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Review

A Comprehensive Review of Environmental and Nutritional Influences on Epigenetic Change

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Running Title: Environmental and Nutritional Epigenetic Influences

Abstract

Epigenetic mechanisms act as a bridge between genetic potential and environmental influence. This review synthesizes current evidence on how nutritional factors and environmental exposures such as diet-derived bioactive, micronutrient status, heavy metals, air pollutants, and endocrine disruptors shape DNA methylation, histone modifications, and non-coding RNA activity across the lifespan. Special emphasis is placed on sensitive developmental windows where epigenetic plasticity is highest and long-term health trajectories are determined. We also outline links to metabolic disease, neurodevelopment, carcinogenesis, and intergenerational effects, while identifying major gaps and future directions in environmental and nutritional epigenomics. Collectively, this evidence positions the epigenome as a modifiable interface linking diet and environmental exposures to long-term health outcomes through epigenetic reprogramming, with important implications for preventive and personalized nutritional strategies.

Keywords:Epigenetic, Environmental exposures, Nutritional epigenomics, DNA methylation

Introduction

Epigenetics refers to heritable changes in gene expression that occur without alterations to the DNA sequence. These regulatory processes, primarily DNA methylation, histone modifications, and non-coding RNAs, govern chromatin architecture and thereby influence cellular phenotype [1]. Environmental and behavioral inputs, including diet, physical activity, psychosocial stress, and chemical exposures, are now recognized as major determinants of epigenetic state [2]. Emerging evidence demonstrates that nutritional factors such as methyl-donor nutrients, polyphenols, and microbiome-derived metabolites can modify epigenetic marks and, in some contexts, attenuate pollutant-induced molecular damage [3]. Conversely, exposure to endocrine-disrupting chemicals, heavy metals, and particulate matter induces maladaptive epigenetic reprogramming that contributes to metabolic, immune, neurologic, and cardiometabolic disease risk [4].

Parallel advances in functional medicine underscore similar principles: system-level interactions between nutrient status, oxidative stress, inflammation, microbiome dynamics, and toxicant burden converge on the epigenome to shape health trajectories [5]. Lifestyle factors central to this model including structured exercise, nutrient-dense dietary patterns, sleep regulation, and reduction of environmental exposures have been shown to induce reproducible epigenetic shifts across multiple tissues [6,7].

This review synthesizes contemporary molecular findings on how modifiable lifestyle and environmental factors regulate the human epigenome and outlines their implications for personalized nutrition and preventive health.

To understand how diet, environmental exposures, and lifestyle factors influence long-term health, it is first necessary to outline the core molecular mechanisms that govern epigenetic regulation. DNA methylation, histone modifications, non-coding RNAs, and epitranscriptomic processes form the regulatory framework through which environmental signals

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are translated into durable changes in gene expression.

2. Epigenetic Mechanisms

2.1 DNA Methylation

DNA methylation, typically at CpG dinucleotides, is mediated by DNA methyltransferases (DNMTs) and depends critically on the cellular pool of methyl donors from one-carbon ametabolism. Nutrients such as folate, vitamin B12, choline, and betaine feed into this cycle, helping generate S-adenosylmethionine (SAMe), the principal methyl-group donor. Insufficient intake of these methyl nutrients leads to reduced SAMe and elevated homocysteine, a functional medicine biomarker often used to assess methylation capacity or dysregulation. Elevated homocysteine has been associated with disrupted DNA methylation patterns that influence gene expression relevant to metabolism, neurodevelopment, and stress regulation (e.g., early-life mental health) [8,9]. Maternal intake of betaine and choline has been shown to correlate with altered DNA methylation in fetal tissues, underscoring how diet in early life can induce stable epigenetic reprogramming during sensitive developmental windows [10]. Deficiencies or imbalances in these one-carbon nutrients have also been linked to disease-associated methylation profiles in adults [11]. Through this biochemical axis, diet becomes a primary determinant of whether methylation patterns support protective gene expression or drive maladaptive trajectories.

2.2 Histone Modifications

Histone acetylation and methylation play central roles in regulating chromatin structure and transcriptional accessibility, and these processes depend on several key nutrient-derived cofactors. Zinc supports the structural integrity and catalytic activity of numerous histone-modifying enzymes, including HDACs, while magnesium is required for the function of ATP-dependent chromatin-remodeling complexes. Niacin (vitamin B3) serves as the precursor for NAD^+, the essential cofactor for sirtuin deacetylases that modulate histone deacetylation and influence cellular longevity and stress responses. In addition, polyphenols such as curcumin and green tea catechins have been shown to modulate histone acetyltransferases (HATs) and HDACs, shifting histone modification patterns toward transcriptionally active or repressed states depending on physiological context, including inflammatory and metabolic signaling. Although nutrient–histone interaction research continues to expand, emerging evidence from precision nutrition highlights the potential for targeted dietary and lifestyle interventions to modulate the epigenome through histone-based mechanisms [12].

2.3 Non-Coding RNAs

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression at the post-transcriptional level, and their profiles are highly responsive to environmental inputs such as diet and stress. A recent systematic review identified more than 100 circulating miRNAs that shift in response to dietary patterns, including energy restriction, variations in fat intake, and plant-based diets. Many of these diet-responsive miRNAs modulate key metabolic and inflammatory pathways, including lipid metabolism, insulin signaling, and immune regulation. Behavioral influences such as psychosocial stress further reshape miRNA expression, linking lifestyle factors to gene-regulatory networks that govern immune function and metabolic resilience. Collectively, these findings underscore the role of non-coding RNAs as rapid-response mediators that translate nutritional and environmental signals into post-transcriptional regulatory changes [13].

2.4 Epitranscriptomics

N6-methyladenosine (m^6A) is the most common internal modification of eukaryotic mRNA and plays a key role in RNA stability, splicing, export, and translation. Recent evidence shows that nutritional status and environmental factors influence the writers (“methylases” like METTL3/METTL14), erasers (e.g., FTO, ALKBH5), and readers (YTH-family proteins) of m^6A marks [13]. For example, high-fat diets, fasting, methyl-donor availability (e.g., betaine), and phytochemicals (like curcumin) can alter m^6A deposition on transcripts of metabolic genes, influencing pathways such as glucose homeostasis, obesity, and stress adaptation [14].

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Given the dynamic and reversible nature of m^6A modifications, this epitranscriptomic layer provides a novel route through which functional nutrition may shape gene expression beyond DNA and histones.

These epigenetic mechanisms do not operate in isolation but are tightly constrained by cellular metabolism and nutrient availability. Dietary inputs determine the supply of key substrates and cofactors required for DNA and histone modification, positioning nutrition as a central upstream regulator of epigenomic stability, plasticity, and disease susceptibility.

3. Nutrition and Dietary Epigenomics

3.1 Methyl-Donor Nutrients

Methyl-donor nutrients including folate, vitamins B12 and B6, choline, betaine, and methionine play a central role in one-carbon metabolism and determine the cell's methylation potential. Folate and B12 facilitate the remethylation of homocysteine to methionine, which is subsequently converted to S-adenosylmethionine (SAMe), the universal methyl donor required by DNA methyltransferases. Choline and betaine provide alternative methyl groups via the betaine–homocysteine methyltransferase pathway, particularly in hepatic and neural tissues. Vitamin B6 supports the transsulfuration arm of one-carbon metabolism, linking methylation processes to antioxidant defenses. In clinical and functional-medicine contexts, biomarkers such as homocysteine and, when available, SAMe/SAH ratios are assessed because deviations reflect methylation efficiency and have been associated with epigenetic dysregulation. Notably, in early-life nutritional programming, maternal intake of folate, choline, and methionine demonstrates how nutrient availability during sensitive developmental windows induces stable epigenetic reprogramming at critical loci, demonstrating how nutrient availability shapes long-term epigenetic patterns [8,9,15].

3.2 MTHFR Polymorphisms and Personalized Nutrition

Genetic variation in one-carbon metabolism, particularly polymorphisms in the MTHFR gene, can significantly influence individual methylation capacity. Common variants such as C677T reduce the enzymatic conversion of folate to its bioactive form, 5-methyltetrahydrofolate (5-MTHF), thereby decreasing methyl-donor availability and predisposing to elevated homocysteine. Within functional nutrition, MTHFR genotyping is often used to inform the selection of folate forms (e.g., methylated folate rather than folic acid) and to guide complementary support with vitamin B12, choline, and other cofactors. However, genotype-based decisions must be contextualized with phenotypic biomarkers including homocysteine, folate status, and B12 levels, to accurately assess methylation efficiency and metabolic impact.

3.3 Phytochemicals and Polyphenols

Dietary polyphenols are among the most powerful epigenetic modulators:

- Curcumin has been shown to inhibit DNMT expression and reduce HDAC activity in cellular models, thereby reactivating tumor suppressor genes [16].
- Resveratrol downregulates various DNMTs and modulates HDACs / SIRT1, contributing to anti-inflammatory and metabolic gene expression changes [17].
- Sulforaphane (SFN), a compound from cruciferous vegetables, inhibits HDACs and DNMTs, reshapes histone marks, and can restore expression of cytoprotective genes via Nrf2 pathways [18].
- Combinations of polyphenols (e.g., EGCG + sulforaphane) show synergistic effects in modulating DNMTs, HDACs, and gene expression tied to detoxification, apoptosis, and inflammation.

These plant-based compounds support detoxification, reduce inflammation, and bolster mitochondrial and stress-response pathways via epigenetic remodeling.

3.4 Dietary Patterns

Whole dietary patterns also influence epigenetic regulation more broadly:

- Ketogenic diets (or nutritional ketosis) raise ketone bodies, especially β-hydroxybutyrate (BHB), which acts as an endogenous HDAC inhibitor and modifies histone acetylation and β-hydroxybutyrylation, thereby influencing gene expression and metabolic health [19].

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● Caloric restriction (CR) and intermittent fasting (IF) increase NAD^+ levels and activate SIRT1, a class III histone deacetylase, thereby promoting chromatin remodeling associated with longevity, improved metabolic regulation, and stress resistance [19].

● These dietary strategies, alone or in combination, can induce epigenetic adaptations that favor resilience, metabolic flexibility, and reduced inflammation.

3.5 Metabolic Memory

Persistent epigenetic alterations underlie metabolic memory the concept that prior exposure to hyperglycemia or metabolic stress induces stable changes in gene expression:

● High glucose, oxidative stress, and inflammation drive aberrant DNA methylation and histone modifications at genes controlling inflammation, fibrosis, and metabolism.

● Such epigenetic marks can persist long after normoglycemia is restored, contributing to the risk of complications in diabetes and obesity.

● In functional nutrition, the strategy to counter metabolic memory includes optimizing methyl-donor intake, using phytochemicals to modulate epigenetic enzymes, and improving metabolic control to reverse or remodel maladaptive epigenetic signatures associated with metabolic memory.

Nutrition shapes the epigenome by supplying key nutrients and bioactive compounds, but environmental toxins can disrupt these processes and contribute to lasting epigenetic changes. Exploring these effects helps us better understand how external exposures influence gene regulation and chronic disease risk.

Table 1: *Environmental Factors and Their Adverse Epigenetic and Health Effects*

Environmental Factor	Adverse Epigenetic and Health Effects	Primary Epigenetic Mechanisms Involved
Heavy Metals (Lead, Mercury, Arsenic)	• Metabolic dysfunction • Neurotoxicity • Developmental effects	• Altered DNA methylation (both global and gene-specific) • Histone modification changes • Perturbed non-coding RNA expression
Endocrine-Disrupting Chemicals (BPA, Phthalates, PFAS)	• Metabolic, reproductive, and neurodevelopmental issues • Altered methylation at IGF2 and hormone/metabolic genes	• DNA methylation changes at imprinted and metabolic loci (particularly following prenatal exposure) • Histone modifications • Altered non-coding RNA profiles
Mold and Mycotoxins (Ochratoxin A, Aflatoxin B1)	• Inflammation • Mitochondrial dysfunction • Neurotoxicity • Gene silencing	• Site-specific DNA methylation changes • Histone post-translational modifications • Non-coding RNA dysregulation
Air Pollution (PM2.5)	• Cardiovascular diseases (MI, stroke, HF) • Atherothrombotic and inflammatory pathways	• Nuclear and mitochondrial DNA methylation changes • Altered microRNA expression
Detoxification Pathways (GST, CYP Genes, Nrf2)	• Altered antioxidant defense • Impaired detoxification • Increased oxidative stress	• Promoter DNA methylation • Histone modification–mediated transcriptional regulation • microRNA-mediated regulation

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4. Environmental Exposures and Toxin-Induced Epigenetic Dysregulation

4.1 Heavy metals (Lead, Mercury, Arsenic)

Heavy metals alter DNA methylation patterns (both global and gene-specific), modify histone marks, and perturb noncoding RNA expression. These changes occur via metal-induced oxidative stress, direct effects on DNA methyltransferases (DNMTs) and ten-eleven translocation (TET) enzymes, and by interfering with one-carbon metabolism (SAM availability). Epidemiological studies report reproducible DNA-methylation signatures associated with lead, arsenic, cadmium exposures in adults and in early-life exposure cohorts [20,21,22].

4.2 Endocrine-Disrupting Chemicals (BPA, phthalates, PFAS)

EDCs induce epigenetic dysregulation (DNA methylation, histone modifications, altered noncoding RNA expression) in exposed individuals, while epigenetic reprogramming occurs primarily during sensitive developmental windows, as demonstrated in animal models and prenatal human exposure studies; prenatal exposures can cause persistent, sometimes transgenerational, epimutations linked to metabolic, reproductive, and neurodevelopmental outcomes. For example, prenatal BPA exposure alters methylation at imprinted/metabolic loci (e.g., IGF2), while phthalates and PFAS show associations with methylation changes at genes regulating hormone/metabolism pathways [23,24].

4.3 Mold and Mycotoxins (ochratoxin A, aflatoxin B1)

Mycotoxins induce epigenetic toxicity through changes in DNA methylation, histone post-translational modifications, and noncoding RNAs. Aflatoxin B1 forms DNA adducts that can lead to site-specific methylation changes and gene silencing; ochratoxin A modulates histone acetylation/deacetylation and can alter DNMT/HAT/HDAC activity, linking exposure to inflammation, mitochondrial dysfunction and neurotoxicity via epigenetic routes. Review papers summarize multiple in-vitro, animal and limited human studies showing these pathways [25,26].

4.4 Air Pollution and Environmental Stressors (PM2.5)

Fine particulate matter (PM2.5) exposures are associated with changes in nuclear and mitochondrial DNA methylation, altered miRNA profiles, and sometimes histone modifications in blood and target tissues (lung, heart). These epigenetic alterations, consistent with exposure-associated epigenetic drift, influence inflammation, endothelial function, oxidative stress pathways, and atherothrombotic processes, providing mechanistic links between PM2.5 exposure and cardiovascular risk (MI, stroke, heart failure). Both short-term and long-term PM2.5 exposures have been tied to specific methylation changes at inflammation/cardiac genes in cohort and animal studies [27,28].

4.5 Detoxification Pathways

Genes encoding detox enzymes (GST family, CYP isoforms) and the master regulator Nrf2 are themselves regulated epigenetically (promoter methylation, histone marks, miRNAs). Promoter methylation or histone modifications can suppress Nrf2 and antioxidant responses; conversely, nutritional phytochemicals can modulate epigenetic regulators: sulforaphane (cruciferous vegetables) inhibits HDACs and lowers DNMT1 activity, thereby increasing Nrf2 expression; quercetin impacts histone acetylation and miRNA expression; N-acetylcysteine (NAC) alters redox balance and can indirectly affect methylation via one-carbon metabolism and glutathione dynamics. These nutrient–epigenetic interactions have been demonstrated in cell and animal models and summarized in reviews [29,30].

Dietary and environmental influences on the epigenome are further shaped by the gut microbiome, which functions as a metabolic interface between external exposures and host gene regulation. Microbiome-derived metabolites and immune signaling pathways provide additional layers of epigenetic control, extending the impact of diet and toxins beyond direct host exposure.

Beyond direct effects on host epigenetic machinery, environmental exposures can influence gene regulation through indirect biological pathways. Among these, the gut

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microbiome plays a central role in mediating epigenetic responses to external stressors.

5. Microbiome and Epigenetic Crosstalk

5.1 Short-chain fatty acids (butyrate) as natural HDAC inhibitors

Short-chain fatty acids (SCFAs), produced by bacterial fermentation of dietary fiber in the colon, act as key epigenetic mediators, most notably butyrate, which functions as a reversible inhibitor of class I/II histone deacetylases (HDACs), leading to increased histone acetylation, relaxed chromatin, and altered transcription of genes involved in barrier function, inflammation, and metabolism [31]. Mechanistically, butyrate's HDAC inhibition occurs at physiologically relevant concentrations in colonic epithelial cells and immune cells, and butyrate also signals via GPCRs (e.g., FFAR2/3, HCAR2) to modify intracellular pathways that intersect with epigenetic regulators [32]. These dual roles (direct chromatin modulation + receptor signaling) explain why butyrate supplementation or fiber-rich diets produce reproducible changes in host gene expression and have been proposed as a therapeutic route to reverse dysbiosis-associated epigenetic alterations [33].

5.2 Gut-brain and gut-liver epigenetic communication

Microbiome-derived metabolites (SCFAs, bile acid metabolites, tryptophan catabolites) and microbe-host immune signaling provide biochemical routes by which the gut microbiota influences the epigenome in distal organs, notably the brain and liver. Metabolites can cross or signal across the gut barrier (via circulation or the vagus nerve) and alter DNA methylation, histone marks, and noncoding RNA expression in neural and hepatic cells, contributing to context-dependent epigenetic modulation of neuroinflammatory and metabolic pathways, thereby modulating neuroinflammation, neurotransmitter systems, metabolic gene networks, and behavior [34]. Recent reviews and mechanistic studies show metabolite-driven epigenetic remodeling in the hippocampus and prefrontal cortex (linked to mood and cognition) and in hepatocytes (affecting lipid and glucose metabolism), supporting a causal gut → epigenome → phenotype axis [35].

5.3 Dysbiosis, inflammation, and epigenetic drift in chronic disease

Chronic dysbiosis and low-grade inflammation promote oxidative stress and altered one-carbon metabolism, which together accelerate epigenetic drift (progressive, stochastic changes in DNA methylation and chromatin state) that is implicated in metabolic disease, inflammatory bowel disease and cancer [36]. Multiple recent reviews synthesize evidence that dysbiosis → altered metabolite profiles (reduced butyrate, increased toxic metabolites) → accelerated epigenetic drift and persistent epigenetic dysregulation of host immune and metabolic genes, thereby linking microbiome perturbation to disease progression and age-related epigenomic change [37]. This model has translational implications: restoring keystone butyrate-producers or supplying SCFAs can partially reverse inflammatory epigenetic signatures in preclinical models, although human interventional data are still emerging.

Through metabolite production and host-microbe signaling, the gut microbiome modulates epigenetic processes across multiple tissues. These mechanisms offer a framework for understanding how microbiome-driven epigenetic dysregulation and epigenetic drift contribute to the development and progression of chronic disease.

6. Epigenetics and Chronic Disease

6.1 Metabolic disorders

Metabolic disease is tightly coupled to epigenetic dysregulation: nutrient excess, altered cellular metabolism, and chronic low-grade inflammation induces persistent epigenetic dysregulation, including alterations in chromatin states and DNA methylation patterns, in metabolic tissues (adipose, liver, pancreas), producing persistent changes in gene expression that promote insulin resistance, dyslipidemia and adipogenesis. In obesity and type 2 diabetes, EWAS and mechanistic studies implicate locus-specific methylation changes (and histone acetylation shifts) at metabolic regulators and inflammatory genes; these changes both reflect and exacerbate metabolic dysfunction. Polycystic

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ovary syndrome (PCOS) exemplifies the metabolic–epigenetic interface, with recent work showing epigenetic marks linking ovarian dysfunction to systemic metabolic pathways. Together, these data support a model in which metabolic milieu → altered availability of metabolic cofactors (acetyl-CoA, SAM, NAD+) → epigenomic remodeling that reinforces disease phenotypes [38].

6.2 Neurodegenerative conditions

Neurodegenerative diseases show convergent evidence for epigenetic involvement: age-related shifts in DNA methylation (epigenetic age acceleration), dysregulated histone modifications, and perturbed noncoding RNA networks contribute to neuronal vulnerability, proteinopathy progression and neuroinflammation. Recent comprehensive reviews and tissue-level EWAS in Alzheimer's and Parkinson's disease identify reproducible methylation/hydroxymethylation changes at synaptic, mitochondrial and immune-related loci, and experimental reversal of some histone/DNA marks modifies neurodegenerative phenotypes in preclinical models highlighting both biomarker and therapeutic potential of targeting the epigenome [39].

6.3 Autoimmune diseases

Autoimmune disorders display characteristic epigenetic signatures that modulate immune cell identity and tolerance; aberrant DNA methylation, histone modification patterns and miRNA dysregulation in T and B lymphocytes are linked to loss of self-tolerance and pathogenic autoantibody production. Systemic lupus erythematosus and autoimmune thyroiditis (Hashimoto's) have well-documented methylation changes at immune-regulatory genes (including interferon pathway genes and FOXP3/CTLA4-related networks), and recent reviews emphasize these epigenetic alterations as both biomarkers and actionable targets for epigenetic-directed therapies [40].

6.4 Cancer epigenetics in the context of detoxification and mitochondrial health

Cancer is fundamentally an epigenetic as well as genetic disease: promoter hypermethylation, global hypomethylation, and altered histone marks rewire oncogene/tumor suppressor expression. In addition, impaired detoxification pathways and mitochondrial dysfunction interact with the epigenome mitochondrial metabolites (Acetyl-CoA, α-KG, NAD+, succinate) and defects in mitochondrial DNA alter chromatin-modifying enzyme activity, while environmental toxins (heavy metals, persistent organic pollutants) induce oxidative damage and epigenetic perturbations that promote carcinogenesis. Recent syntheses show that integrating mitochondrial metabolism, xenobiotic exposure and chromatin state yields a richer mechanistic model for tumor initiation and progression and suggests combined metabolic-epigenetic therapeutic strategies [41].

6.5 How diet, toxin reduction, and circadian alignment can modulate disease-associated epigenetic states

Interventions that restore metabolic balance, reduce toxicant burden, and re-align circadian biology can produce measurable epigenetic shifts that translate into improved phenotypes. Dietary modulation (fiber to increase SCFA production, methyl-donor balance, caloric timing) alters the availability of epigenetic cofactors and microbiome-derived metabolites, reversing maladaptive histone and DNA marks in metabolic and immune tissues. Detoxification and toxin-exposure reduction lower oxidative stress and DNA/adduct load, limiting driver epigenetic changes. Circadian alignment (sleep regularity, timed feeding, light hygiene) normalizes clock-controlled chromatin rhythms and downstream gene regulation. Recent integrative reviews argue that systems-level interventions combining diet, toxin mitigation, and circadian therapy produce synergistic epigenetic remodeling and partial normalization of disease-associated epigenetic states and should be investigated in longitudinal human trials as disease-modifying strategies [42].

Taken together, evidence across metabolic, neurodegenerative, autoimmune, and oncologic conditions converges on a shared principle: chronic disease is accompanied by reproducible, and in many cases modifiable, epigenetic alterations shaped by metabolic state, environmental exposures, and circadian biology. These insights shift epigenetics from a

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descriptive framework toward a translational one, raising the question of how epigenetic mechanisms can be leveraged to inform therapeutic strategies, risk reduction, and personalized clinical interventions.

7. Therapeutic and Clinical Applications

7.1 Nutritional epigenetic modulators

Dietary methyl donors (folate, vitamin B12, choline, betaine) directly feed one-carbon metabolism and influence S-adenosylmethionine (SAM) availability for DNA and histone methylation; clinical and translational studies show that varying intake of these nutrients alters locus-specific methylation and can modify epigenetic-age biomarkers in humans. Antioxidants and polyphenols (e.g., quercetin, resveratrol) act via multiple routes reducing oxidative damage that perturbs methylation homeostasis and directly modulating chromatin regulators (DNMTs, HATs/HDACs) with controlled trials and mechanistic studies reporting changes in methylation and gene expression after dietary interventions. Evidence for traditional "adaptogens" (e.g., Rhodiola, ashwagandha) influencing the human epigenome is emerging but mostly preclinical; mechanistic plausibility exists through effects on stress signaling and redox balance, which intersect with epigenetic enzymes. Overall, nutritional interventions are among the most actionable routes to epigenetic reprogramming, but effect sizes and durability vary and depend on dose/timing and baseline nutritional status [43].

7.2 Lifestyle medicine

Lifestyle interventions reproducibly influence epigenetic markers. Improving sleep quality and restoring circadian alignment are associated with slower epigenetic-age acceleration and changes in methylation patterns at clock- and metabolic-related loci in cohort studies. Intermittent fasting and time-restricted eating affect metabolic cofactor levels (NAD^+, Acetyl-CoA) and gut microbiome metabolites, which in turn alter histone acetylation and DNA methylation in metabolic tissues animal models and short human trials show changes in gene expression and epigenetic clocks after fasting regimens. Stress-reduction modalities (mind–body interventions) lower HPA activation and inflammatory signalling, and multiple small trials report normalization of methylation at stress-responsive loci and improvements in telomerase activity. Taken together, these lifestyle measures offer mechanistically coherent, low-risk ways to nudge the epigenome toward healthier set-points, though larger RCTs with long follow-up are still needed [44].

7.3 Environmental detoxification

Reducing environmental toxicant load is mechanistically important because many xenobiotics (heavy metals, persistent organic pollutants, mycotoxins) induce oxidative stress, form DNA adducts, and perturb one-carbon metabolism processes that drive adverse epigenetic remodeling implicated in chronic disease and cancer. Practical public-health measures (mold remediation, filtration of indoor air and drinking water, removal of contaminated materials) provide clear exposure reduction and are supported by environmental health literature as primary prevention. Clinical modalities that claim to "detoxify" (sweating/sauna, chelation, binding agents) can increase excretion of certain compounds, but the evidence for durable epigenetic or disease-modifying benefits in humans is limited and heterogeneous; thus these approaches should be considered adjunctive to exposure remediation and used cautiously with clinical oversight [45].

7.4 Precision functional medicine

A precision approach layers' germline genetic variation (e.g., MTHFR and other one-carbon SNPs), metabolomic profiling (methylation cycle intermediates, NAD^+, glutathione), and epigenetic biomarkers (DNA methylation clocks, locus-specific methylation) to create individualized intervention plans. Multi-omics integration is increasingly feasible and clinically informative: genomics + metabolomics + methylome data can predict physiological age, exposure signatures, and disease risk better than single modalities and may guide targeted nutritional, pharmacologic and lifestyle therapies. However, clinical translation requires validated biomarkers, standardized assays, and demonstration that biomarker-guided interventions improve meaningful outcomes; the field is advancing rapidly but still maturing [46].

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In summary, the evidence that has been reviewed on the different aspects, such as molecular mechanisms, nutritional and environmental factors, interactions with microbiome, and disease outcomes, points towards one common concept, which is, epigenetic regulation is a key determinant of human health across the lifespan and is strongly influenced by modifiable environmental and lifestyle factors.

Conclusion

Epigenetics confirms the core of functional medicine: genes set the baseline, but environment and lifestyle determine expression. Genes load the gun; the environment pulls the trigger. By showing that diet, toxins, stress, sleep, and circadian cues can actively reprogram gene regulation, epigenetics underscores the need to merge molecular insights with lifestyle-based prevention and reversal strategies.

AI Use Declaration

The authors confirm that this review article was written entirely by the authors without the use of artificial intelligence tools for content generation.

Artificial intelligence tools (e.g., ChatGPT) were used only for minor language refinement, such as grammar and spelling corrections.

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