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REVIEW

Targeting epigenetic checkpoints in autoimmune diseases: Nutritional and style interventions

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Abstract

Autoimmune diseases are complex disorders arising from interactions among genetic susceptibility, epigenetic regulation, and environmental exposures. Accumulating evidence indicates that DNA methylation, histone modifications, and non-coding RNAs (ncRNAs) may mediate some of the effects of environmental factors on immune function and inflammatory responses. This narrative review examines how nutritional and lifestyle-related factors may influence epigenetic pathways relevant to autoimmune diseases. Evidence from *in vitro* studies, preclinical models, observational research, and emerging clinical investigations is synthesized, with particular emphasis on methyl-donor nutrients, selected bioactive compounds such as curcumin, vitamin D, physical activity, sleep and circadian regulation, and chronic psychological stress. Current findings suggest that these factors may modulate immune-related epigenetic processes; however, their clinical relevance remains constrained by differences in bioavailability, tissue specificity, individual biological variability, study design, and long-term adherence. Further longitudinal and intervention studies are therefore required to establish causality and clinical effectiveness. Overall, integrating nutritional and lifestyle factors with epigenetic and clinical profiling may support the future development of personalized adjunctive strategies for autoimmune disease management.

Keywords: Autoimmune diseases, DNA methylation, lifestyle factors, non-coding RNAs, phytochemicals, precision nutrition.

Introduction

Autoimmune diseases comprise a heterogeneous group of more than 140 disorders in which immune tolerance to self-antigens is disrupted, resulting in immune-mediated injury to cells, tissues, or organs (Leone et al., 2026; Office of Autoimmune Disease Research [OADR-ORWH], 2025). Their development is influenced by complex interactions among genetic susceptibility, environmental exposures, and epigenetic regulation (Cho & Gregersen, 2011; Farh et al., 2014). Disruption of immune self-tolerance can promote the abnormal activation of T and B lymphocytes, autoantibody production, chronic inflammation, and progressive tissue dysfunction, although the relative contribution of these processes varies among diseases (Pisetsky, 2023).

A large population-based study of approximately 22 million individuals in the United Kingdom reported that 10.2% of the study population had at least one of the 19 autoimmune disorders investigated, highlighting the substantial population burden of these conditions (Conrad et al., 2023). Genetic studies have identified numerous variants associated with autoimmune diseases; however, these variants explain only part of the observed disease susceptibility (Jonkers & Wijmenga, 2017; Sadee et al., 2014). This discrepancy forms part of the broader “missing heritability” problem described in complex diseases (Augustine et al., 2022; Manolio et al., 2009). These findings suggest that genetic variation alone is insufficient to explain the onset and progression of autoimmune disorders and that environmental and regulatory mechanisms must also be considered. Among these mechanisms, epigenetic regulation can alter gene expression without changing the underlying DNA sequence and may provide a molecular interface between genetic susceptibility and environmental exposure (Meral et al., 2026; Surace & Hedrich, 2019).

The principal epigenetic mechanisms relevant to immune regulation include DNA methylation, post-translational histone modifications, chromatin remodeling, and regulatory non-coding RNAs. DNA methylation is catalyzed by DNA methyltransferases (DNMTs), which transfer methyl groups predominantly to the C5 position of cytosine within CpG dinucleotides. Depending on its genomic location and cellular context, DNA methylation can influence chromatin organization and transcriptional activity; promoter-associated methylation is frequently, but not invariably, associated with transcriptional repression (Saleh et al., 2020). Histone post-translational modifications, including acetylation, methylation, and phosphorylation, can alter chromatin structure and regulate the accessibility of DNA to transcriptional machinery (Bannister & Kouzarides, 2011). Unlike a strict distinction between permanent and transient regulation, both DNA methylation and histone modifications can display context-dependent stability and reversibility.

Non-coding RNAs (ncRNAs) constitute another diverse layer of gene regulation. These transcripts are not translated into proteins but can regulate gene expression through interactions with messenger RNAs, chromatin-associated proteins, and transcriptional machinery (Panni et al., 2020). MicroRNAs (miRNAs), for example, generally regulate gene expression post-transcriptionally by promoting mRNA degradation or inhibiting translation, whereas long non-coding RNAs (lncRNAs) can act at transcriptional, post-transcriptional, and chromatin-associated levels (Esteller, 2011; Hombach & Kretz, 2016). Although not all ncRNAs function through strictly epigenetic mechanisms, selected ncRNAs can interact with chromatin-modifying complexes and thereby contribute to the regulation of immune-cell differentiation, inflammatory signaling, and immune tolerance.

Epigenetic patterns are dynamic and can change across the life course despite preservation of the underlying DNA sequence. The gradual accumulation of age-associated alterations in DNA methylation and other epigenetic marks is commonly referred to as “epigenetic drift” (Issa, 2014; Surace & Hedrich,

2019). Environmental exposures may influence DNA methylation, histone modifications, and transcription-factor accessibility, potentially contributing to interindividual differences in disease susceptibility (Kim & Kim, 2026). In autoimmune diseases, environmental exposures such as toxicants, nutritional imbalance, and adverse lifestyle factors have been proposed to interact with genetic susceptibility through epigenetic mechanisms; however, the direction, persistence, and clinical significance of these changes remain disease- and tissue-dependent (Costenbader et al., 2011).

Nutrition represents one potential source of environmental influence on the epigenome. Dietary constituents can provide substrates or cofactors for epigenetic reactions and may also modulate the activity of epigenetic enzymes (Alegría-Torres et al., 2011). Folate, choline, and methionine contribute to one-carbon metabolism, which generates S-adenosylmethionine (SAM), the principal methyl donor used by DNMTs and other methyltransferases (Ducker & Rabinowitz, 2016). Variations in the availability and metabolism of these nutrients may therefore affect DNA methylation and gene regulation. Although methyl-donor nutrients have been studied extensively in metabolic and cancer-related settings, their effects on immune homeostasis and autoimmune disease are likely to depend on nutritional status, dose, tissue type, and disease context (Mahmoud & Ali, 2019; Meda et al., 2011; Mentch & Locasale, 2016).

Bioactive dietary compounds may also influence epigenetic regulation through mechanisms that extend beyond their role as metabolic substrates. Polyphenols have been reported to modulate the activity or expression of DNMTs, histone acetyltransferases (HATs), histone deacetylases (HDACs), and regulatory ncRNAs in experimental systems (Bagni et al., 2025). Curcumin, a polyphenolic compound derived from *Curcuma longa*, has been associated with modulation of DNMT and HAT activity, potentially affecting chromatin accessibility and the expression of inflammation-related genes (Boyanapalli & Kong, 2015; Jiao et al., 2025). Other dietary compounds, including the polyphenol epigallocatechin gallate (EGCG) and the isothiocyanate sulforaphane, have also been investigated as modulators of HDAC-related and other epigenetic pathways (Jalouli et al., 2025; Kciuk et al., 2023; Tortorella et al., 2014). Nevertheless, much of this evidence originates from *in vitro*, cancer, or non-autoimmune experimental models, and its direct relevance to human autoimmune diseases requires further investigation.

Vitamin D represents another link between nutrition, transcriptional regulation, and immune function. The vitamin D receptor (VDR) is a ligand-activated transcription factor that interacts with chromatin-remodeling and histone-modifying proteins at specific genomic loci (Fetahu et al., 2014). Through these interactions, vitamin D signaling can influence the transcription of genes involved in innate and adaptive immunity. For example, vitamin D has been associated with enhanced interleukin-10 production by regulatory T cells in patients with systemic sclerosis, although this finding does not by itself establish direct epigenetic regulation of the IL10 locus (Di Liberto et al., 2019). Vitamin D deficiency has also been associated with several autoimmune diseases; however, the extent to which epigenetic mechanisms mediate these associations and whether supplementation can reverse disease-associated epigenetic alterations remain uncertain (Sîrbe et al., 2022).

In addition to nutrition, lifestyle-related factors may influence epigenetic regulation. Physical activity has been associated with changes in DNA methylation and the activity of chromatin-regulating enzymes, including DNMTs and HDACs (Ostaiza-Cardenas et al., 2025; Yang et al., 2025). In lymphocytes obtained from older women, physical exercise was associated with increased global DNA methylation and gene-specific methylation at the IL17 and IFNG loci (Machado et al., 2021). Exercise-related epigenetic adaptations have also been investigated in cardiovascular and metabolic contexts, where they may contribute to altered inflammatory signaling (Yang et al., 2024). However, these observations should not be interpreted as direct evidence that exercise-induced methylation of IFNG reduces disease activity in autoimmune patients, as disease-specific intervention studies remain limited.

Sleep and circadian rhythms are reciprocally associated with epigenetic regulation and immune function (Osum & Kalkan, 2025). Core circadian regulators, including the CLOCK–BMAL1 complex, coordinate rhythmic gene expression through interactions with chromatin-modifying enzymes and temporal patterns of histone acetylation (Takahashi, 2017). Experimental sleep loss has been shown to induce tissue-specific alterations in DNA methylation and metabolic gene expression, demonstrating that circadian disruption can affect the human epigenome (Cedernaes et al., 2018). Circadian and epigenetic mechanisms also interact with immune signaling pathways, although their effects vary across immune-cell populations, tissues, and experimental conditions (Orozco-Solis & Aguilar-Arnal, 2020).

Chronic psychological stress may further affect immune regulation through neuroendocrine and epigenetic pathways. Sustained activation of the hypothalamic–pituitary–adrenal axis alters glucocorticoid signaling and has been associated with changes in DNA methylation across stress-responsive genes (Arvind et al., 2025; Ekmekci & MuftareviÇ, 2023; Miller et al., 2025). Particular attention has been given to NR3C1, which encodes the glucocorticoid receptor. Altered NR3C1 methylation has been associated with adverse stress exposure and variation in glucocorticoid responsiveness, particularly in psychiatric and stress-related research settings (Xu et al., 2025; Zannas, 2019). Although impaired glucocorticoid signaling could theoretically contribute to persistent inflammatory activity, direct causal evidence connecting stress-induced NR3C1 methylation to autoimmune disease progression remains limited. The proposed relationships among nutritional factors, lifestyle-related exposures, epigenetic regulation, and immune homeostasis are summarized in Figure 1.

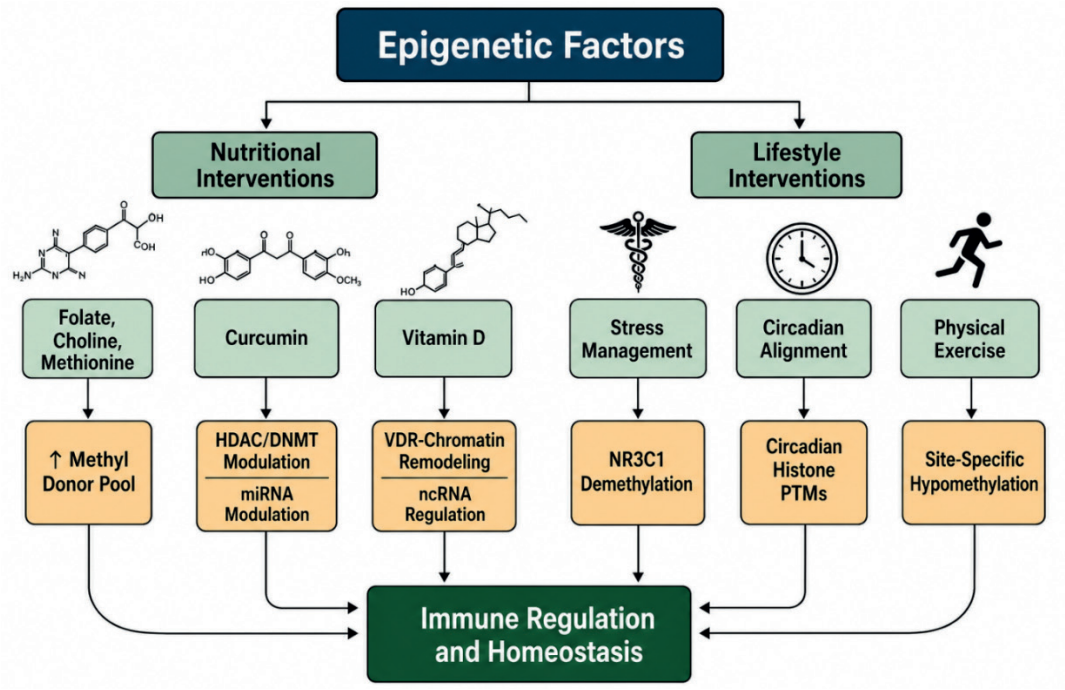

Figure 1. Proposed conceptual model of nutritional and lifestyle factors that may influence epigenetic regulation in autoimmune diseases through DNA methylation, histone modifications, and non-coding RNA (ncRNA)-mediated pathways. Based on preclinical and translational evidence, these interconnected mechanisms may support immune regulation and homeostasis.

Given the important role of epigenetic dysregulation in the pathogenesis of autoimmune diseases, identifying non-pharmacological approaches that may influence epigenetic regulation represents an area of considerable scientific and clinical interest. This review examines current evidence regarding the associations of nutritional and lifestyle factors—including dietary components, physical activity, sleep, circadian rhythms, and psychological stress—with epigenetic mechanisms involved in immune function. Particular emphasis is placed on the roles of DNA methylation, histone modifications, and non-coding RNAs in shaping immune responses. Unlike previous reviews that have considered nutritional factors, lifestyle-related factors, or epigenetic mechanisms separately, the present review adopts an integrative perspective to explore how these factors may converge on shared epigenetic pathways relevant to autoimmune disease pathogenesis. By synthesizing evidence across these domains, this review aims to provide a framework for understanding how modifiable environmental factors may inform the future development of personalized preventive and supportive approaches to autoimmune diseases.

Methodology

This article was conducted as a narrative review supported by a structured literature search to examine the potential influence of nutritional and lifestyle-related factors on epigenetic regulation in autoimmune diseases. Structured search terms and queries were used across multiple databases to identify relevant literature; however, the manuscript presents a narrative synthesis rather than a formal systematic review or meta-analysis. The review aimed to synthesize current evidence concerning DNA methylation, histone modifications, non-coding RNAs, and related epigenetic mechanisms potentially influenced by nutritional substrates, phytochemicals, physical activity, sleep, circadian regulation, and psychosocial stress.

Data Sources and Search Strategy

A literature search was conducted using PubMed/MEDLINE, Web of Science, Scopus, and Google Scholar, supplemented by targeted searches of Nature Portfolio journals. Searches were performed between January 2025 and May 2026. Medical Subject Headings (MeSH) and relevant free-text keywords were combined using Boolean operators. The search terms included “epigenetics”, “DNA methylation”, “histone modification”, “non-coding RNA”, “microRNA”, “long non-coding RNA”, “autoimmune disease”, “autoimmune pathogenesis”, “nutrition”, “nutritional epigenetics”, “methyl donors”, “vitamin D”, “polyphenols”, “curcumin”, “exercise”, “sleep”, “circadian rhythm”, “stress”, and “lifestyle interventions”.

Study Selection Criteria

Studies were considered for inclusion if they investigated epigenetic mechanisms relevant to autoimmune diseases; examined nutritional, phytochemical, or lifestyle-related factors associated with epigenetic regulation; or provided relevant evidence from human studies, clinical trials, observational studies, experimental investigations, systematic reviews, or meta-analyses. Priority was given to recent peer-reviewed publications, although seminal older studies were included when they provided important mechanistic or historical context.

Publications with limited relevance to autoimmune diseases, epigenetic regulation, or the defined scope of the review were generally excluded. Conference abstracts, editorials, and articles lacking sufficient methodological or mechanistic detail were used only when necessary to provide contextual information.

Data Evaluation and Synthesis

The literature was evaluated according to its relevance to the review objectives, methodological quality, study design, and contribution to understanding the relationships among environmental exposures, epigenetic regulation, and autoimmune disease. Clinical studies, systematic reviews, meta-analyses, and relevant mechanistic investigations were prioritized. Evidence obtained from non-autoimmune experimental models was considered when it provided mechanistic context, but it was interpreted cautiously regarding its applicability to autoimmune diseases. The selected literature was synthesized narratively, with emphasis on shared epigenetic pathways linking nutrition, lifestyle-related factors, immune regulation, and autoimmune disease pathogenesis.

Literature Overview and Mechanisms

Methyl Donors (Folate, Choline, and Methionine)

The dietary availability of methyl-group donors is important for one-carbon metabolism and related DNA methylation processes. Folate, choline, and methionine contribute to the one-carbon metabolic network, which generates S-adenosylmethionine (SAM), the principal methyl donor used by DNA methyltransferases (DNMTs) and other methyltransferases (Bernasocchi & Mostoslavsky, 2024). SAM availability may therefore influence DNA methylation processes involved in the regulation of inflammatory and immune-related genes (Choi & Friso, 2023). Folate-dependent reactions support the remethylation of homocysteine to methionine, thereby contributing to the maintenance of intracellular SAM concentrations.

Alterations in one-carbon metabolism and methyl-donor availability have been associated with changes in DNA methylation; however, the direction and magnitude of these changes depend on nutritional status, cell type, genetic background, and disease context (Ducker & Rabinowitz, 2016). In systemic lupus erythematosus (SLE), DNA hypomethylation in immune cells, particularly T lymphocytes, has been associated with increased expression of immune-related genes and enhanced autoreactive T-cell activity (Weeding & Sawalha, 2018). Nevertheless, these findings do not establish that dietary methyl-donor deficiency is the sole or direct cause of global DNA hypomethylation in patients with SLE.

Choline can also contribute methyl groups through its oxidation to betaine, which supports an alternative pathway for the remethylation of homocysteine to methionine. This pathway may help maintain one-carbon metabolism when folate-dependent methyl-group availability is limited (Sareen et al., 2026). Collectively, these observations suggest that adequate intake of folate, choline, and methionine supports one-carbon metabolism and normal methylation processes. However, whether supplementation with these nutrients can reverse disease-associated epigenetic alterations or improve clinical outcomes in autoimmune diseases remains uncertain and requires controlled clinical investigation.

Polyphenols as Dietary Epigenetic Modulators: Curcumin, EGCG, and Sulforaphane

Unlike methyl-donor nutrients, which provide substrates for one-carbon metabolism, certain bioactive dietary compounds may influence the activity or expression of epigenetic enzymes. Polyphenols and other naturally occurring compounds have been reported to modulate DNA methyltransferases, histone-modifying enzymes, non-coding RNAs, and related signaling pathways. Curcumin, a non-flavonoid polyphenol derived from turmeric (Curcuma longa), has been widely investigated for its an-

ti-inflammatory and epigenetic activities (Kumar et al., 2025). Experimental evidence indicates that curcumin can influence both DNA methylation and histone-modifying pathways, although its effects vary according to the biological model, dose, and cellular context (Armas Díaz et al., 2023).

Curcumin has been reported to modulate DNMT activity and DNA methylation patterns in several experimental systems. These findings have generated interest in its possible relevance to autoimmune and inflammatory conditions, including type 1 diabetes (T1D). In non-obese diabetic mice, curcumin treatment delayed the development of T1D and reduced pro-inflammatory cytokine production; however, the extent to which these effects were mediated directly by changes in DNA methylation was not established (Ramos-Martínez et al., 2026). Curcumin has also been investigated as a modulator of histone acetyltransferase activity. Through its effects on histone acetylation and inflammation-related signaling pathways, curcumin may influence the expression of mediators such as TNF-α and IL-6 in experimental models (Ciechomska & O'Reilly, 2016). Nevertheless, direct evidence demonstrating that curcumin reverses disease-specific epigenetic alterations in patients with rheumatoid arthritis remains limited.

Other dietary compounds, including epigallocatechin gallate (EGCG) and sulforaphane, have also been investigated as modulators of HDAC-related and other epigenetic pathways (Kciuk et al., 2023; Zhao et al., 2025). EGCG is a polyphenol, whereas sulforaphane is an isothiocyanate; therefore, these compounds should not be classified within the same phytochemical group. Experimental studies indicate that they may influence chromatin accessibility and inflammatory signaling through partly distinct mechanisms. Sulforaphane has been reported to inhibit HDAC activity, which may help maintain a more transcriptionally accessible chromatin state at selected genomic regions (Tortorella et al., 2014). It has also been shown to modulate inflammatory responses in primary human T cells, although these effects involve oxidative and redox-dependent mechanisms in addition to epigenetic regulation (Liang et al., 2018). Regulatory T-cell activity is relevant to the control of autoreactive immune responses in diseases such as multiple sclerosis (Guo et al., 2026). However, direct evidence that EGCG or sulforaphane improves regulatory T-cell function through a defined epigenetic mechanism in patients with multiple sclerosis remains insufficient. Overall, these compounds may influence pathways associated with immune regulation, but their clinical relevance in autoimmune diseases requires further investigation.

Vitamin D as an Epigenetic Modulator of Immune Regulation

Vitamin D is increasingly recognized as a regulator of immune and epigenetic processes. Its biological effects are mediated primarily through the vitamin D receptor (VDR), a ligand-activated transcription factor that binds to regulatory regions of target genes and interacts with transcriptional coregulators and chromatin-modifying proteins (Carlberg & Velleuer, 2024). These interactions allow vitamin D signaling to influence chromatin accessibility and the transcription of genes involved in innate and adaptive immune responses.

Vitamin D has also been investigated in relation to tolerogenic immune-cell phenotypes. Regulatory dendritic cells conditioned with vitamin D3 and interleukin-10 display distinct epigenetic and transcriptional characteristics, suggesting that vitamin D may contribute to the establishment of regulatory immune programs (Liu et al., 2024). In addition, vitamin D signaling can suppress pro-inflammatory programs in T helper 1 cells and promote immune-regulatory responses (Chauss et al., 2021). These findings support a functional relationship among vitamin D signaling, chromatin regulation, and immune-cell behavior, although the specific epigenetic mechanisms are likely to vary among cell types and disease settings.

Vitamin D deficiency has been associated with several immune-mediated disorders, but association alone does not establish a causal epigenetic mechanism. In inflammatory bowel disease (IBD), disrupted vitamin D–VDR signaling has been discussed in relation to epigenetic regulation, intestinal inflammation, and altered mucosal immune responses (Marangoni et al., 2023). However, it remains uncertain whether vitamin D supplementation can directly reverse disease-associated, tissue-specific epigenetic alterations in humans. Well-designed longitudinal studies and controlled clinical trials are required to determine the clinical significance and reversibility of these changes.

Non-Coding RNAs as Emerging Epigenetic Mediators

Non-coding RNAs (ncRNAs), particularly microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are increasingly recognized as important regulators of immune homeostasis. These molecules can regulate gene expression through interactions with messenger RNAs, chromatin-associated proteins, transcription factors, and other components of the transcriptional machinery. Through these mechanisms, ncRNAs may influence immune-cell differentiation, cytokine production, and inflammatory signaling pathways. However, not all ncRNAs act through strictly epigenetic mechanisms; many miRNAs primarily regulate gene expression at the post-transcriptional level.

Dysregulated ncRNA expression has been associated with numerous immune-mediated and autoimmune diseases, suggesting that ncRNA networks may link environmental exposures, cellular stress, and immune dysfunction (Bechara et al., 2023; Nemeth et al., 2024). Several miRNAs have been implicated in the regulation of immune-cell activation and inflammatory signaling. Among them, miR-21 and miR-146a have been widely investigated in rheumatoid arthritis and other autoimmune disorders, although their expression patterns and functional effects may differ according to disease stage, tissue type, and treatment status (Wei et al., 2024).

Long non-coding RNAs, including NEAT1 and MALAT1, have also been investigated as regulators of transcriptional and inflammatory pathways. Their functions may involve interactions with chromatin-associated complexes, transcriptional regulators, and RNA-processing machinery (Ferrer & Dimitrova, 2024). Although the precise mechanisms remain incompletely understood, accumulating evidence indicates that dysregulation of ncRNA networks may contribute to abnormal immune activation and chronic inflammation in autoimmune diseases (Kumar et al., 2023). Further disease-specific and cell-type-resolved studies are required before individual ncRNAs can be considered reliable biomarkers or therapeutic targets.

Exercise-Induced Epigenetic Modulation

The human epigenome is influenced not only by dietary factors but also by lifestyle-related behaviors (von Hattburg, 2025). Physical activity has been identified as a potential epigenetic stimulus because skeletal muscle contraction and increased metabolic demand can influence signaling pathways associated with DNMTs, HDACs, and chromatin remodeling (Ferioli et al., 2019). Nevertheless, exercise-induced epigenetic responses depend on exercise type, intensity, duration, participant characteristics, tissue type, and the timing of sample collection.

In lymphocytes obtained from older women, physical exercise was associated with increased global DNA methylation and gene-specific methylation at the IL17 and IFNG loci (Machado et al., 2021). Because this study was not conducted specifically in patients with autoimmune diseases, its findings should not be interpreted as direct evidence of disease modification. IFN-γ is an important mediator of Th1-associated inflammatory responses and has been implicated in the pathogenesis of several

autoimmune diseases. In multiple sclerosis, dysregulated Th1 responses and IFN-γ signaling may contribute to blood–brain barrier dysfunction and immune-mediated damage to myelin (Manna et al., 2024). Exercise-associated epigenetic changes could therefore be relevant to the regulation of inflammatory pathways, but this relationship remains to be demonstrated directly in disease-specific intervention studies.

Systematic reviews indicate that appropriately prescribed exercise may improve physical function, disease symptoms, and selected inflammatory markers in several autoimmune diseases (Luo et al., 2024). However, clinical evidence specifically linking these benefits to persistent epigenetic modifications remains preliminary. Future studies should integrate standardized exercise protocols with longitudinal epigenetic measurements in relevant immune-cell populations and disease-affected tissues.

Circadian Rhythms and Sleep: Epigenetic Regulation of the Immune Clock

Circadian rhythms and immune regulation are linked through metabolic, transcriptional, and epigenetic mechanisms. Sirtuin 1 (SIRT1) is a metabolic sensor and NAD+-dependent deacetylase whose rhythmic activity contributes to the molecular regulation of the circadian clock (Masri & Sassone-Corsi, 2014). Under homeostatic conditions, SIRT1 interacts with components of the CLOCK–BMAL1 complex and contributes to the temporal regulation of circadian gene expression (Fagiani et al., 2022).

SIRT1 may also influence inflammatory signaling by deacetylating the p65 subunit of NF-κB, thereby reducing the transcriptional activity of selected pro-inflammatory genes (Ghisays et al., 2015). However, this mechanism should not be interpreted as evidence that all pro-inflammatory transcripts are uniformly suppressed during the nocturnal phase. Sleep loss and circadian disruption have instead been associated with activation of inflammatory pathways and altered immune regulation (Irwin et al., 2008).

Promoter methylation of circadian clock genes, including PER1 and CRY1, has been associated with altered gene expression and clinical characteristics in human observational studies (Xu et al., 2023). However, the cited evidence was obtained from a non-autoimmune clinical population and therefore provides mechanistic context rather than direct evidence for autoimmune disease. In autoimmune disorders, circadian disruption and impaired sleep have been associated with fatigue, disease activity, and reduced quality of life (Awuah et al., 2023). These observations highlight the potential relevance of circadian regulation to autoimmune disease management, but further studies are required to establish whether epigenetic alterations in clock genes mediate these clinical associations.

Stress-Mediated Epigenetic Remodeling and Immune Dysregulation

Chronic or recurrent psychological stress can activate a complex neuroendocrine response involving the hypothalamic–pituitary–adrenal (HPA) axis (Balakin et al., 2025). Activation of the HPA axis increases systemic cortisol concentrations. Under physiological conditions, cortisol helps regulate and resolve inflammatory responses through glucocorticoid receptor signaling (Hardy et al., 2012). In contrast, prolonged or dysregulated glucocorticoid exposure has been associated with changes in stress-responsive epigenetic pathways that may affect immune and inflammatory regulation (Zannas, 2021).

A frequently investigated gene in this context is NR3C1, which encodes the glucocorticoid receptor. Experimental evidence indicates that stress-related conditions can be associated with altered DNA methylation of NR3C1 and corresponding changes in gene expression. For example, developmental conditions were associated with NR3C1 methylation, transcript expression, and glucocorticoid-relat-

ed physiological responses in a zebra finch model (Jimeno et al., 2019). Because this evidence was obtained from an avian model, it should not be presented as direct evidence of NR3C1 promoter hypermethylation in human autoimmune disease.

Human observational studies have also associated stress exposure with altered NR3C1 methylation and glucocorticoid responsiveness, although findings vary across tissues, populations, and the genomic regions examined (Zannas, 2021). Reduced glucocorticoid receptor function can contribute to glucocorticoid resistance and diminished cellular responsiveness to endogenous or therapeutic anti-inflammatory signals (Kino et al., 2024). Altered glucocorticoid signaling has been investigated extensively in major depressive disorder and other stress-related conditions, where it may coexist with systemic and neuroinflammatory changes (Kaufman et al., 2016; Ye et al., 2025).

Chronic stress has also been associated with increased inflammatory activity and symptom aggravation in autoimmune disorders, including rheumatoid arthritis and psoriasis (Chaudhary et al., 2023). Nevertheless, direct evidence demonstrating that stress-induced NR3C1 methylation causes autoimmune disease progression in human cohorts remains limited. Longitudinal studies integrating psychological assessments, cortisol measurements, cell-specific epigenetic analyses, and clinical disease outcomes are needed to clarify this relationship.

Comparative Analysis

Comparative Analysis of Nutritional Substrates and Phytochemical Modulators

The comparative data presented in Table 1 highlight important differences among nutritional substrates and phytochemical modulators that may influence epigenetic regulation. Methyl-donor nutrients, including folate, choline, and methionine, contribute to one-carbon metabolism and the synthesis of S-adenosylmethionine (SAM), the principal methyl donor used in cellular methylation reactions (Ducker & Rabinowitz, 2016). SAM is used by DNA methyltransferases (DNMTs) to transfer methyl groups to cytosine residues, predominantly within CpG dinucleotides (Kamal et al., 2024). However, DNA methylation should not be characterized uniformly as a long-term or preventive process because its stability and functional consequences depend on genomic location, cell type, developmental stage, and environmental context. Adequate dietary intake of methyl-donor nutrients supports one-carbon metabolism and normal methylation processes, although increased intake does not necessarily produce beneficial changes in DNA methylation or genomic stability (Hussain et al., 2026).

In contrast to methyl-donor nutrients, polyphenols and vitamin D may influence epigenetic regulation through interactions with enzymes, receptors, and intracellular signaling pathways. Curcumin has been reported to modulate DNMT and histone acetyltransferase activity in in vitro and preclinical models (Boyanapalli & Kong, 2015; Jiao et al., 2025). Through these and other signaling mechanisms, curcumin may influence the expression of pro-inflammatory mediators such as TNF-α (Ciechomska & O'Reilly, 2016). However, these effects should not be classified uniformly as acute or interventional because their onset and duration vary across experimental models. Furthermore, the limited systemic bioavailability of unformulated curcumin represents an important translational limitation and has encouraged the development of specialized delivery systems (Pratama et al., 2025). This limitation should not be generalized to all polyphenols, which differ substantially in their absorption, metabolism, and tissue distribution.

Vitamin D acts primarily through the vitamin D receptor (VDR), a ligand-activated transcription factor that interacts with transcriptional coregulators and chromatin-modifying enzymes (Fetahu et al.,

2014). Vitamin D signaling has been associated with increased production of the anti-inflammatory cytokine IL-10 by regulatory T cells in patients with systemic sclerosis; however, this observation does not by itself demonstrate that IL-10 expression was stimulated through a specific epigenetic modification (Di Liberto et al., 2019). Unlike rapidly metabolized phytochemicals such as curcumin, vitamin D is fat-soluble, and its absorption, storage, metabolism, and biological availability depend on dietary, physiological, genetic, and environmental factors (Borel et al., 2013; Qahtan et al., 2026). Seasonal variation can affect serum vitamin D concentrations, but its epigenetic effects should not be categorized simply as “cumulative” or “seasonal”.

Overall, methyl-donor nutrients provide biochemical substrates that support SAM-dependent methylation reactions, whereas compounds such as curcumin and vitamin D may influence more selective regulatory pathways. Nevertheless, the distinction between “substrates” and “modulators” is not absolute, as these factors may act through multiple interconnected metabolic, transcriptional, and epigenetic mechanisms. In addition to DNA methylation and histone modifications, nutritional and phytochemical factors may influence non-coding RNA networks. Vitamin D status and signaling have been associated with altered expression of immune-related microRNAs in macrophages and in patients with multiple sclerosis (Fernandez et al., 2022; Khedr et al., 2022). Certain polyphenols have also been reported to modulate microRNA expression in experimental systems. However, the direction and clinical significance of these responses remain dependent on the compound, dose, cell type, and disease context. Non-coding RNA-mediated pathways may therefore represent an additional mechanism through which nutritional factors influence immune and epigenetic regulation, although direct evidence from controlled studies in autoimmune diseases remains limited (Kumar et al., 2023).

Despite their shared potential to influence epigenetic regulation, methyl-donor nutrients, polyphenols, and vitamin D differ considerably in their mechanisms of action, biological availability, tissue specificity, and translational limitations. Methyl-donor nutrients contribute substrates to one-carbon metabolism, whereas curcumin and vitamin D can influence receptor-mediated, enzymatic, and transcriptional pathways. The magnitude and consistency of these responses may be affected by dose, formulation, baseline nutritional status, genetic variation, tissue type, disease stage, and concomitant treatment. Consequently, nutritional epigenetic strategies should not be regarded as universally effective interventions. Their clinical application will require disease-specific evidence, appropriate biomarker assessment, and consideration of individual biological variability.

Table 1. Comparative Analysis of Nutritional Substrates and Phytochemical Modulators.

Factor	Specific Pathway (Target)	Molecular Mechanism	Bioavailability Profile	Timing of Effect	References
Methyl Donors (Folate, Choline, Methionine)	One-Carbon Metabolism (OCM)	Methyl-group donor	High (Dietary absorption)	Long-term/ Preventive	(Ducker & Rabinowitz, 2016; Hussain et al., 2026)
Polyphenols (Curcumin)	HAT/DNMTs	Enzyme Inhibitor, miRNA modulation	Low (Rapid hepatic metabolism)	Acute / Interventional	(Boyanapalli & Kong, 2015; Jiao et al., 2025; Kumar et al., 2023; Pratama et al., 2025)

Vitamin D	VDR/HAT	Receptor-mediated chromatin accessibility, miRNA modulation	Medium (Lipid-dependent absorption)	Cumulative / Seasonal	(Borel et al., 2013; Fetahu et al., 2014; Kumar et al., 2023; Qahtan et al., 2026)

Abbreviations: DNMT, DNA methyltransferase; HAT, histone acetyltransferase; miRNA, microRNA; SAM, S-adenosylmethionine; VDR, vitamin D receptor.

*** Bioavailability Classifications:**

High: High oral bioavailability (>50% intestinal absorption) with efficient systemic distribution of active dietary precursors.

Moderate: Moderate lipophilic absorption requiring lipid-assisted transport, subject to tissue-specific conversion and storage dynamics.

Low: Rapid hepatic metabolism, rapid phase II conjugation, and limited parent compound reaching systemic circulation (<5% systemic bioavailability in unformulated oral administration).

† Temporal Dynamics Definitions:

Long-term / Preventive: Sustained physiological exposure over months to years required to establish stable genomic and epigenetic marks.

Acute / Interventional: Rapid cellular signaling responses occurring within hours to days following exposure, requiring repeated administration due to transient biological half-life.

Cumulative / Seasonal: Progressive epigenetic adaptations developing over weeks to months, correlated with systemic vitamin D status and seasonal exposure.

Comparative Analysis of Lifestyle Modulators and Psychosocial Stressors

As summarized in Table 2, physical activity, sleep and circadian rhythms, and psychological stress may influence the epigenetic landscape through distinct but interconnected mechanisms. Physical activity has been recognized as a potential epigenetic modifier that can influence DNA methylation, histone modifications, and non-coding RNA expression (Zheng et al., 2025). Acute exercise has been associated with transient DNA demethylation at promoters of selected metabolic genes in skeletal muscle (Barrès et al., 2012). Physical exercise has also been associated with increased DNA methylation at selected inflammation-related loci, including IFNG, in circulating lymphocytes from older women (Machado et al., 2021). These findings demonstrate that exercise-induced epigenetic responses are locus-, tissue-, and context-specific. Although such changes may contribute to the regulation of inflammatory pathways, current evidence is insufficient to conclude that they consistently establish a systemic anti-inflammatory epigenetic phenotype.

The sleep–circadian cycle is regulated partly by the CLOCK–BMAL1 complex, which coordinates temporal patterns of gene expression and physiological activity. BMAL1 activity in specific neuronal populations has been shown to contribute to the regulation of sleep architecture, illustrating the close relationship between the molecular clock and sleep organization (Yu et al., 2014). Sleep and circadian alignment have also been associated with regulation of NF-κB-mediated inflammatory activity and other immune pathways, whereas sleep disruption can promote inflammatory signaling (Irwin, 2022). However, the degree to which sleep-related epigenetic alterations can be reversed by restor-

ing healthy sleep patterns has not been established conclusively. Therefore, circadian and sleep-related changes should not be classified uniformly as highly reversible.

Chronic psychological stress can alter hypothalamic–pituitary–adrenal (HPA) axis activity and glucocorticoid signaling. Altered methylation of NR3C1, which encodes the glucocorticoid receptor, has been associated with adverse life experiences and stress-related psychological outcomes in human observational studies (Xu et al., 2025). Studies of adults and children exposed to early-life adversity have also identified methylation differences at selected NR3C1 promoter regions in peripheral samples (Tyrka et al., 2012, 2015). These findings suggest that stress exposure may be associated with persistent regulation of glucocorticoid receptor expression. However, they do not demonstrate uniformly that NR3C1 hypermethylation occurs simultaneously within the brain and peripheral immune cells or that it directly causes glucocorticoid resistance in autoimmune diseases.

The persistence and reversibility of stress-associated epigenetic changes remain incompletely understood. Sleep and physical-activity patterns have been associated with epigenetic age-related measures, while early-life adversity has been investigated in relation to the biological embedding and possible intergenerational transmission of stress-associated epigenetic patterns (Banker et al., 2024; Zhou & Ryan, 2023). Nevertheless, these studies do not provide sufficient evidence to classify stress-induced epigenetic alterations as having uniformly low reversibility. Their stability is likely to depend on the timing and duration of exposure, the tissue examined, the genomic locus, and subsequent environmental conditions.

Preclinical and human observational studies further suggest that lifestyle-related factors may influence non-coding RNA expression. Physical activity, sleep disruption, circadian dysregulation, and psychological stress have each been associated with changes in selected microRNAs involved in metabolic adaptation, immune-cell signaling, cytokine production, and inflammatory pathways. Exercise has been linked to alterations in non-coding RNAs associated with immune regulation, whereas chronic stress has been associated with microRNAs involved in stress-responsive and inflammatory signaling (Kotewitsch et al., 2024; Musazzi et al., 2023). Although these findings indicate potential molecular links among lifestyle factors, non-coding RNAs, and immune regulation, direct causal evidence in patients with autoimmune diseases remains limited (Nemeth et al., 2024).

Despite their different upstream triggers, physical activity, circadian regulation, sleep, and psychological stress may converge on pathways involving cellular metabolism, hormonal signaling, chromatin regulation, and inflammatory gene expression. Physical activity affects metabolic demand and energy-sensing pathways, whereas circadian rhythms coordinate the temporal regulation of gene expression and immune activity. Psychological stress acts primarily through neuroendocrine pathways, including glucocorticoid-mediated signaling within the HPA axis. These mechanisms may interact with epigenetic regulators that influence inflammatory gene expression and immune-cell function. However, the extent to which combined lifestyle interventions produce broader or more durable epigenetic benefits than individual interventions has not yet been established.

Collectively, the available evidence indicates that lifestyle-related factors differ in the direction, magnitude, tissue specificity, and potential persistence of their associated epigenetic changes. Physical activity and healthy sleep patterns are generally associated with favorable metabolic and inflammatory outcomes, whereas chronic psychological stress is more frequently associated with dysregulated neuroendocrine and inflammatory signaling. Nevertheless, these relationships are influenced by study design, exposure

duration, disease context, and the biological samples examined. Lifestyle-related epigenetic mechanisms may ultimately inform supportive approaches to autoimmune disease management, but their clinical utility and reversibility require confirmation through longitudinal and controlled intervention studies.

Table 2. Comparative Analysis of Lifestyle Modulators and Psychosocial Stressors.

Factor	Primary Molecular Mediator	Direction of Inflammatory Shift	Tissue/Cell Specificity	Reversibility Profile	References
Exercise	HAT/DNMTs (IFN-γ)	Anti-inflammatory	Skeletal Muscle & Peripheral Blood (Leukocytes)	High	(Barrès et al., 2012; Machado et al., 2021)
Circadian Rhythms and Sleep	CLOCK-BMAL1 Complex (NF-κB)	Anti-inflammatory	Systemic / Immune Subsets	High	(Irwin, 2022; Yu et al., 2014)
Chronic Stress	HPA Axis Dysregulation; Glucocorticoids Receptor (NR3C1)	Pro-inflammatory	Central Nervous System (HPA) & Immune Cells	Low	(Tyrka et al., 2012, 2015; Zhou & Ryan, 2023)

Abbreviations: DNMT, DNA methyltransferase; HAT, histone acetyltransferase; HPA, hypothalamic-pituitary-adrenal; IFN-γ, interferon-gamma; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NR3C1, nuclear receptor subfamily 3 group C member 1 (glucocorticoid receptor).

* Epigenetic Reversibility Classifications:

High: Rapid recalibration of DNA methylation marks and histone PTMs following lifestyle modification (within days to weeks of consistent behavioral changes), restoring baseline transcriptional profiles without pharmacological intervention.

Moderate / Restorative-Dependent: Epigenetic plasticity contingent upon structural behavior restoration (e.g., recovery of circadian sleep architecture); requires sustained physiological rhythmicity to reverse aberrant transcriptional outputs.

Low: Persistent DNA hypermethylation or chromatin remodeling that remains stable over long durations despite removal of the original stressor, requiring targeted behavioral or pharmacological therapeutic interventions to achieve normalization.

Limitations

Limitations of Nutritional and Phytochemical Modulators

Although the comparative analysis identifies several mechanisms through which nutritional substrates and phytochemical compounds may influence epigenetic regulation, important limitations restrict their translation into clinical practice.

1. Limited Systemic Bioavailability

Limited systemic bioavailability is an important concern for several phytochemical compounds, particularly curcumin. Poor aqueous solubility, limited intestinal absorption, rapid metabolism, and extensive conjugation can substantially reduce the concentration of unformulated curcumin reaching

systemic tissues. Consequently, the biological and epigenetic effects observed in in vitro experiments may not be reproduced at comparable levels in vivo. Specialized delivery systems, including nano-formulations, have been investigated to improve curcumin stability, absorption, and tissue delivery; however, their long-term safety and clinical effectiveness require further evaluation (Laurindo et al., 2023). This limitation should not be generalized to all nutrients because their absorption, metabolism, and bioavailability differ considerably.

2. Limited Genomic Site Specificity

Dietary methyl donors contribute substrates to the S-adenosylmethionine (SAM) pool through the one-carbon metabolism pathway (Ducker & Rabinowitz, 2016). However, increasing the availability of methyl-donor nutrients does not direct DNA methyltransferases specifically toward inflammation-related genes or other therapeutically relevant loci. The effects of supplementation on DNA methylation depend on baseline nutritional status, enzyme activity, cell type, metabolic demand, and the existing chromatin environment. Therefore, changes in methyl-donor availability may produce heterogeneous methylation responses rather than predictable, locus-specific effects. Although unintended methylation changes are theoretically possible, their extent and clinical significance have not been established sufficiently in autoimmune disease intervention studies.

3. Genetic and Biological Variability

Individual responses to nutritional and phytochemical factors may be influenced by genetic variation. Functional polymorphisms in genes involved in one-carbon metabolism, including MTHFR, have been associated with differences in folate metabolism and susceptibility to several autoimmune diseases (Sun et al., 2025). Similarly, polymorphisms in the vitamin D receptor and genes involved in vitamin D metabolism may modify biological responses to vitamin D supplementation (Usategui-Martín et al., 2022). However, these variants do not necessarily render individuals completely unresponsive to dietary interventions. Rather, they may contribute to variability in nutrient metabolism, biomarker responses, and the magnitude of potential clinical effects. These differences limit the suitability of a uniform, one-size-fits-all nutritional strategy.

The translational potential of nutritional epigenetic approaches may also be influenced by baseline nutritional status, disease type and stage, tissue specificity, concomitant medication, dosage, treatment duration, and adherence. Individuals with different autoimmune diseases or nutritional deficiencies may therefore respond differently to similar dietary inputs. Vitamin D research, for example, demonstrates that baseline vitamin D status and genetic background can influence biological responses to supplementation (Dhanapal & Vimaleswaran, 2022; Mazur et al., 2022). In addition, the potential interactions of nutritional and phytochemical compounds with immunosuppressive or immunomodulatory medications have not been characterized adequately. Carefully designed clinical studies are therefore required to determine appropriate doses, identify responsive patient subgroups, evaluate potential interactions, and establish whether observed epigenetic changes are associated with meaningful clinical outcomes.

Limitations of Lifestyle Modulators and Psychosocial Stressors

Although lifestyle-related factors and chronic psychological stress have been associated with epigenetic changes, several methodological and translational limitations should be considered when evaluating their potential clinical relevance.

1. Subjectivity and Measurement Standardization

A major limitation in studies of psychological stress and sleep quality is the reliance on self-reported information. Perceived stress, sleep quality, and restorative sleep are complex constructs that cannot be characterized adequately using a single measurement. Although objective methods such as cortisol measurements, actigraphy, polysomnography, and heart-rate variability can complement self-reported data, these measurements also vary according to sampling time, environmental conditions, medication use, and individual physiology.

Tyrka et al. (2012) reported an association between childhood adversity and altered methylation of selected NR3C1 promoter regions in leukocytes from healthy adults. However, this study was an observational investigation rather than a systematic review and did not establish a specific cortisol threshold that induces persistent epigenetic alterations. The dose–response relationships among stress intensity, duration, cortisol exposure, and the persistence of epigenetic changes remain insufficiently characterized across heterogeneous populations.

2. Adherence and Confounding Variables

Lifestyle interventions require sustained adherence, which may be difficult for individuals with chronic autoimmune diseases. Pain, fatigue, impaired mobility, sleep disturbance, psychological distress, and fluctuating disease activity can limit participation in exercise programs or adherence to recommended sleep and stress-management strategies. These barriers may be particularly relevant in conditions associated with musculoskeletal or systemic involvement.

Lifestyle-related factors also occur within complex behavioral and social environments. Poor sleep may coexist with physical inactivity, psychological stress, medication use, socioeconomic disadvantage, and active disease. Consequently, determining the independent epigenetic contribution of a single lifestyle-related factor represents a substantial analytical challenge. Observational associations may additionally be influenced by reverse causation because autoimmune disease activity can itself alter sleep, physical activity, stress levels, and epigenetic profiles. Longitudinal studies and controlled interventions are therefore needed to distinguish causal effects from correlated behavioral and disease-related factors.

3. Tissue and Cellular Proxy Limitations

Many lifestyle-associated epigenetic changes are tissue- and cell-type-specific. Exercise-related alterations may occur predominantly in skeletal muscle, whereas stress-related responses may involve neuroendocrine tissues and peripheral immune-cell populations. Because direct sampling of many target tissues is invasive or impractical, human studies frequently rely on whole blood or circulating leukocytes as accessible proxy samples.

Epigenetic profiles differ among leukocyte subtypes and between circulating cells, endothelial cells, and disease-affected tissues (Korolenya et al., 2025). Changes detected in peripheral blood may therefore reflect alterations in leukocyte composition rather than epigenetic remodeling within a specific cell population. Moreover, blood-based measurements may not accurately represent changes occurring in target tissues such as the skin, joints, intestinal mucosa, central nervous system, or internal organs. Future studies should account for cell-type composition and, where feasible, use purified cell populations, single-cell approaches, or paired analyses of peripheral and disease-relevant tissues.

Future Perspectives

To address the limitations identified above, future studies should adopt integrative approaches that connect nutritional biochemistry, lifestyle-related exposures, immune function, and epigenetic regulation. Longitudinal multi-omics studies, controlled interventions, and disease-specific analyses will be particularly important for distinguishing causal mechanisms from observational associations. The following areas represent promising directions for the investigation of epigenetically informed supportive strategies in autoimmune diseases.

Personalized Nutri-Epigenetic and Lifestyle Profiling

Future research should move beyond a one-size-fits-all approach. Integrating genetic information, including functional variants in genes such as MTHFR and VDR, with nutritional status, disease characteristics, and longitudinal physiological measurements may support the design of individualized research protocols. Wearable devices can provide repeated measurements of physical activity, sleep duration, heart rate, and heart-rate variability, thereby complementing self-reported information and conventional clinical assessments (Jafleh et al., 2024). However, these measurements should be interpreted cautiously because consumer-grade wearable devices differ in accuracy, validation, and data-processing methods.

Integrating DNA methylation, histone modifications, gene expression, and non-coding RNA profiles may also help identify molecular patterns associated with disease activity, treatment response, or individual biological variability. Non-coding RNAs are particularly relevant because they can connect transcriptional, post-transcriptional, and inflammatory regulatory networks (Nemeth et al., 2024). Nevertheless, such molecular profiles should not be considered clinically validated risk-stratification tools until they have been replicated in independent, disease-specific cohorts. Future studies should therefore combine multi-omics data with clinical outcomes and appropriate external validation before using these profiles to guide personalized nutritional or lifestyle-related interventions.

Targeted and Combination Delivery Systems

Limited bioavailability and inadequate tissue delivery restrict the translational potential of several phytochemical compounds. Preclinical studies are evaluating advanced delivery systems, including nanoencapsulation and ligand-conjugated formulations, to improve compound stability, absorption, and tissue distribution (Guha et al., 2024). These approaches may increase the concentration of phytochemical modulators reaching relevant cells or tissues in experimental models.

Targeted delivery could theoretically reduce systemic exposure and improve tissue specificity. However, it has not yet been established whether these formulations can selectively modify disease-relevant epigenetic pathways without affecting regulatory processes in non-target cells. Future studies should therefore evaluate biodistribution, pharmacokinetics, immune compatibility, long-term safety, and epigenetic specificity in addition to demonstrating improved bioavailability. Combination strategies involving nutritional compounds and standard therapies should also be investigated carefully for pharmacological interactions and additive toxicity.

Longitudinal Epigenetic Mapping and Disease-Specific Intervention

Longitudinal cohort studies are needed to determine the stability, persistence, and potential reversibility of epigenetic alterations throughout the course of autoimmune diseases. Repeated sampling before and after nutritional, behavioral, or pharmacological interventions could help distinguish transient re-

sponses from stable disease-associated changes. Such studies should account for cell-type composition, disease activity, medication use, age, sex, nutritional status, and environmental exposure.

This approach may be particularly informative in autoimmune diseases characterized by progressive fibrosis, such as systemic sclerosis. Promoter hypermethylation and related epigenetic mechanisms have been implicated in fibroblast activation and fibrogenesis, suggesting that some epigenetic changes may contribute to the persistence of fibrotic phenotypes (Zeisberg & Zeisberg, 2012). However, the proposed existence of an irreversible epigenetic “point of no return” has not been established clinically. Studies of early-stage systemic sclerosis could examine whether specific epigenetic alterations precede fibrosis, change during disease progression, or respond to treatment and lifestyle-related factors.

Identifying reproducible and disease-relevant epigenetic markers may ultimately support disease monitoring and patient stratification. However, candidate biomarkers must undergo analytical validation, replication in independent cohorts, and assessment of their incremental value beyond existing clinical indicators. Interventions should also be designed with feasibility and patient burden in mind to support long-term adherence.

Conclusion

This review highlights the potential role of nutritional and lifestyle-related factors in modulating epigenetic processes relevant to autoimmune diseases. Current evidence indicates that methyl-donor nutrients, selected phytochemical compounds, vitamin D, physical activity, sleep and circadian regulation, and psychological stress may be associated with changes in DNA methylation, histone modifications, non-coding RNA expression, and related immune pathways. However, much of the available evidence is derived from in vitro studies, preclinical models, observational investigations, or non-autoimmune populations. Direct evidence of causality and clinical effectiveness in patients with autoimmune diseases remains limited.

The translation of these findings into clinical practice is constrained by limited bioavailability, tissue and cell specificity, genetic and biological variability, measurement limitations, confounding factors, and challenges related to long-term adherence. Non-coding RNAs may represent an additional regulatory layer connecting environmental exposures with immune and inflammatory responses, but their disease-specific roles and clinical utility require further validation.

Future research should prioritize longitudinal, controlled, and disease-specific studies that integrate clinical outcomes with nutritional assessment, objective lifestyle monitoring, and cell-type-resolved epigenetic analyses. Such approaches may clarify which epigenetic changes are modifiable, whether these changes mediate clinically meaningful outcomes, and which patient groups are most likely to benefit. Integrating precision nutrition, epigenetic profiling, and objective lifestyle assessment may eventually support personalized, multimodal strategies that complement established approaches to autoimmune disease management. At present, however, these strategies should be regarded as investigational rather than as validated methods for disease prevention or treatment.

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The authors declare that they have no conflict of interest related to this study.

Data availability statement

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Ethics committee approval

Not applicable.

Authors' contribution statement

Conceptualization: Z.S.; Writing – original draft: Z.S.; Writing review & editing: Z.S., E.S.A.; Supervision: Z.S., E.S.A.

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