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# Nutrigenomics and Food Safety in Chronic Disease Prevention: From Bioactive Nutrients to Contaminants

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## Abstract

Nutrigenomics explore how foods and bioactive compounds interact with our genes and epigenome to influence overall health, while food safety examines how dietary hazards can disrupt these pathways. Integrating both fields aids in the prevention and management of chronic non-communicable diseases (NCDs). Nutrients such as polyphenols, omega-3 fatty acids and methyl donors can modulate key epigenetic mechanisms, including DNA methylation, histone modifications and non-coding RNA regulation, helping protect against metabolic disorders and some types of cancer. Conversely, exposure to harmful substances, including mycotoxins, heavy metals, endocrine-disrupting chemicals and food processing by-products, can trigger oxidative stress, disturb the gut microbiome and alter epigenetic regulation, increasing disease risk.

This narrative, non-systematic review synthesizes evidence published between 2000 and 2025, emphasizing the surge in studies since 2020. Relevant articles were retrieved from PubMed, Scopus, Web of Science and Google Scholar using combinations of keywords related to nutrigenomics, epigenetics, food safety, and chronic diseases. In total, 235 publications were analyzed, highlighting nutrigenomics and food safety as an emerging scientific hotspot.

Recent advances in multi-omics and microbiome research have enabled precision nutrition approaches and more accurate risk assessment models for NCDs. Despite challenges such as inconsistent methodologies and limited longitudinal data, integrating nutrigenomics with food safety offers a promising approach for improving metabolic health, achieving sustainable weight management, and reducing the global burden of chronic disease. Priorities include large-scale clinical trials, standardized omics pipelines and validated biomarkers to ensure accessibility to and translational impact in public health.

**Keywords**: Nutrigenomics, Food safety, Epigenetic, Genetic, Bioactive, Chronic disease

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## Introduction

Chronic non-communicable diseases (NCDs) such as cardiovascular disease, obesity, type 2 diabetes mellitus (T2DM), and cancer continue to be significant contributors to illness and death on a global scale. Among these, T2DM and obesity have become particularly concerning. The International Diabetes Federation reported that over 537 million adults had diabetes in 2021, with this number expected to increase to 783 million by 2045 (1). Obesity, often coexisting with insulin resistance, is a major driver of both diabetes and cardio-metabolic disorders. The onset and progression of these conditions reflect a dynamic interplay of genetic predisposition, environmental exposures, and lifestyle factors, with diet emerging as one of the most powerful yet modifiable determinants of metabolic health. Notably, individuals respond differently to similar dietary patterns, variability now understood to arise largely from genetic, epigenetic, and microbial diversity.

Nutrigenomics and nutrigenetics offer complementary frameworks to explain this heterogeneity. Nutrigenomics examines how nutrients and dietary bioactives regulate gene expression, shape epigenetic signatures, and influence cellular signaling pathways, while nutrigenetics explores how genetic polymorphisms determine responsiveness to specific nutrients or dietary patterns. Together, these disciplines form the scientific foundation for precision and personalized nutrition aimed at preventing and managing obesity and T2DM. (2,3). Additionally, variations in genes related to lipid metabolism , such as TCF7L2 and FTO, modulate glycemic outcomes and adiposity in response to dietary protein, carbohydrate and fat intake (4).

Food safety research expanded from its original focus on acute toxicity include the long-term and the chronic molecular effects of low-level exposure to dietary hazards. Mycotoxins, heavy metals, endocrine-disrupting chemicals (EDCs), and contaminants formed during food processing are known to play a significant role in the risk of diabetes and obesity risk.

These exposures can disrupt insulin signaling, adipogenesis and energy balance. For example, aflatoxin can worsen hepatic insulin resistance by epigenetically regulating metabolic genes, while cadmium and arsenic associated with oxidative stress, inflammation, and impaired pancreatic β-cell function (5,6). Similarly, EDCs such as bisphenol A (BPA) and phthalates interfere with adipokine secretion, lipid metabolism, and estrogen signaling, thereby promoting obesity and metabolic dysfunction (7).

Previous studies frequently focused on individual nutrients or contaminants, which has restricted the comprehension of their collective impacts. Nevertheless, the emergence of multi-omics technologies such as transcriptomics, epigenomics, metabolomics, and microbiome analysis has revolutionized the field. By combining these datasets, researchers can now obtain a comprehensive understanding of how dietary factors and environmental influences intersect to influence genomic stability and metabolic homeostasis (8,9).

The inclusion of microbiome data has had a significant impact, as microbial metabolites like short-chain fatty acids can affect DNA methylation and histone acetylation, influencing insulin sensitivity and adipose tissue inflammation (10). Conversely, dysbiosis caused by high-fat diets or exposures to toxins can worsen metabolic imbalances by disrupting bile acid signaling and altering epigenetic regulation of glucose and lipid pathways.

Despite notable progress, there are still important gaps in research. Most of the mechanistic insights come from in vitro or animal models, with limited validation in human populations. Human studies integrating multi-omics and microbiome data remain scarce, and the precise epigenetic mechanisms linking diet, contaminants, and metabolic outcomes are not fully understood. The variability in individual genetics is often overlooked, hindering the translation of

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findings into personalized nutrition approaches. Furthermore, many epidemiological studies are short-term or observational making it difficult to establish causation, and the long-term effects of chronic low-dose exposure to emerging contaminants like EDCs are not well studied. These limitations highlight the urgent need for comprehensive, human-centered research to elucidate how diet, genetics, epigenetics, microbiome, and food safety collectively impact the risk of obesity and T2DM (11-14).

This review brings together mechanistic insights, epidemiological evidence, and recent human studies to investigate how bioactive dietary compounds (e.g., polyphenols, omega-3 fatty acids, and methyl donors), dietary contaminants, and the gut microbiome interact to influence the molecular mechanisms underlying diabetes and obesity. It further addresses challenges in research methods, potential for translation into clinical practice, and implications for policy, with the goal of providing valuable information for healthcare professionals, scientists, and policymakers. The review underscores the potential of precision nutrition and advanced food safety approaches in addressing the worldwide challenges of obesity and diabetes.

## Mechanistic insights

The interaction between diet, food safety hazards, and the human genome operates through a series of molecular and epigenetic mechanisms. These mechanisms provide the foundation for understanding how nutrients confer protection and how contaminants exert harm.

### DNA methylation and one-carbon metabolism

DNA methylation is a fundamental epigenetic mechanism that regulates gene expression and maintains genomic stability. Central to this process is S-adenosylmethionine (SAM), the primary methyl group donor for DNA methyltransferases. SAM synthesis relies on methyl donors such as folate, vitamin B12, choline, and betaine, which participate in the one-carbon metabolism pathway. Adequate intake of these nutrients ensures proper DNA methylation patterns, which are essential for normal development and immune function. Conversely, deficiencies in these nutrients can lead to global hypomethylation and locus-specific hypermethylation, increasing the risk of diseases like cancer (16,17). For instance, prenatal folate intake has been associated with DNA methylation changes in development- and immunity-related genes in neonates (18,19).

Emerging evidence indicates that aberrant DNA methylation is also implicated in the pathogenesis of T2DM. Altered methylation of CpG sites in genes involved in insulin secretion, glucose transport, and mitochondrial function has been repeatedly reported in affected individuals (15,11). Epigenome-wide association studies (EWAS) have identified methylation signatures in pancreatic islets, adipose tissue and blood that correlate with glycemic traits and T2DM risk (11). Functional investigations further support the idea that epigenetic dysregulation may impair β-cell identity, reduce insulin expression, and compromise mitochondrial dynamics, contributing to diabetes progression (15). Together, these findings suggest that disturbances in one-carbon metabolism and DNA methylation not only affect cancer risk but may also play a direct role in diabetes etiology.

### Histone modifications and chromatin dynamics

Histone acetylation and deacetylation play crucial roles in modulating chromatin structure and gene expression. Histone acetyltransferases (HATs) add acetyl groups to histones, leading to an open chromatin conformation and active transcription, while histone deacetylases (HDACs) remove these acetyl groups, resulting in chromatin condensation and gene repression. Bioactive compounds such as resveratrol and curcumin have been shown to modulate HAT/HDAC activity, influencing gene expression and inflammatory pathways (12). Additionally, sulforaphane, a natural HDAC

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inhibitor, exhibits chemopreventive effects by altering histone modifications (20). In contrast, exposure to environmental toxins like aflatoxins and acrylamide can lead to aberrant histone modifications, promoting carcinogenesis (13,21).

## Non-coding RNAs

Non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are integral to post-transcriptional gene regulation. Flavonoids such as quercetin have been reported to modulate miRNA expression, shifting profiles toward anti-inflammatory states (22,23). Conversely, bisphenol A (BPA) exposure has been associated with disrupted miRNA expression in estrogen-responsive pathways, with implications for reproductive health and cancer risk (14,22-24).

## Oxidative stress and inflammatory signaling

Oxidative stress and inflammation are closely linked to epigenetic alterations. Diets rich in antioxidants can attenuate reactive oxygen species (ROS)-driven activation of nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1), reducing DNA damage and inflammation (5,21). In contrast, exposure to contaminants such as acrylamide and cadmium elevates oxidative signaling and genotoxic stress, contributing to epigenetic dysregulation (5).

## Gut microbiome-mediated mechanisms

The gut microbiome influences epigenetic regulation through the production of short-chain fatty acids (SCFAs) like butyrate, propionate, and acetate. Butyrate acts as an HDAC inhibitor, modulating histone acetylation and influencing gene expression related to immune function and inflammation (25,26). Additionally, microbial bile acid transformations engage farnesoid X receptor (FXR) and Takeda G-protein-coupled receptor 5 (TGR5), integrating detoxification, lipid, and glucose metabolism pathways (10,25).

## Translational implications

## Dietary Bioactive

Dietary bioactives are central to nutrigenomics, offering protective roles against genomic instability and chronic disease. Unlike macronutrients, which primarily serve as sources of energy and structural components, bioactives exert regulatory effects on gene expression, epigenetic remodeling, oxidative stress, and inflammation. These compounds are derived mainly from plant-based foods but can also be found in certain animal sources. Their activity is not uniform across populations; it is shaped by dose, bioavailability, inter-individual genetic variation, and interactions with the gut microbiome. As such, dietary bioactives represent a promising avenue for personalized nutrition and the prevention of chronic NCDs (13,12,23).

Polyphenols represent one of the most studied groups of bioactives and are widely distributed in fruits, vegetables, teas, coffee, red wine, and spices. Resveratrol, curcumin, epigallocatechin-3-gallate (EGCG), and quercetin have received particular attention due to their pleiotropic actions. Initially characterized as antioxidants, polyphenols are now recognized as modulators of key molecular pathways, including epigenetic regulation and inflammatory signaling. Mechanistically, polyphenols can inhibit DNA methyltransferases (DNMTs), modify the activity of histone acetyltransferases (HATs) and histone deacetylases (HDACs), and regulate non-coding RNAs such as microRNAs. For instance, resveratrol activates the $NAD^+$-dependent deacetylase SIRT1, which remodels chromatin, enhances mitochondrial function, and promotes anti-inflammatory gene expression (12). Curcumin reduces histone acetylation, suppresses NF-κB signaling, and decreases the transcription of pro-inflammatory cytokines. EGCG has been shown to regulate DNMTs and miRNAs involved in lipid metabolism and immune pathways (8). These molecular effects have also been confirmed in human studies. A recent pilot trial demonstrated that polyphenol-rich


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supplementation improved immune epigenetic markers of biological aging, underscoring the translational potential of polyphenols (26). The major polyphenols, their dietary sources, and molecular mechanisms are summarized in Table 1.

Omega-3 fatty acids, notably eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), exert pleiotropic health effects extending beyond cardiovascular protection. Mechanistic evidence shows that omega-3s activate peroxisome proliferator-activated receptors (PPARs), suppress NF-κB activity, and regulate microRNAs involved in lipid metabolism and adipogenesis. Human studies indicate clinically relevant outcomes: genotype-tailored omega-3 interventions are associated with favorable methylation profiles, reduced inflammation, and improved lipid status (3). Variants in fatty acid desaturase (FADS) genes influence response, highlighting the importance of nutrigenomic stratification.

Carotenoids and isothiocyanates also demonstrate epigenetic and chemopreventive properties. Lycopene and β-carotene, abundant in tomatoes, carrots, and other colorful fruits and vegetables, enhance antioxidant defense through nuclear factor erythroid 2-related factor 2 (Nrf2) signaling. This pathway upregulates detoxifying and cytoprotective enzymes, also reduce oxidative damage and preserving genomic integrity. Sulforaphane, derived from cruciferous vegetables, functions as a potent HDAC inhibitor, shifting histone acetylation patterns toward tumor suppressor expression (12). Human trials report that sulforaphane supplementation improves histone acetylation in peripheral immune cells, supporting its translational role as an epigenetic modulator.

Clinical and translational evidence increasingly validates these mechanisms. Dietary patterns enriched with polyphenols and fibers are associated with beneficial DNA methylation shifts in obesity- and diabetes-related genes (8). Personalized nutrition approaches combining genetic testing with tailored dietary advice have demonstrated superior adherence and outcomes compared with standard counseling (26). Moreover, the result of a study provided early evidence that bioactive-rich diets may improve immune-related epigenetic aging markers, highlighting potential applications in both disease prevention and healthy longevity (33). Collectively, these findings emphasize the role of methyl donors, omega-3 fatty acids, carotenoids, and isothiocyanates as dietary modulators of the epigenome and as cornerstones for precision nutrition strategies. Clinical evidence on the epigenetic effects of key dietary bioactives was summarized in Table 2.

In summary, dietary bioactives-including polyphenols, methyl donors, omega-3 fatty acids, carotenoids, and isothiocyanates-play integral roles in regulating the epigenome and influencing metabolic, cardiometabolic and immune health. Their mechanisms of action span DNA methylation, histone modifications, regulation of non-coding RNAs, and modulation of oxidative stress and inflammatory pathways (3,12,17,34,35).

**Table 1. Major polyphenols and their mechanistic targets in epigenetic regulation**

| Compound | Food sources | Main molecular/epigenetic targets | Representative effects | References |
|---|---|---|---|---|
| **Resveratrol** | Grapes, red wine, berries | Activates SIRT1; modulates histone acetylation | Enhances mitochondrial function, anti-inflammatory signaling | 27 |
| **Curcumin** | Turmeric, curry spices | Inhibits HATs/HDACs; suppresses NF-κB | Reduces histone acetylation; lowers pro-inflammatory cytokines | 28 |
| **EGCG** | Green tea | Modulates DNMTs and miRNAs | Influences lipid metabolism, reduces oxidative stress | 29 |
| **Quercetin** | Onions, apples, citrus fruits | Regulates miRNAs, inhibits NF-κB, affects histone code | Antioxidant, improves vascular function | 30 |
| **Anthocyanins** | Berries, red cabbage | Modulates ncRNAs and Nrf2 pathways | Enhances antioxidant defense, supports genomic stability | 31 |



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**Table 2. Evidence of dietary bioactives on epigenetic outcomes in humans**

| Bioactive group | Study design | Patient Details, Age | Type of treatment/ Sample Size (N) | Main findings on epigenetic outcomes | Year/ References |
|---|---|---|---|---|---|
| **Polyphenols** (mixture) | Pilot clinical study | Generally healthy (body mass index <40 kg/m$^{2}$), (20 males, 30 females), 18- 85 years | Polyphenol-rich supplement / 50 | Improved immune-related epigenetic age markers | 2024/26 |
| **Curcumin** | Clinical trial | Healthy human (9 males, 9 females), 18-69 years | Oral supplementation /18 | Reduced histone acetylation; suppression of NF-κB activity | 2024/ 34 |
| **Omega-3 fatty acids** | Review article | General human populations (Not limited to a specific age group) | omega-3 long-chain polyunsaturated fatty acid (LC-PUFA) supplementation or dietary intake | Genotype-dependent methylation changes; reduced inflammation/ | 2020/ 3 |
| **One-carbon nutrients** | Review article | General human populations (Not limited to a specific age group) | Folate, Vitamin B6, Vitamin B12, Methionine, Choline, Betaine, Serine dietary/ nutrient interventions | Altered DNA methylation at cardiometabolic genes; improved metabolic profiles | 2023/ 17 |
| **Sulforaphane** | Systematic review 8 RCTs | Prostate, breast, pancreatic cancers, melanoma | Broccoli sprout supplementation | changes in gene expression and biomarkers related to cancer | 2022/12 |
| **Carotenoids** | Systematic review and meta-analysis of 26 RCTs | Healthy participants/ participants with metabolic or inflammatory disorders Type of Treatment | Carotenoid supplementation (including astaxanthin, lutein/zeaxanthin, β-cryptoxanthin, lycopene, and others) | Enhanced antioxidant defense via Nrf2 signaling; supports genomic integrity | 2022/35 |

RCTs: Randomized controlled trials

Clinical and translational evidence increasingly supports their role in preventing obesity, insulin resistance, and T2DM, highlighting their potential in precision nutrition strategies. However, inter-individual variability mediated by genetic and microbial factors underscores the importance of integrating nutrigenomic profiling into dietary recommendations. The expanding evidence base positions dietary bioactives as a cornerstone of diabetes and obesity prevention, offering a path toward improved health through targeted dietary modulation of the epigenome (11,13-14).

## Challenges and Gaps

The presence of heterogeneous methodologies remains a major obstacle, especially in research on the interaction between diet and the epigenome in obesity and diabetes. Discrepancies in how diets are assessed variations in exposure biomarkers, and inconsistencies in the handlings of biospecimen bioinformatics analyses pipelines hinder the ability to compare findings across different studies (36). Epigenetic effects are also highly specific to different tissue- and cell-type; overall measurements can be confounded by changes in the composition of adipose tissue or circulating immune cells, which play crucial roles in obesity and T2DM (37). Emerging techniques, such as single-cell epigenomics and computational deconvolution, offer potential solutions to these challenges.

For nutrigenomics to meaningfully inform food safety and metabolic disease policies, validated biomarkers and clinically relevant endpoints like HbA1c , insulin sensitivity or lipid profiles are needed, along with cost-effectiveness analyses (38). Collaboration across sectors, including research, healthcare, and regulatory agencies, will be essential to establish standardized and ensure that findings translate into tangible health benefits, especially for populations at high risk of obesity and diabetes.

## Conclusion

Integration of nutrigenomics into food safety frameworks represents a promising and innovative approach to addressing obesity and (T2DM) by considering the complex interactions between genetics, diet, lifestyle, and environmental exposures. Recent advancements in multi-omics and clinical studies have deepend our understanding of how


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beneficial nutrients and harmful contaminants modulate epigenetic mechanisms and metabolic processes, thereby influencing disease susceptibility. Personalized interventions based on genetic, epigenetic, and microbiome profiles offer valuable and targeted strategies for prevention and management of metabolic disorders. However, further large-scale, diverse, and long-term studies are required to validate molecular biomarkers and clarify the role of bioactive compounds such as quercetin and resveratrol in metabolic health. Ultimately, incorporating nutrigenomics evidence into public health policies and dietary guidelines may strengthen food safety regulations and reduce the global burden of obesity, including and diabetes in Iran.

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## Conflict of Interest

The authors declare no conflict of interest.

## Authors' contributions

Authors were responsible for the conception, literature review, manuscript drafting, and final approval of the version to be published.

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