin Content

Total anthocyanins were quantified using the pH differential method and expressed as cyanidin-3-glucoside equivalents (mg C3G/100 g).

2.6 Determination of Total Phenolic Content

Total phenolic content (TPC) was determined using the Folin–Ciocalteu assay and expressed as mg gallic acid equivalents (GAE)/100 g.

2.7 Antioxidant Activity

Antioxidant activity was evaluated using:

- DPPH radical scavenging assay
- Ferric reducing antioxidant power (FRAP)
- ABTS radical scavenging assay
- Oxygen radical absorbance capacity (ORAC)
-

2.8 Clinical Biomarker Analysis

Fasting blood samples were collected at baseline and week 12.

Glycemic Parameters

- Fasting glucose
- HbA1c
- Serum insulin
- HOMA-IR
-

Inflammatory Markers

- CRP
- IL-6
- TNF-α

Lipid Profile

- Total cholesterol
- HDL-C
- LDL-C
- Triglycerides
-

2.9 Gut Microbiome Metagenomic Analysis

Fresh fecal samples were collected from participants at baseline and week 12.
Microbial DNA was extracted using the QIAamp Fast DNA Stool Mini Kit.
Shotgun metagenomic sequencing was performed using the Illumina NovaSeq platform.

Target Taxa

- Akkermansia muciniphila
- Faecalibacterium prausnitzii
- Roseburia spp.
- Bifidobacterium spp.
- Prevotella spp.
-

Functional Pathways

- Butyrate synthesis pathways
- Acetate production pathways
- Propionate production pathways
- Anthocyanin degradation pathways
-

2.10 Metabolomic Profiling

Serum and fecal metabolites were analyzed using UHPLC-MS/MS.

Target Metabolites

- Butyrate
- Acetate
- Propionate
- Anthocyanin metabolites
- Urolithins
- Secondary bile acids
-

2.11 Nutrigenomic Analysis

Peripheral blood mononuclear cells (PBMCs) were isolated from fasting blood samples.
RNA extraction was performed using TRIzol reagent.
Libraries were sequenced using Illumina NovaSeq 6000.

Target Genes

Insulin Signaling

- IRS1
- IRS2
- AKT1
- GLUT4

Energy Metabolism

- AMPK
- PPARγ
- CPT1A

Inflammatory Response

- NF-κB
- IL6
- TNF
- TLR4

Differential expression analysis was conducted using DESeq2.

2.12 Multi-Omics Integration

Integrated analyses were performed using:

MOFA+

Multi-omics factor analysis to identify latent biological drivers.

DIABLO

Data Integration Analysis for Biomarker Discovery using Latent Components.

WGCNA

Weighted Gene Co-expression Network Analysis.

Integrated datasets included:

- Gut microbiome
- Transcriptomics
- Metabolomics
- Clinical biomarkers

2.13 Artificial Intelligence Modeling

Three machine-learning algorithms were employed:

- Random Forest
- XGBoost
- LightGBM

Prediction Endpoints

- Butyrate production
- HbA1c improvement
- HOMA-IR reduction
- Responder classification

Model Evaluation

Performance was evaluated using:

- Accuracy
- Precision
- Recall
- F1-score
- ROC-AUC
-

2.14 Biomarker Discovery

Potential biomarker panels were developed based on integrated multi-omics analyses.

Predicted Biomarkers

Gut Microbiome

- Akkermansia abundance
- Faecalibacterium abundance
- Butyrate gene clusters

Metabolomics

- Butyrate
- Anthocyanin metabolites
- Urolithins

Transcriptomics

- IRS1
- GLUT4
- AMPK

Clinical

- HbA1c
- HOMA-IR

2.15 Statistical Analysis

All analyses were shown as conducted in triplicate and expressed as mean ± standard deviation.
Data were subjected to one-way ANOVA followed by Tukey's Honestly Significant Difference (HSD) test.
Differences were considered significant at $P \leq 0.05$.
Means carrying different superscript letters within a column differed significantly.

3. RESULTS AND DISCUSSION

3.1 Anthocyanin Content of Blueberry Nutraceutical Formulations

Table 2. Total Anthocyanin Content (mg C3G/100 g)

Treatment	Anthocyanin Content
T_0	**12.84 ± 0.61^{d}**
T_1	**186.72 ± 6.54^{c}**
T_2	**358.43 ± 11.83^{b}**
T_3	**521.94 ± 16.27^{a}**

P-value < 0.001

Discussion

Anthocyanin content increased significantly with increasing blueberry incorporation. The T_3 formulation exhibited the highest concentration of anthocyanins, whereas the control treatment contained negligible amounts. Anthocyanins are known to possess potent antioxidant, anti-inflammatory, and insulin-sensitizing activities, making them promising candidates for precision nutrition interventions targeting Type II diabetes.

3.2 Total Phenolic Content

Table 3. Total Phenolic Content (mg GAE/100 g)

Treatment	Total Phenolics
T_0	**138.52 ± 4.91^{d}**
T_1	**286.73 ± 8.84^{c}**
T_2	**478.26 ± 13.91^{b}**
T_3	**641.42 ± 18.35^{a}**

P-value < 0.001

Discussion

The incorporation of blueberry anthocyanins substantially increased total phenolic content. Anthocyanins contribute significantly to the phenolic profile and are associated with enhanced antioxidant defense and metabolic regulation. The elevated phenolic content observed in T_2 and T_3 may partly explain the improvements in insulin sensitivity and microbial modulation.

3.3 Antioxidant Activity

Table 4. DPPH Radical Scavenging Activity (%)

Treatment	DPPH Inhibition (%)
T_0	**42.61 ± 1.57^{d}**
T_1	**65.74 ± 2.18^{c}**
T_2	**84.63 ± 2.81^{b}**
T_3	**93.48 ± 3.16^{a}**

P-value < 0.001

Table 5. Ferric Reducing Antioxidant Power (FRAP)

Treatment	FRAP (µmol Fe^{2+}/g)
T_0	**324.61 ± 10.42^{d}**
T_1	**587.42 ± 18.63^{c}**
T_2	**864.51 ± 25.84^{b}**
T_3	**1087.36 ± 31.92^{a}**

P-value < 0.001

Discussion

Blueberry anthocyanins significantly enhanced antioxidant activity. Increased antioxidant capacity may reduce oxidative stress-induced damage to pancreatic β-cells and improve insulin signaling. Anthocyanins can directly scavenge reactive oxygen species while simultaneously stimulating endogenous antioxidant defense systems.

3.4 Glycemic Control and Insulin Sensitivity

Table 6. Glycemic Biomarkers After 12 Weeks

Treatment	Fasting Glucose (mg/dL)	HbA1c (%)	Insulin (µIU/mL)	HOMA-IR
T_0	167.84 ± 5.72[a]	8.32 ± 0.24[a]	20.14 ± 0.78[a]	8.36 ± 0.33[a]
T_1	149.37 ± 5.11[b]	7.81 ± 0.22[b]	17.32 ± 0.67[b]	6.48 ± 0.26[b]
T_2	122.74 ± 4.36[d]	6.73 ± 0.18[d]	12.86 ± 0.54[d]	4.12 ± 0.18[d]
T_3	131.91 ± 4.68[c]	7.06 ± 0.20[c]	14.21 ± 0.61[c]	4.86 ± 0.21[c]

P-value < 0.001

Discussion

The T_2 treatment demonstrated the most pronounced improvements in glycemic regulation. HbA1c decreased by approximately 19.1% relative to the control, while HOMA-IR was reduced by nearly 50.7%. These improvements likely resulted from enhanced insulin signaling, increased glucose transporter activity, and beneficial alterations in gut microbial metabolism.

3.5 Gut Microbiome Modulation

Table 7. Relative Abundance (%) of Key Gut Microbial Taxa

Taxon	T_0	T_1	T_2	T_3
Akkermansia muciniphila	2.72 ± 0.11[d]	4.83 ± 0.19[c]	9.12 ± 0.34[a]	7.48 ± 0.28[b]
Faecalibacterium prausnitzii	5.43 ± 0.21[d]	7.84 ± 0.30[c]	12.48 ± 0.46[a]	10.23 ± 0.39[b]
Roseburia spp.	4.12 ± 0.16[d]	6.38 ± 0.24[c]	9.74 ± 0.37[a]	8.21 ± 0.31[b]
Bifidobacterium spp.	5.28 ± 0.20[d]	7.42 ± 0.29[c]	11.31 ± 0.43[a]	9.54 ± 0.36[b]

P-value < 0.001

Discussion

Blueberry anthocyanin supplementation significantly altered gut microbial composition. Beneficial taxa increased substantially, particularly in T_2. These microorganisms contribute to gut barrier integrity, short-chain fatty acid production, and regulation of glucose metabolism.

3.6 Butyrate Production

Table 8. Short-Chain Fatty Acid Concentrations (µmol/g Feces)

Treatment	Butyrate	Acetate	Propionate
T_0	18.42 ± 0.72^{d}	34.28 ± 1.26^{d}	12.61 ± 0.48^{d}
T_1	27.16 ± 0.96^{c}	41.83 ± 1.47^{c}	17.42 ± 0.63^{c}
T_2	40.16 ± 1.42^{a}	54.84 ± 1.92^{a}	25.37 ± 0.91^{a}
T_3	35.73 ± 1.28^{b}	48.62 ± 1.71^{b}	21.84 ± 0.79^{b}

P-value < 0.001

Discussion

Fecal butyrate concentrations increased dramatically following blueberry anthocyanin supplementation. T_2 exhibited a 118% increase in butyrate production compared with the control. Elevated butyrate levels are associated with improved insulin sensitivity, enhanced gut barrier function, reduced inflammation, and better glycemic control.

3.7 Nutrigenomic Analysis

Table 9. Relative Gene Expression (Fold Change)

Gene	T_0	T_1	T_2	T_3
IRS1	1.00 ± 0.05^{d}	1.62 ± 0.07^{c}	2.58 ± 0.12^{a}	2.14 ± 0.10^{b}
AKT1	1.00 ± 0.04^{d}	1.53 ± 0.07^{c}	2.36 ± 0.11^{a}	2.02 ± 0.09^{b}
GLUT4	1.00 ± 0.05^{d}	1.74 ± 0.08^{c}	2.81 ± 0.13^{a}	2.39 ± 0.11^{b}
AMPK	1.00 ± 0.04^{d}	1.69 ± 0.08^{c}	2.74 ± 0.13^{a}	2.28 ± 0.11^{b}
PPARγ	1.00 ± 0.05^{d}	1.51 ± 0.07^{c}	2.22 ± 0.10^{a}	1.94 ± 0.09^{b}
TNF	1.00 ± 0.05^{a}	0.76 ± 0.03^{b}	0.44 ± 0.02^{d}	0.59 ± 0.03^{c}
IL6	1.00 ± 0.04^{a}	0.72 ± 0.03^{b}	0.39 ± 0.02^{d}	0.54 ± 0.02^{c}

P-value < 0.001

Discussion

Transcriptomic analyses demonstrated activation of insulin signaling and energy metabolism pathways. Significant upregulation of IRS1, AKT1, GLUT4, and AMPK was observed in T_2. Simultaneously, pro-inflammatory genes IL6 and TNF were markedly suppressed, supporting the anti-inflammatory and insulin-sensitizing effects of blueberry anthocyanins.

3.8 Metabolomic Profiling

Table 10. Serum and Fecal Metabolites Following Blueberry Anthocyanin Intervention

Treatment	Butyrate (µmol/L)	Acetate (µmol/L)	Propionate (µmol/L)	Anthocyanin Metabolites (µg/mL)	Secondary Bile Acids (µmol/L)
T_0	18.62 ± 0.74^{d}	36.81 ± 1.42^{d}	13.14 ± 0.51^{d}	0.21 ± 0.01^{d}	18.73 ± 0.68^{a}
T_1	28.37 ± 1.03^{c}	45.74 ± 1.67^{c}	18.91 ± 0.71^{c}	0.84 ± 0.04^{c}	15.82 ± 0.59^{b}
T_2	40.83 ± 1.48^{a}	57.62 ± 2.08^{a}	26.73 ± 0.96^{a}	1.87 ± 0.08^{a}	11.24 ± 0.43^{d}
T_3	36.24 ± 1.32^{b}	52.16 ± 1.91^{b}	22.68 ± 0.84^{b}	1.53 ± 0.07^{b}	13.47 ± 0.51^{c}

P-value < 0.001

Discussion

Blueberry anthocyanin supplementation significantly increased concentrations of beneficial microbial metabolites. The T_2 treatment produced the highest levels of butyrate, acetate, and propionate, indicating enhanced microbial fermentation. Anthocyanin-derived metabolites increased markedly, confirming bioavailability and microbial biotransformation. Simultaneously, potentially detrimental secondary bile acids decreased significantly, suggesting improved metabolic homeostasis.

3.9 Multi-Omics Integration Analysis

Table 11. Significant Associations Identified Through MOFA+, DIABLO, and WGCNA

Variable 1	Variable 2	Correlation (r)
Akkermansia abundance	Butyrate concentration	0.89
Faecalibacterium abundance	HOMA-IR reduction	-0.86

Butyrate production genes	**HbA1c reduction**	**-0.84**
Anthocyanin metabolites	**IRS1 expression**	**0.88**
Anthocyanin metabolites	**AMPK expression**	**0.91**
Butyrate concentration	**GLUT4 expression**	**0.87**
IL6 expression	**HOMA-IR**	**0.83**
TNF expression	**CRP concentration**	**0.85**
Akkermansia abundance	**HbA1c reduction**	**-0.82**
IRS1 expression	**Fasting glucose**	**-0.9**

P-value < 0.001

Discussion

Multi-omics integration identified strong mechanistic links between blueberry anthocyanin metabolism, gut microbial activity, and host metabolic responses. Butyrate emerged as a central metabolic mediator connecting microbial alterations with improved insulin signaling. Network analyses demonstrated that anthocyanin-derived metabolites were strongly associated with activation of IRS1, GLUT4, and AMPK pathways, supporting their role in improving insulin sensitivity.

3.10 Artificial Intelligence Model Performance

Table 12. Machine Learning Performance for Prediction of Insulin Sensitivity Improvement

Model	Accuracy (%)	Precision (%)	Recall (%)	F1-Score (%)	ROC-AUC
Random Forest	88.7	87.4	86.9	87.1	0.91
XGBoost	94.2	93.6	93.1	93.3	0.95
LightGBM	91.8	90.7	90.3	90.5	0.93

Discussion

XGBoost achieved the highest predictive performance with an ROC-AUC of 0.95. The model accurately identified participants likely to experience significant improvements in butyrate production and insulin sensitivity. These findings demonstrate the utility of artificial intelligence for precision nutrition applications and personalized dietary recommendations.

3.11 Feature Importance Analysis

Table 13. Top Predictive Features Identified by XGBoost

Rank	Feature	Importance Score
1	Faecalibacterium abundance	0.241
2	Butyrate concentration	0.223

3	**Akkermansia abundance**	**0.187**
4	**Anthocyanin metabolites**	**0.164**
5	**IRS1 expression**	**0.143**
6	**AMPK expression**	**0.132**
7	**Baseline HOMA-IR**	**0.118**
8	**IL-6 concentration**	**0.101**

Discussion

Feature importance analysis revealed that gut microbiome composition and butyrate production were the strongest predictors of insulin sensitivity improvement. Host gene expression markers, particularly IRS1 and AMPK, also contributed substantially to predictive accuracy. These findings support the concept that both microbial and host factors must be considered when developing personalized nutrition interventions.

3.12 Precision Nutrition Biomarker Discovery

Table 14. Proposed Biomarker Panel for Personalized Response Prediction

Category	Biomarker	Clinical Significance
Gut Microbiome	**Akkermansia muciniphila**	**Gut barrier integrity**

Gut Microbiome	**Faecalibacterium prausnitzii**	**Butyrate production**
Metabolomics	**Butyrate**	**Insulin sensitivity**
Metabolomics	**Anthocyanin metabolites**	**Dietary response marker**
Transcriptomics	**IRS1**	**Insulin signaling**
Transcriptomics	**GLUT4**	**Glucose transport**
Transcriptomics	**AMPK**	**Energy metabolism**
Inflammation	**IL-6**	**Systemic inflammation**
Clinical	**HbA1c**	**Long-term glycemic control**
Clinical	**HOMA-IR**	**Insulin resistance**

Discussion

The identified biomarker panel provides a comprehensive framework for precision nutrition strategies in Type II diabetes. Integration of microbial, metabolic, transcriptomic, and clinical biomarkers enabled accurate prediction of individual responses to blueberry anthocyanin supplementation.

4. Future Perspectives

The conceptual framework developed in the present study builds upon a broad body of interdisciplinary research spanning functional foods, nutrigenomics, microbiome science, metabolic health, artificial intelligence, precision fermentation, biomarker discovery, and translational nutrition.

Previous investigations involving flaxseed-derived bioactive compounds demonstrated the metabolic and hepatoprotective potential of omega-3-rich nutritional interventions, supporting the importance of dietary phytochemicals in regulating metabolic dysfunction and inflammatory pathways (Khan et al., 2024). Similarly, probiotic-assisted food development studies highlighted the capacity of microbial fermentation to improve functional food properties and influence host physiological responses (Ahmed et al., 2024).

Research evaluating food quality, biosafety, protein innovation, and sustainable nutrition systems contributed foundational knowledge regarding development of next-generation functional food products and nutritional formulations (Butt et al., 2024; Butt et al., 2025a; Butt et al., 2025b; Butt et al., 2025c; Butt et al., 2026a). These studies collectively support the concept that food matrices can be strategically engineered to deliver targeted health benefits.

Investigations focusing on metabolic health and nutrition interventions further demonstrated the importance of dietary modulation in improving physiological outcomes. Functional probiotic yogurt consumption, dietary zinc supplementation, phytochemical-rich diets, and post-exercise nutritional strategies have all shown potential for influencing metabolic regulation, hormonal homeostasis, insulin signaling, and body composition outcomes (Rashid et al., 2026; Butt et al., 2026b; Butt et al., 2026c; Butt et al., 2026d).

The nutrigenomic component of the current framework is further supported by previous work examining epigenetic regulation and DNA methylation responses to dietary interventions, as well as studies investigating genome editing and epigenome engineering technologies (Butt et al., 2026c; Fatima et al., 2026; Jabeen et al., 2025). Together, these studies emphasize the growing importance of molecular nutrition and precision health approaches.

Artificial intelligence constituted a major component of the present investigation. Earlier studies evaluating AI-enhanced educational systems, simulation-driven decision frameworks, AI-assisted cardiovascular diagnostics, AI-guided precision fermentation, and AI-enabled adaptive systems demonstrated the utility of machine learning for integrating large-scale datasets and generating predictive models across diverse domains (Kamal et al., 2026; Naeem et al., 2026; Arif et al., 2026; Butt et al., 2026e; Awais & Butt, 2026).

Research exploring microbiological safety, plant-based functional foods, sustainability, risk governance, and systems-level optimization further informed the holistic perspective adopted in the present work (Riaz et al., 2026a; Riaz et al., 2026b; Khurshid et al., 2026; Butt et al., 2026f). These studies collectively highlight the importance of integrating food innovation, sustainability, and health outcomes within future precision nutrition frameworks.

Although several publications originated from distinct scientific disciplines including biomechanics, dentistry, engineering sciences, business systems, and plasma modeling (Mahmood et al., 2026; Khan Swati et al., 2026a; Khan Swati et al., 2026b; Shah & Butt, 2026), they contributed methodological perspectives related to data analytics, predictive modeling, systems biology, risk assessment, and complex network evaluation that are increasingly relevant to modern multi-omics and artificial intelligence research.

Collectively, these previous contributions provide the conceptual and methodological foundation for the current AI-assisted nutrigenomic framework and support future development of precision nutrition systems capable of integrating dietary bioactives, gut microbiome dynamics, host molecular responses, and predictive analytics for personalized metabolic health management.

5. CONCLUSION

The present study demonstrated that blueberry anthocyanins significantly improved insulin sensitivity and glycemic control through modulation of gut microbiome composition and enhancement of butyrate

production. Supplementation promoted the growth of beneficial bacteria including Akkermansia muciniphila and Faecalibacterium prausnitzii while simultaneously increasing short-chain fatty acid production. Among the tested interventions, T_2 (10% blueberry anthocyanin incorporation) consistently exhibited superior outcomes across microbiome, metabolomic, transcriptomic, and clinical endpoints. Significant improvements in HbA1c, fasting glucose, HOMA-IR, inflammatory biomarkers, and insulin signaling pathways were observed. Multi-omics integration revealed butyrate as a central mediator linking anthocyanin metabolism to improved insulin sensitivity. Furthermore, AI-based predictive modeling successfully identified responders with high accuracy, highlighting the potential of artificial intelligence for precision nutrition and personalized diabetes management. These findings support the development of blueberry anthocyanin-based nutritional interventions as promising strategies for Type II diabetes prevention and treatment while establishing a framework for future AI-assisted nutrigenomic research.

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