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Review Article

Cigarette Smoking-Induced MicroRNA Dysregulation: From Molecular Mechanisms to Systemic Disease Networks and Therapeutic Implications

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ABSTRACT

Background: MicroRNAs (miRNAs) are small non-coding transcripts that regulate gene expression and modulate diverse cellular processes, including proliferation, apoptosis, and immune responses. Cigarette smoking (CS) remains the leading preventable cause of global morbidity and mortality, with tobacco smoke comprising over 7,000 chemicals that inflict cellular damage through oxidative stress, DNA adduction, and epigenetic reprogramming. Accumulating evidence has established miRNAs as critical mediators of CS-induced pathogenesis, with miRNA dysregulation now recognized as a fundamental mechanism linking smoking to a wide spectrum of human diseases. This review synthesizes current knowledge on the roles of miRNAs in smoking-related malignancies, chronic respiratory diseases, cardiovascular disorders, psychiatric illnesses, dermatological conditions, and gastrointestinal diseases.

Materials and Methods: This narrative review searched PubMed, Web of Science, Scopus, and ScienceDirect (2007–2025). Seventy-three eligible studies on miRNA dysregulation in smoking-related diseases were qualitatively synthesized to assess molecular mechanisms and clinical potential.

Results: The Rotterdam Study identified 41 circulating smoking-related miRNAs, 38 of which reversed after cessation. Cigarette smoke alters miRNA pathways involved in angiogenesis, COPD, inflammatory bowel disease, psychiatric disorders, and skin aging. These miRNA profiles may support non-invasive risk stratification, diagnosis, and treatment monitoring, although further validation and standardization are required.

Conclusion: This review integrates epidemiological, experimental, and clinical findings to provide a comprehensive framework for understanding smoking-induced miRNome remodeling and its contribution to disease burden, while identifying critical knowledge gaps for future research.

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Introduction

MicroRNAs (miRNAs) constitute a class of endogenous small non-coding RNAs, typically 22 nucleotides in length, that exert post-transcriptional control over gene expression via sequence-specific recognition of complementary motifs within the 3' untranslated regions of target transcripts, resulting in either translational suppression or mRNA destabilization; this regulatory layer is integral to the orchestration of diverse biological processes, ranging from cell cycle progression and lineage specification to programmed cell death and innate/adaptive immune modulation [1]. With an estimated regulatory reach exceeding 60% of the mammalian genome, and with each miRNA capable of recognizing hundreds of mRNA targets, microRNAs constitute one of the most extensive post-transcriptional control mechanisms known to date [2]. Consequently, aberrant miRNA expression has been observed in a range of diseases, including cancer, metabolic diseases, inflammatory disorders, and cardiovascular pathologies [1, 3]. Cigarette smoking (CS) remains the leading preventable cause of chronic non-communicable diseases globally, responsible for approximately 7 million deaths annually, a figure projected to rise to 8.3 million by 2030, with one-third due to malignancies and the remainder primarily to cardiovascular and respiratory conditions [4]. Tobacco smoke is a complex mixture comprising more than 7,000 distinct chemical constituents, among which no fewer than 70 are established carcinogens. These hazardous agents include reactive oxygen and nitrogen species, heavy metals, volatile organic compounds, and PAHs [5]. These toxicants cause extensive cellular damage through direct DNA adduction, oxidative stress, and disruption of epigenetic machinery. Notably, smoke-induced epigenetic changes can persist long after cessation, creating a “molecular memory” that sustains elevated disease risk [6].

In recent years, accumulating evidence has established miRNAs as key mediators of in the pathogenic effects of cigarette smoke (CS). Smoking alters miRNA biology through multiple mechanisms, including oxidative stress-mediated modulation of the Drosha-DGCR8 and Dicer complexes, disruption of miRNA gene transcription via altered promoter methylation and histone modifications, and nicotine signaling through nicotinic acetylcholine receptors [7, 8]. These changes result in consistent, tissue-specific alterations in miRNA expression in pulmonary tissues, bronchial epithelial cells, alveolar macrophages, and circulating biofluids [9]. The Rotterdam Study cohort identified 41 plasma miRNAs significantly associated with smoking status, 38 of which showed partial reversibility after cessation. Moreover, several of these miRNAs were prospectively linked to incident lung cancer, underscoring their potential as early biomarkers [10]. In the lung, alveolar macrophages exposed to CS extract exhibit miRNA profiles (including hsa-miR-34a-5p, miR-17-5p, miR-16-5p, miR-106a-5p, miR-223-5p, and miR-20a-5p) that shift toward those observed in COPD patients, suggesting a pathogenic role in inflammatory airway disease [11]. In lung cancer, which is attributable to smoking in ~85% of cases, smoke exposure downregulates miR-1 in endothelial cells, promoting VEGF-dependent angiogenesis and field cancerization. Reduced miR-1 expression correlates with smoking burden and poor prognosis [12, 13]. Beyond the respiratory system, smoking-induced miRNA dysregulation extends systemically. Nicotine exerts tissue- and context-dependent effects via nAChR signaling. For instance, it suppresses miR-124 in liver fibrosis models while upregulating STAT-3, yet produces opposite effects in certain colorectal cancer cells [14]. In cardiovascular disease, smoking-related downregulation of miR-34a and miR-126-3p contributes to endothelial dysfunction and atherosclerosis [15].

To provide a structured and comprehensive overview of this rapidly evolving field, the present review is organized as follows. Section 2 details the methodological approach employed for the literature search and data synthesis. Subsequently, Section 3 is divided into two main subsections: Section 3.1 delineates the fundamental pathogenic mechanisms of cigarette smoking (CS), with a particular emphasis on oxidative stress, direct DNA damage, and epigenetic reprogramming, while Section 3.2 systematically examines the role of miRNA dysregulation across a spectrum of smoking-related disease categories, including malignancies, chronic respiratory diseases, cardiovascular disorders, psychiatric illnesses, dermatological pathologies, and gastrointestinal conditions. Finally, Section 4 synthesizes the key findings, discusses their translational implications for biomarker development and therapeutic strategies, and identifies prevailing knowledge gaps, while Section 5 proposes future research directions and addresses the challenges on the path to clinical translation to advance our understanding of miRNA-mediated pathophysiology in the context of tobacco exposure.

Methods

Search Strategy

A literature search was undertaken across prominent electronic repositories, specifically PubMed, Web of Science, Scopus, and Science Direct, in order

to retrieve both empirical articles and narrative or systematic reviews disseminated over the period spanning 2007 to 2025, utilizing an extensive array of keyword combinations including "MicroRNAs", "cigarette smoking", "lung cancer", "cardiovascular disease", "psychiatric disorders", "gastrointestinal diseases", "epigenetic regulation", "COPD", "Pathological Conditions", and "Dermatological". We also used the terms "mechanism" and "clinical trial". In this article, a total of 73 relevant articles were included and reviewed.

Study Selection and Eligibility Criteria

All retrieved records were evaluated against predefined inclusion and exclusion criteria.

Inclusion Criteria: We included original research articles (both in vivo and in vitro studies), clinical trials, and narrative or systematic reviews that investigated: (a) the role of microRNAs (miRNAs) in the pathogenesis of smoking-related diseases; (b) the molecular mechanisms of miRNA dysregulation induced by CS or its constituents (e.g., nicotine); and (c) the potential of miRNAs as diagnostic or therapeutic targets in the context of smoking. Studies involving human subjects, animal models, and cell culture experiments were all considered eligible for inclusion.

Exclusion Criteria: Articles were excluded if they: (a) were not published in English; (b) were duplicate publications; (c) were in the form of conference abstracts, editorials, or letters without sufficient original data; (d) did not have full-text availability; or (e) focused solely on the epidemiological aspects of smoking without assessing any molecular or miRNA-related mechanisms.

Data Extraction and Synthesis

The article selection process was performed in two stages. Initially, all authors screened the titles and abstracts of all retrieved records to remove irrelevant studies. Subsequently, the full texts of the remaining potentially eligible articles were assessed against the inclusion criteria. Any disagreements among the authors during the selection process were resolved through consensus. Following this rigorous screening, a final set of 73 articles was identified as highly relevant and included in the qualitative synthesis of this narrative review. A manual search of the reference lists of the included articles was also performed to identify any additional pertinent studies.

Results and Discussion

CS and Its Pathogenic Role

CS represents the foremost modifiable risk factor for global morbidity and mortality, with approximately 1.2 billion current smokers worldwide. The pathogenic effects of tobacco smoke stem from its complex chemical composition, comprising over 5,000 identified compounds [5]. Nicotine, the primary psychoactive alkaloid, exerts its effects predominantly through nicotinic acetylcholine receptors expressed across diverse tissues. Beyond its role in addiction, nicotine-triggered signaling cascades significantly contribute to the progression and initiation of smoking-related diseases [16]. Smoke-induced pathology arises from multiple converging mechanisms, notably oxidative stress, direct DNA damage, and profound epigenetic modifications. CS alters both the expression of miRNA genes, many of which reside in fragile chromosomal regions, and the miRNA biogenesis machinery [8, 7]. Such dysregulation, particularly the downregulation of tumor-suppressive miRNAs, promotes oncogenesis by derepressing oncogenic targets, while upregulation of certain miRNAs can silence key tumor suppressors [17]. A key concept in smoking-related carcinogenesis is the "field of injury" or "cancer field," whereby chronic smoke exposure induces widespread molecular alterations throughout the respiratory epithelium and adjacent tissues, creating a permissive environment for neoplastic transformation [18]. These changes extend beyond the epithelium to endothelial and immune cells, reflecting the systemic impact of tobacco smoke [19]. A prominent example is the selective degradation of mature miR-1 in endothelial cells via a VEGF-driven pathway, which promotes angiogenesis, a hallmark of malignancy. Tumor miR-1 levels correlate inversely with smoking burden and exhibit a spatial gradient consistent with field cancerization. Notably, endothelial-specific miR-1 overexpression inhibits KRAS mutant-P53 knockout tumor formation by more than 90% [12]. In addition to direct oncogenic effects, smoking impairs innate immunity by altering alveolar macrophage function. Exposure to CS shifts miRNA profiles (e.g., hsa-miR-34a-5p, miR-16-5p, miR-17-5p, miR-223-5p, miR-106a-5p, and miR-20a-5p) in healthy macrophages toward signatures observed in COPD patients, thereby promoting chronic inflammation and disease progression [11, 20]. Systemically, smoking-associated decreases in circulating miR-30b-5p correlate with increased all-cause mortality, while nicotine-mediated downregulation of miR-24 accelerates pulmonary fibrosis through enhanced growth factor signaling and reduced anti-inflammatory activity [21]. Collectively, these findings position CS as a potent modulator of the miRNome, with resulting miRNA dysregulation

serving as a critical mechanistic link between tobacco exposure and the development of diverse smoking-related diseases [22]. Figure 1 illustrates these pathogenic pathways and their downstream disease consequences.

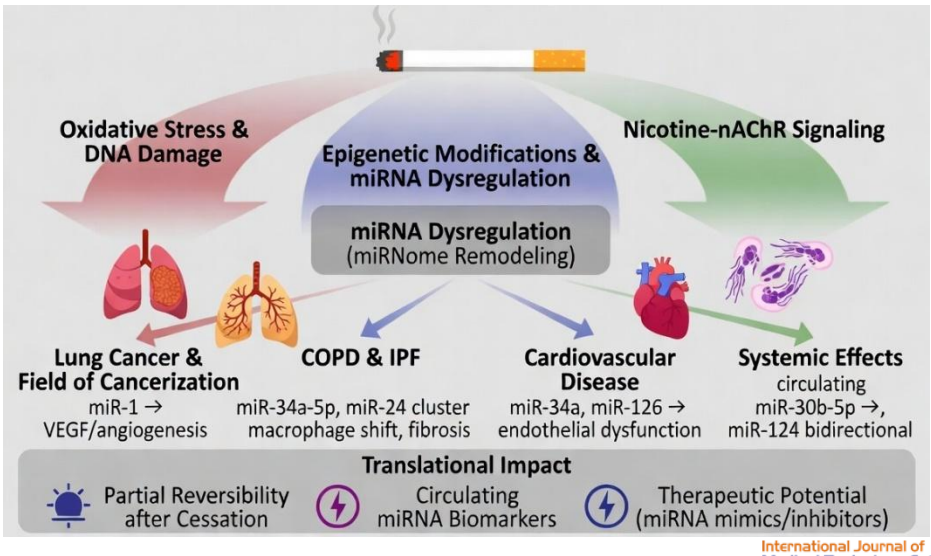

Figure 1. CS induces pathogenic effects through oxidative stress, DNA damage, and epigenetic alterations. CS contains over 7,000 chemicals that cause cellular damage via three converging mechanisms: (1) oxidative stress (ROS/RNS), (2) direct DNA adduct formation and mutations, and (3) epigenetic reprogramming (altered DNA methylation, histone modifications, and disrupted miRNA biogenesis). These mechanisms create a "field of injury" predisposing tissues to malignancy and chronic disease.

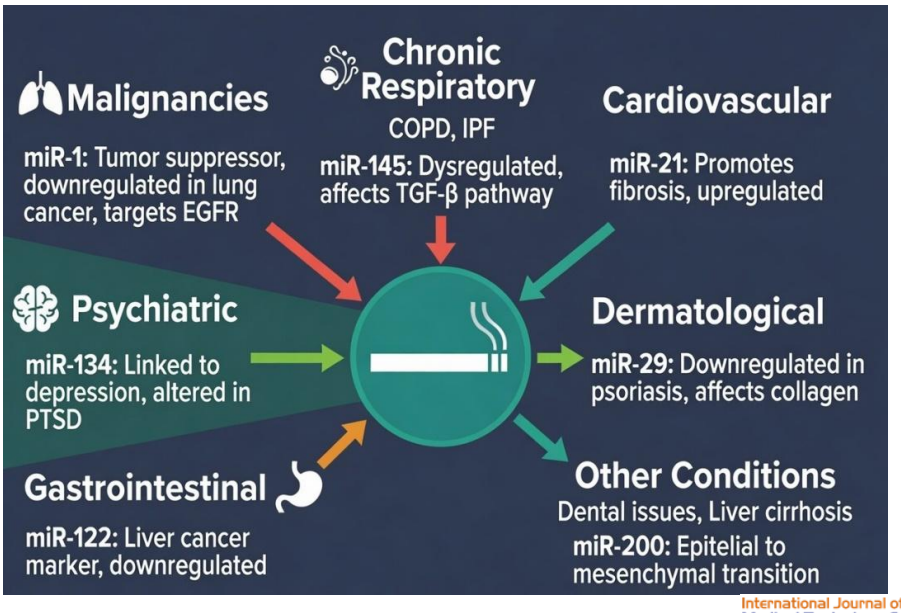

Figure 2. miRNA-Mediated Pathogenic Cascades in Smoking-Related Diseases. CS-induced miRNA dysregulation triggers tissue-specific pathogenic cascades: (A) miR-1 downregulation promotes angiogenesis and lung cancer; (B) altered miRNA signatures in macrophages contribute to COPD; (C) miR-34a and miR-126-3p downregulation links to cardiovascular disease; (D) miR-128-3p and miR-19a-3p dysregulation associates with psychiatric disorders; (E) miR-124/STAT3 axis mediates IBD effects; (F) 17 miRNAs regulate ferroptosis in skin aging.

miRNAs and CS-Related Diseases

Measuring approximately 22 nucleotides in length, miRNAs represent a class of evolutionarily ancient, non-coding RNA molecules that act as pivotal controllers of gene expression following transcription. Through translational repression or messenger RNA degradation, miRNAs modulate an extensive array of cellular processes, including differentiation, proliferation, immune responses, and apoptosis [7]. Given that each miRNA can target hundreds of distinct mRNA transcripts, these molecules exert profound influence over virtually all biological pathways, and

their dysregulation has been unequivocally linked to a broad spectrum of pathophysiological conditions, encompassing malignancies, chronic inflammatory disorders, and cardiovascular pathologies [17, 23].

CS constitutes the foremost preventable risk factor for global morbidity and mortality, with its pathogenic consequences mediated through the induction of oxidative stress, direct DNA damage, and profound epigenetic reprogramming [24]. Mounting evidence suggests that CS exposure induces widespread and reproducible alterations in miRNA expression profiles across multiple tissue types and biological matrices, and this smoke-induced miRNA dysregulation is now recognized as a central pathogenic mechanism bridging tobacco exposure to the progression and development of diverse human diseases [22]. Table1 and Figure 2 provide a comprehensive overview of these miRNA alterations across various disease categories [7, 11-15, 25-35].

miRNAs in Smoking-Related Malignancies

The role of miRNA dysregulation in smoking-associated carcinogenesis has been most extensively characterized in lung cancer, where CS is the primary etiological agent accounting for approximately 85% of all cases [36]. CS induces both genetic and epigenetic damage to miRNA genes, many of which are located at fragile chromosomal sites and harbor single nucleotide polymorphisms that may increase susceptibility to dysregulation [7]. Importantly, smoking-induced miRNA alterations exhibit dose-response and temporal characteristics, with longer exposure at threshold levels required to establish irreversible changes [8].

Among the most compelling recent discoveries is the identification of miR-1 inhibition as a critical event in smoking-induced lung carcinogenesis. A landmark 2025 investigation demonstrated that miR-1 levels in three independent non-small cell lung cancer cohorts exhibit inverse linked to smoking burden, and that miR-1 levels follow a spatial gradient within the lung lowest in tumors, enhanced in adjacent tissues, and maximal in remote tissues consistent with the "field of injury" or "cancer field" concept where molecular alterations progressively accumulate in the respiratory epithelium [12]. Critically, CS specifically downregulates miR-1 in pulmonary endothelial cells through a VEGF-driven pathway that selectively degrades mature miR-1, thereby inducing angiogenic activation through the PI3K/AKT pathway, including targets such as PI3KCA, GADD45B, FOXO1, mTOR, and AKT2. This downregulation establishes a "field of injury" in which miR-1 levels follow a spatial gradient: lowest in tumors, elevated in adjacent tissues, and highest in remote tissues, consistent with the concept of field cancerization [12].

Beyond lung cancer, smoking-induced miRNA dysregulation has been implicated in other malignancies. In pancreatic cancer, miRNAs exhibit differential expression patterns during malignant transformation, with progressive increases in miR-196a from precursor lesions to invasive carcinomas and inhibition of miR-375 and miR-148a/b [7]. miRNAs also directly impact epithelial-mesenchymal transition in pancreatic cancer by modulating miR-200a and miR-30 family members, which regulate transcription factors including ZEB1, ZEB2, SNAIL, vimentin, SLUG, and TWIST [7]. These findings underscore the systemic nature of smoking-induced miRNA alterations and their role in promoting oncogenesis beyond the pulmonary compartment. Although the present review primarily focuses on smoking-associated lung cancer, emerging evidence highlights the importance of other molecular targets in melanoma pathogenesis. For instance, the CD73/adenosine pathway has been identified as a promising therapeutic axis in melanoma, where its inhibition can modulate the tumor immune microenvironment. This underscores the broader applicability of non-coding RNA and immunomodulatory strategies beyond smoking-related cancers [37].

miRNAs in Chronic Respiratory Diseases

COPD represents another major domain in which smoking-induced miRNA dysregulation contributes significantly to disease pathogenesis [38]. Alveolar macrophages serve as sentinel effector cells of the innate immune system in the lung, and smoking impairs their phagocytic capacity and pathogen-response capabilities through mechanisms including miRNA-mediated epigenetic modifications [20]. A 2025 investigation revealed that in vitro exposure of alveolar macrophages from healthy individuals to CS induced dysregulation of six miRNAs (miR-17-5p, hsa-miR-34a-5p, miR-16-5p, miR-223-5p, miR-106a-5p, and miR-20a-5p), shifting their expression signatures toward profiles previously observed in patients with COPD. This transition suggests that these miRNAs may function as risk factors in the development of smoking-related inflammatory lung conditions [11].

Notably, following smoke exposure, the expression levels of several of these miRNAs shifted toward the signature previously observed in patients with COPD, indicating that these miRNAs might function as risk factors in the development of smoking-related inflammatory lung conditions [11]. This observation highlights the potential utility of these miRNA signatures as early biomarkers for disease

predisposition and as targets for intervention strategies. In the context of IPF, tobacco use represents the chief modifiable risk factor, with prevalence reaching up to 80% among IPF patients [39]. Nicotine, the primary bioactive alkaloid in tobacco, has been demonstrated to downregulate anti-inflammatory miRNAs [21]. A substantial proportion of the computationally predicted targets of miR-24 encompass pro-inflammatory cytokines and fibroblast growth factors, both of which are known to contribute to the pathogenic mechanisms underlying IPF. In parallel, nicotine has been shown to upregulate the expression of several pro-fibrotic mediators, including platelet-derived growth factor, fibroblast growth factor, and vascular endothelial growth factor, thereby inducing fibroblast proliferation and promoting extracellular matrix deposition through collagen accumulation. Collectively, these observations implicate nicotine whether administered in isolation or as a constituent of CS in the potential exacerbation of IPF pathophysiology. This deleterious effect appears to be mediated by two convergent molecular mechanisms: direct stimulation of fibrogenic growth factor signaling and concurrent suppression of anti-inflammatory microRNAs [21]. Beyond CS, various exogenous agents, including amiodarone, can induce significant structural damage and fibrosis in lung tissue. Notably, experimental studies have demonstrated that human placental extract exerts protective and ameliorative effects against amiodarone-induced pulmonary injury. These findings suggest that anti-inflammatory and regenerative agents may effectively mitigate pathological lung tissue remodeling, a process that is also substantially modulated by smoking-associated dysregulation of miRNAs [40].

miRNAs in Cardiovascular Disease

The cardiovascular consequences of smoking are similarly mediated, in part, through miRNA dysregulation. MiR-34a downregulation in CAD patients is driven by smoking status, not by the extent of atherosclerosis. Conversely, miR-126-3p was downregulated in non-smokers with significant CAD, indicating that this miRNA may be more closely associated with atherosclerotic processes themselves [15]. Notably, a significant interaction was observed between smoking dose (pack-years) and severity of CAD for miR-199, demonstrating a complex interaction pattern: while the main effects favored upregulation, the interaction effect favored downregulation. This highlights the intricate interplay between smoking exposure, disease severity, and miRNA expression [15]. These findings underscore the potential of miRNAs as biomarkers for smoking-related cardiovascular risk stratification and the importance of considering both smoking status and disease severity when interpreting miRNA expression patterns. As recently reviewed in a comprehensive analysis of cardiovascular diseases in substance use disorders [41], epigenetic mechanisms ,particularly miRNA dysregulation ,play a pivotal role across different classes of addictive substances. The cardiovascular consequences of smoking are similarly mediated, in part, through miRNA dysregulation.

miRNAs in Psychiatric Disorders

The neurobiological consequences of smoking extend to psychiatric conditions, where miRNA dysregulation plays a significant mediating role. Studies have indicated that smoking alters miRNA expression in brain regions critical for mood regulation and cognition. For instance, miR-128-3p is upregulated in the amygdala of rats exhibiting depressive-like behavior and shows trending upregulation in smokers' serum, suggesting its potential involvement in smoking-associated depression [25]. Similarly, miR-19a-3p demonstrates differential regulation: while it is downregulated in the prefrontal cortex of suicide victims, it is upregulated in the female prefrontal cortex following nicotine self-administration, indicating sex-specific effects in smoking-related mood disorders [25].

In a study examining sex differences in microRNA expression in the prefrontal cortex following chronic nicotine exposure, male and female rats were compared. Following 22 days of intravenous nicotine self-administration, RNA sequencing revealed a significant upregulation of the miR-199a/214 cluster in nicotine-exposed individuals, whereas no notable change was observed in males. Collectively, these findings demonstrate that the miR-199a/214–SIRT regulatory axis represents a sex-dependent molecular mechanism underlying the response to chronic nicotine use. This pathway might provide a foundation for the development of sex-specific therapeutic strategies for nicotine addiction [26]. Furthermore, research has shown that variation in the dopamine D1 receptor gene, a major receptor mediating dopamine actions in the brain and associated with tobacco dependence, is regulated by miR-504, indicating that miRNA-mediated regulation may directly influence genetic susceptibility to nicotine dependence [27].

In schizophrenia, smoking is highly prevalent, and a 2019 investigation examining miRNA expression in the DLPFC identified specific miRNA alterations associated with smoking status, suggesting that CS exposure may modulate miRNA networks implicated in the pathophysiology of psychotic disorders [28].

These observations collectively underscore the importance of miRNA-mediated mechanisms in understanding the comorbidity between smoking and psychiatric illness. Emerging research suggests that several nutraceuticals and natural compounds, notably probiotics, vitamin D, curcumin, and crocin, may positively influence inflammatory processes, cognitive domains, and psychological well-being [42-46].

miRNAs in Dermatological Disorders

The deleterious effects of CS on skin health are well-documented, and emerging evidence implicates miRNA dysregulation in this process. A study investigating the mechanisms of smoke-induced skin damage found that exposure to CS can induce ferroptosis, an iron-dependent form of regulated cell death driven by lipid peroxide accumulation in female skin [29]. Importantly, bioinformatic analysis revealed that ferroptosis-associated genes in smoke-exposed skin might be regulated by 17 miRNAs, establishing a direct mechanistic link between CS exposure, miRNA dysregulation, and cutaneous pathology [29] (Figure 3).

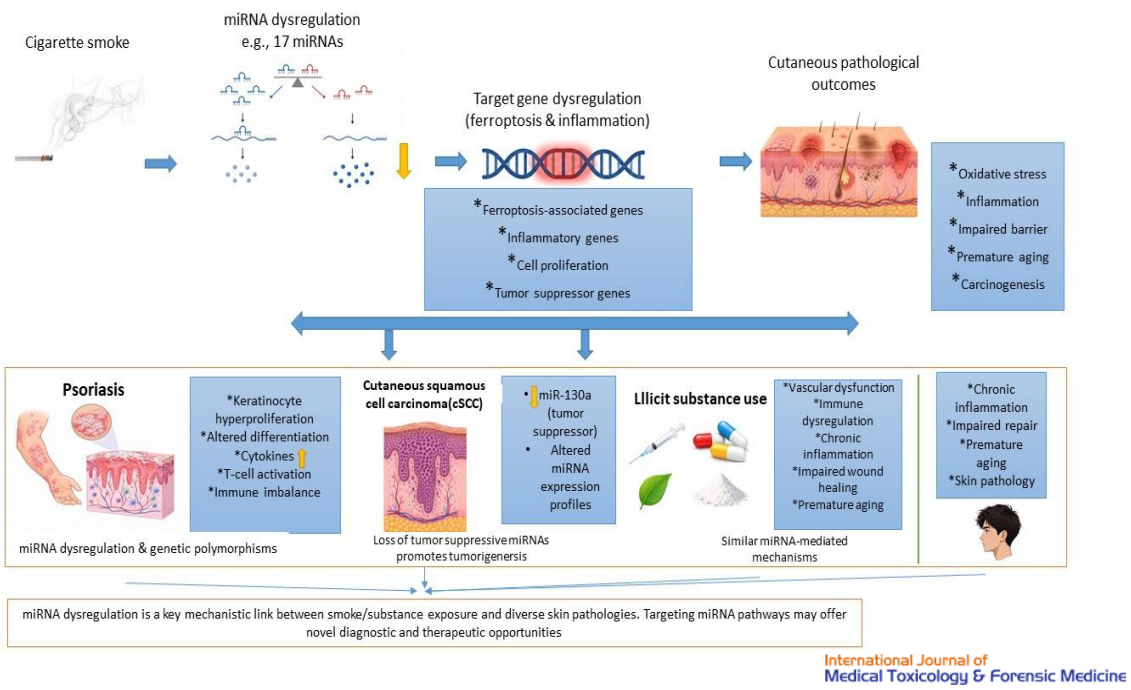

Figure 3. miRNA-Mediated Mechanisms in Smoking-Related Dermatological Disorders. CS induces ferroptosis in skin cells regulated by 17 miRNAs, linking smoking to skin aging and impaired wound healing. In psoriasis, dysregulated miRNAs affect keratinocyte function and T-cell responses, contributing to cutaneous inflammation.

These findings provide an important theoretical basis for understanding smoking-related skin aging and developing potential anti-aging interventions targeting miRNA pathways.

In the context of inflammatory skin diseases, miRNAs have emerged as key regulators of psoriasis pathogenesis. Psoriasis is a chronic immune-mediated skin condition in which the balance between keratinocytes and immune cells is disturbed. Deregulated miRNA expression in psoriasis affects keratinocyte differentiation, proliferation, and cytokine responses, as well as T-cell activation and survival [30]. Genetic polymorphisms in miRNA genes or miRNA binding sites of target genes may contribute to disease susceptibility, and changes in miRNA-mediated gene regulation may represent a major contributor to the disturbed immune balance, resulting in skin inflammation. While direct evidence linking smoking-induced miRNA changes specifically to psoriasis requires further investigation, the established role of both smoking as an exacerbating factor in psoriasis and miRNA dysregulation in its pathogenesis suggests a plausible mechanistic connection. Additionally, in cutaneous squamous cell carcinoma (cSCC), miR-130a has been identified as a tumor suppressor miRNA that is downregulated in cSCC compared with healthy skin, and altered miRNA expression profiles have been observed in these malignancies [30]. The dermatologic consequences of substance use extend beyond tobacco, as a recent systematic review has documented a wide range of skin manifestations associated with illicit drugs, including vascular, immune, and behavioral pathways. Notably, many of these cutaneous pathologies such as chronic inflammation, impaired wound healing, and premature aging resemble those induced by CS, suggesting that similar miRNA-mediated mechanisms may be involved in illicit substance-related skin damage [47].

miRNAs in Gastrointestinal Disorders

The relationship between CS and IBDs represents one of the most intriguing examples of smoking's bidirectional effects on human disease. Epidemiological investigations have consistently demonstrated that smoking exerts a protective effect in ulcerative colitis (UC) while paradoxically exacerbating Crohn's disease (CD) conditions characterized by Th2-mediated and Th1-mediated responses, respectively [31]. The evidence shows that nicotine, the primary bioactive alkaloid in tobacco, mediates these opposing effects through miRNA-dependent regulation of the Th1/Th2 balance (Figure 4).

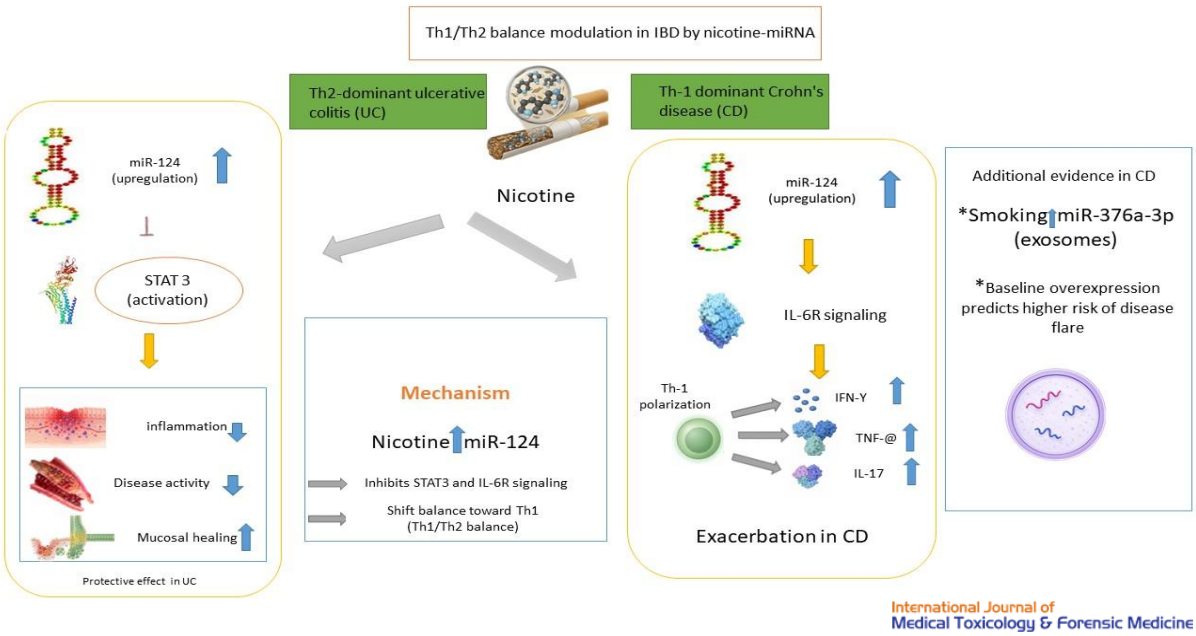

Figure 4. The miR-124/STAT3/IL-6R Axis in Inflammatory Bowel Diseases. Nicotine upregulates miR-124, which inhibits STAT3 via IL-6R targeting, shifts Th1/Th2 balance toward Th1 polarization. This explains nicotine's protective effect in Th2-dominant UC versus its exacerbating effect in Th1-dominant CD.

Research has demonstrated that the role of miR-124 in smoking-related gastrointestinal disorders is context-dependent and bidirectional. In ulcerative colitis (UC), nicotine upregulates miR-124, which inhibits STAT3 activation by targeting IL-6R, shifts the Th1/Th2 balance toward Th1 polarization, and exerts a protective effect in this Th2-dominant disease [31, 32]. Conversely, in a rat model of cholestatic liver fibrosis, nicotine administration significantly suppressed miR-124 (a known anti-inflammatory miRNA) while concomitantly upregulating STAT-3 and exacerbating fibrotic and inflammatory indices [14]. This duality explains the paradoxical effects of smoking in different gastrointestinal conditions. Overexpression of miR-124 protected against DSS-induced colitis with Th1 polarization, while miR-124 knockdown worsened colitis with Th2 polarization and eliminated the Th1-shifting effect of nicotine. These findings explain why nicotine may protect against Th2-dominant UC while exacerbating Th1-dominant CD, providing a molecular framework for understanding the paradoxical effects of smoking on inflammatory bowel diseases [31]. Furthermore, a recent study identified altered expression of miR-20a-5p and miR-376a-3p in blood exosomes of CD patients, with smoking identified as an independent factor associated with miR-376a-3p overexpression, and baseline overexpression of this miRNA was associated with an increased risk of disease flare during follow-up. It is postulated that perturbation of these epigenetic regulators might engender a homeostatic recalibration of autophagic activity and inflammatory responses ,two interrelated biological axes whose dysregulation is ostensibly associated with the progressive pathophysiology characteristic of CD [33]. In gastric cancer ,a malignancy with an established smoking-related risk, nicotine has been indicated to promote cell proliferation through upregulation of miR-21 and miR-16 via a nuclear factor kappa B-dependent mechanism. Specifically, nicotine enhances the binding of NF-κB to the promoters of miR-21 and miR-16, and this effect is mediated through prostaglandin E2 receptors EP4 and EP2. Transfection with anti-miR-21 or anti-miR-16 significantly abrogated nicotine-induced cell proliferation, suggesting that these miRNAs represent potential therapeutic targets for mitigating smoking-related gastric cancer risk [34] (Figure 5).

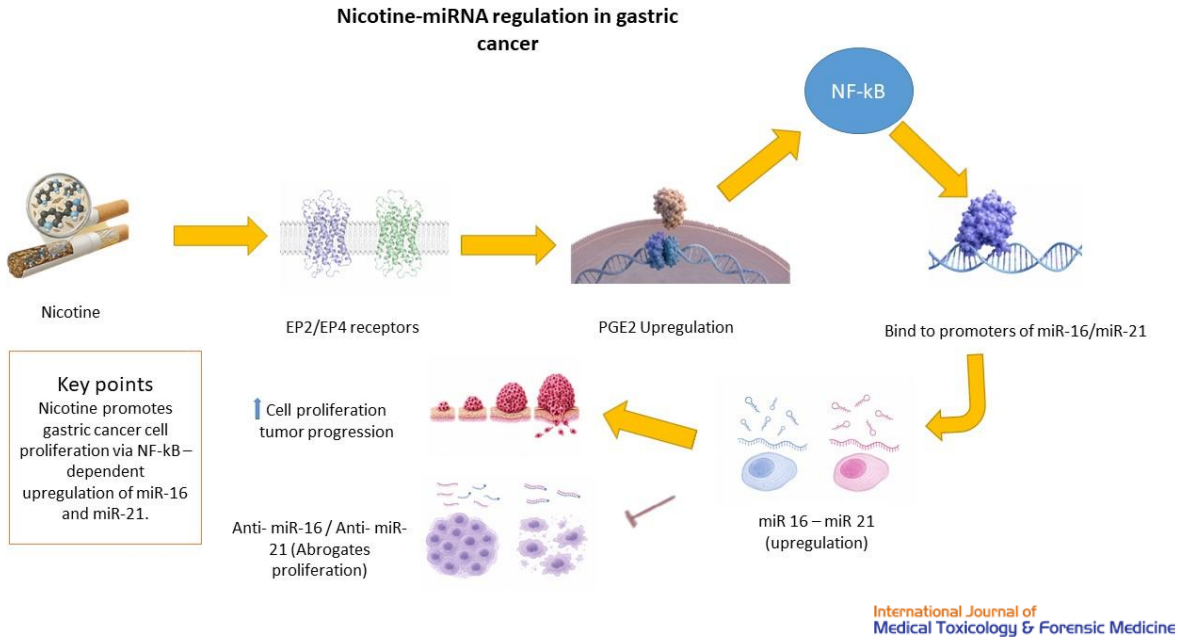

Figure 5. Nicotine-Induced miRNA Dysregulation in Gastric Cancer. Nicotine enhances NF-κB binding to miR-21 and miR-16 promoters via prostaglandin E2 receptors (EP4/EP2), upregulating these miRNAs and promoting cell proliferation. Transfection with anti-miR-21 or anti-miR-16 abrogates this effect, suggesting therapeutic potential.

miRNAs in Other Pathological Conditions

The impact of smoking on miRNA expression extends to diverse tissues and pathological conditions. A study investigating the biological consequences of extended CS exposure on dental pulp stem cells indicated that chronic exposure to CS condensate significantly impaired the regenerative capacity of these cells through miRNA-mediated mechanisms [35]. Bioinformatic analysis revealed that cell cycle, cancer, and signal transduction pathways, including TNF, p53, TGF-β, mTOR, PI3K-Akt, and ErbB, were associated with altered miRNA profiles. Specifically, miR-26b-5p, miR-26a-5p, and miR-29b-3p were identified as key regulators that fine-tune p53 and cell-cycle signaling pathways to modulate dental pulp stem cell activity, demonstrating the broader implications of smoking-induced miRNA dysregulation for tissue regeneration [35]. This work highlights the broader implications of smoking-induced miRNA dysregulation for tissue regeneration and disease prevention.

The liver represents another organ system susceptible to smoking-induced miRNA alterations. A recent systematic review examining the mechanisms of liver dysfunction induced by CS identified that miRNA-mediated post-transcriptional modifications play a central role in the pathogenesis of smoking-related hepatic injury [48]. Additionally, nicotine has been shown to modulate miR-124 expression in liver fibrosis models. In a rat model of cholestatic liver fibrosis, nicotine administration significantly suppressed miR-124, a known anti-inflammatory miRNA, while concomitantly upregulating STAT-3 and exacerbating fibrotic and inflammatory indices [14]. These findings suggest that miR-124 downregulation participates in smoking-related hepatic injury and may represent a therapeutic target for mitigating liver damage in smokers. In addition, Plasma and serum miRNAs hold potential as diagnostic and monitoring tools for tobacco-related diseases [49], while miRNA-based therapeutics have demonstrated efficacy in experimental models [50]. Nevertheless, translating these findings into clinical practice requires overcoming hurdles in biomarker validation, standardization of quantification, and drug delivery safety [51].

Convergent Mechanistic Pathways

The findings synthesized in this review unequivocally demonstrate that the pathogenic effects of CS cannot be attributed to any single molecular mechanism in isolation. Rather, oxidative stress, inflammation, and epigenetic regulation function as interconnected and mutually reinforcing layers of a unified pathogenic cascade. For instance, ROS generated by CS not only cause direct cellular damage but also activate the NF-κB pathway, which in turn promotes the transcription of pro-inflammatory miRNAs (e.g., miR-155 and miR-146a) while simultaneously repressing anti-inflammatory miRNAs

Table 1. Summary of Key miRNAs Dysregulated by CS Across Different Disease Categories

MicroRNA	Expression Change	Disease Category	Specific Disease/Condition	Target Gene/Pathway	Mechanism/Function	Model System
miR-1	Downregulated	Malignancies	Lung Cancer	VEGF, PI3K/AKT (PI3KCA, GADD45B, FOXO1, mTOR, AKT2)	Promotes angiogenic activation; endothelial-specific overexpression inhibits tumor formation	Human tissue, In vivo
miR-196a	Upregulated	Malignancies	Pancreatic Cancer	-	Progressive increase from precursor lesions to invasive carcinomas	Human
miR-148a/b, miR-375	Downregulated	Malignancies	Pancreatic Cancer	-	Downregulated during malignant transformation	Human
miR-200a, miR-30	Modulated	Malignancies	Pancreatic Cancer	ZEB1, ZEB2, vimentin, SNAIL, SLUG, TWIST	Impacts epithelial-mesenchymal transition	Human
miR-16-5p, miR-34a-5p, miR-223-5p, miR-17-5p, miR-106a-5p, miR-20a-5p	Dysregulated	Chronic Respiratory	COPD	-	Shift toward COPD signature following smoke exposure; risk factor in inflammatory lung disease	In vitro
miR-24	Downregulated	Chronic Respiratory	IPF	Proinflammatory cytokines, FGF	Downregulates anti-inflammatory miRNAs; nicotine stimulates FGF, PDGF, VEGF, promoting fibroblast proliferation	In vitro
miR-34a	Downregulated	Cardiovascular	CAD	-	Primarily affected by smoking status rather than atherosclerotic burden	Human
miR-126-3p	Downregulated	Cardiovascular	CAD	-	Atherosclerotic processes themselves; downregulated in non-smokers with CAD	Human
miR-199	Complex (interaction effect)	Cardiovascular	CAD	-	Interaction between smoking dose and CAD severity; interaction favors downregulation	Human
miR-128-3p	Upregulated	Psychiatric	Depression, Smoking-associated mood disorders	-	Upregulated in amygdala of depressive rats; trending upregulation in smokers' serum	In vivo, Human
miR199a/214	Upregulated	Psychiatric	Nicotine self-administration	-	Decreased SIRT1 and upregulated cleaved caspase-3 were detected in the brains of female rats following nicotine administration	Female rats exposed to nicotine
miR-504	Regulates	Psychiatric	Nicotine Dependence	DRD1	Influences genetic susceptibility to nicotine dependence through miRNA-mediated regulation	Human
Various miRNAs	Altered	Psychiatric	Schizophrenia	-	Specific miRNA alterations in DLPFC associated with smoking status; modulate miRNA networks	Human
17 miRNAs	Regulate	Dermatological	Skin aging, Ferroptosis	Ferroptosis-associated genes	Smoke-induced ferroptosis regulated by 17 miRNAs; mechanistic link to cutaneous pathology	Human
Various miRNAs	Deregulated	Dermatological	Psoriasis	Elevated miR-210 and reduced miR-138 levels together interfere with the proper balance among $CD4^+$ T cell subsets	Modulating critical transcription factors implicated in psoriasis pathogenesis (e.g., STAT3 and NF-κB)	Review
miR-124	Upregulated	Gastrointestinal	Ulcerative Colitis	STAT-3, IL-6R	Nicotine upregulates miR-124; inhibits STAT3 activation; shifts Th1/Th2 balance toward Th1; protective effect	In vivo, in vitro

MicroRNA	Expression Change	Disease Category	Specific Disease/Condition	Target Gene/Pathway	Mechanism/Function	Model System
miR-124	Downregulated	Gastrointestinal	Liver Fibrosis	STAT-3	Nicotine suppresses miR-124; upregulates STAT-3; exacerbates fibrotic and inflammatory indices	In vivo
miR-376a-3p, miR-20a-5p	Upregulated	Gastrointestinal	Crohn's Disease	Autophagy, inflammatory pathways	Smoking independent factor related to overexpression; linked to enhanced risk of disease flare, relates to smoking habit; regulates autophagy and inflammatory substrates	Human
miR-21, miR-16	Upregulated	Gastrointestinal	Gastric Cancer	NF-κB, prostaglandin E2 receptors	Nicotine enhances NF-κB binding to the miR-16 promoter; promotes cell proliferation	In vitro
miR-26b-5p, miR-26a-5p, miR-29b-3p	Regulated	Other	Dental Pulp Stem Cells	p53 pathway	Fine-tunes p53 and cell cycle signaling; modulates stem cell regenerative capacity	In vitro

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(e.g., miR-124) through promoter hypermethylation. Conversely, dysregulated miRNAs can amplify inflammatory responses by targeting negative regulators of NF-κB signaling (e.g., miR-146a targeting TRAF6 and IRAK1), establishing a bidirectional feedback loop that sustains chronic inflammation and creates a permissive microenvironment for carcinogenesis and tissue fibrosis. Table 2 lists additional smoking-related miRNAs with their targets and experimental details.

Challenges on the path to clinical translation

Despite the immense therapeutic and diagnostic potential of miRNAs, their translation from bench to bedside is impeded by several formidable challenges. First, the delivery of miRNA-based therapeutics (mimics or antimiRs) faces significant hurdles. Currently available carriers, including lipid-based nanoparticles and viral vectors (e.g., AAVs), suffer from inherent limitations such as immunogenicity, rapid hepatic clearance, poor tissue penetration, and lack of cell-type specificity. For instance, while lipid nanoparticles have shown promise in hepatic delivery, targeting pulmonary endothelial cells (to modulate miR-1 in lung cancer) or alveolar macrophages (to reverse COPD-associated signatures) remains a formidable obstacle due to biological barriers like the mucosal epithelium and extracellular matrix [102]. Second, the intrinsic biology of miRNAs poses a major specificity challenge. A single miRNA can potentially regulate hundreds of downstream mRNA targets. Therefore, the therapeutic inhibition (e.g., using antimiR-21) or replacement (e.g., miR-34a mimic) of a single miRNA inevitably alters a vast array of signaling pathways, increasing the risk of off-target toxicity. Furthermore, as highlighted in this review, many diseases involve the simultaneous dysregulation of entire miRNA families or clusters (e.g., the let-7 or miR-200 families). The concurrent modulation of these multiple effectors is far more complex than traditional small-molecule inhibition and demands sophisticated multi-target approaches that are currently in their infancy [103]. Third, the application of circulating miRNAs as clinical biomarkers is severely hampered by a lack of standardization. There is no consensus on optimal quantification methods, with a stark divide between the precision and low cost of qPCR (limited to pre-selected targets) and the comprehensive but expensive and analytically complex nature of Next-Generation Sequencing (NGS) [104]. Moreover, pre-analytical variables, particularly hemolysis during blood processing, can profoundly distort miRNA profiles (e.g., by spuriously elevating levels of erythrocyte-derived miRNAs such as miR-16 and miR-451), leading to non-reproducible and erroneous results [105]. The absence of universally accepted reference genes for data normalization further complicates cross-study comparisons. Addressing these hurdles through rigorous methodological harmonization and the development of safe, targeted delivery systems is paramount for realizing the clinical promise of the smoke-induced miRNome.

Future Directions and Unanswered Questions

Despite remarkable progress, fundamental knowledge gaps persist and warrant dedicated investigation. First, the causal relationships between specific miRNA changes and individual disease phenotypes require rigorous validation through functional studies using tissue-specific knockout or overexpression animal models. Second, the "molecular memory" of smoking — epigenetic changes that sustain disease risk even after cessation — remains poorly understood; longitudinal studies investigating the persistence and reversibility of miRNA alterations over

Table 2. Selected miRNAs in smoking-related diseases

MicroRNA	Target group	Expression	Target gene	Function	Model	Sample size /cell line	Citation
miR-21	Smokers	Downregulated	-	Protective immune response	Human	39	52
miR-1180	Smokers	Upregulated	-	Modulate inflammatory signaling via CRP and IL-6	Human	283	53
miR-155, miR-21	Atherosclerosis	Upregulated	VCAM-1, MCP1, ICAM-1, gp91phox and p22phox	Increased vascular inflammation and NADPH oxidase expression	ApoE KO mice	-	54
miR-126	Atherosclerosis	Downregulated	VCAM-1, MCP1, ICAM-1, gp91phox and p22phox	Increased vascular inflammation and NADPH oxidase expression	ApoE KO mice	-	54
miR-21	COPD	Up regulated	16HBE cells	Inhibited autophagy activity and decreased apoptosis	C57BL/6	-	55
miR-200c-3p, miR-141-3p, miR-146a-5p	Cell Culture and CS Exposure	Up regulation	HDGF, EPHA2, PGK1, GNA13, XPOT, TUBB3, IFIT1, CFL2, ISG15, SPATS2L, IFIT3, ICAM1, PTGS2, LAMC2	Activation of NRF2 and actin-cytoskeleton signaling, and repression of protein kinase A signaling	In vitro	H358	56
miR-148a-3p , miR-146b-5p	Cell Culture and CS Exposure	Down regulated	DECR1, UMPS, UHRF1, SQSTM1, SLC38A2, GPRC5A, VAV2, POFUT1, YWHAB, SORD	Activation of NRF2 and actin-cytoskeleton signaling, and repression of protein kinase A signaling	In vitro	H358	56
miR-10b-5p, miR-183-5p, miR-1271-5p, miR-204-5p, miR-99b-5p, miR-296-5p, miR-193a-3p	CS and Chewing Tobacco in Esophageal Epithelial Cells	Up regulated	KLF4, ESCC, HOXA5, FOXM1, Claudin 11, Caudal-related homeobox, ERBB4	Promotes migration and metastasis, Inhibits invasion and epithelial-mesenchymal Transition, Increases proliferation	In vitro	Het-1A-Smoke cells	57
miR-195	COPD	Down regulation	PHLPP2	Regulates	Human	28	58

MicroRNA	Target group	Expression	Target gene	Function	Model	Sample size /cell line	Citation
				Akt signaling via suppressing PHLPP2			
miR-3202	COPD	Up regulated	FAIM2	Inhibited TNF-α and INF-γ levels, Inhibited HBE cells apoptosis	Human	60	59
miR-150	COPD	Down regulation	p53 NF-ḰB	Up regulation of miR-150 protect BEAS-2B cells from CSE induced apoptosis	In vivo	-	60
miR-218	COPD	Down regulation	MUC5AC, TNFR1	Regulates CSE-induced MUC5AC hyper-production and inflammatio n	Human	41	61
miR-31, miR-155	COPD	Up regulation		Inflammator y parameters	In vivo, Human	12	62
miR-218, let-7c	COPD	Down regulation		inflammator y parameters	In vivo, Human	12	62
miR-101, miR-486, miR-181b, miR-1301	Neck and head squamous cell carcinoma	Up regulation		Tumor stage, metastasis, anatomic site, and patient survival	human	145	63
Mir-181c	COPD	Down regulation	CCN1	Decreased the inflammator y response, neutrophil infiltration, ROS generation, and inflammator y cytokines	In vivo, human	34	64
miR-124, miR-21	Chronic exposure to CS	Up regulation		Involve in metabolis, cell communicati on, and nucleic acid metabolism	In vitro	H292	65
miR-124, miR-374a, miR-204, miR-155	Chronic exposure to CS	Down regulation		Involve in metabolism, cell communicati on, and nucleic acid metabolism	In vitro	H292	65
miR-146a	COPD	Down regulation		involved in epithelial fibroblast communicati on	In vitro	PHLFs	66

MicroRNA	Target group	Expression	Target gene	Function	Model	Sample size /cell line	Citation
				and negatively regulates epithelial-derived IL-1α induction of IL-8			
let-7f	Ischaemia-induced neovascularization after CS exposure	Up regulation	ALK5	Activation of the antiangiogenic TGF-b/ALK5 pathway	In vivo, in vitro	TGF-b/ALK5 pathway	67
miR-149-3p	COPD	Down regulation	Toll-like receptor-4	Increase the inflammatory response	In vitro	THP-1	68
let-7c	HBE cell transformation	Down regulation	c-Myc	Involve in HBE cell transformation	In vitro	Human bronchial epithelial	69
miR-96	Chronic CS exposure	Up regulation	Antioxidant gene sulfiredoxin 1 and FOXO3a	Role the AhR in regulating lung miRNA	In vivo	-	70
miR-146a/b and miR-182	lung tissue compared with CS	Up regulation	THS2.2	Exposure to THS2.2 did not result in effects similar to those observed upon exposure	In vivo	-	71
miR-126-3p	COPD	Down regulation	-	Apoptosis and senescence of EPCs	Human	358	72
miR-34a	COPD	Up regulation		Represents reduced numbers of EPCs in blood cell	Human	358	72
miR-29b-3; miR-29b-3p	Cardiorenal fibrosis	Down regulation	-	Renal tissue injury and promotes accelerated cardiac	In vivo	-	73
miR-21	Coronaryarter disease	Down regulation	IL-12p35	Attenuated the IL-12 proinflammatory axis	Human	330	74
hsa-miR-1914-3p, hsa-miR-4470, hsa-miR-4327, hsa-miR-4665-3p, hsa-miR-548q, hsa-miR-4673, hsa-miR-550b-2-5p, hsa-miR-6165, hsa-miR-6074, hsa-miR-939-5p	Rectal Cancer	Up regulation		CIMP high and MSI tumor molecular phenotype	Human	206	75

MicroRNA	Target group	Expression	Target gene	Function	Model	Sample size /cell line	Citation
miR-15a, miR-182,miR-30, miR-804	CS-exposed mice	Down regulation		Involved in cell proliferation, apoptosis, inflammation, epithelial-mesenchymal transition, invasion, oncogene inhibition, and intercellular adhesion	In vivo		76
miR-218	the malignant transformation of HBE cells induced via CS extract	Down regulation	HBE cells	CCAT1 induces an altered cell cycle transition via BMI1 and provides a new mechanism for CSE-induced	In vivo		77
hsa-miR-20a	COPD	Down regulation	rs6435156 CNT and rs1048829 GNT variants in BMPR2	Binding with hsa-miR-20a, thus leading to downregulated BMPR2 expression in lung epithelial and immune cells	Human	594	78
miR-107, miR-1202, miR-1268a, miR-140-3p, miR-15a-5p, miR-16-5p, miR-17-5p, miR-185-5p, miR-19b-3p, miR-19a-3p, miR-20a-5p, miR-20b-5p, miR-25-3p, miR-4271, miR-4298, miR-451a, miR-4738-3p, miR-5196-5p, miR-6076, miR-6085, miR-6124, miR-6127, miR-6165, miR-93-5p	Middle-aged smokers and healthy young adult smokers	Up regulation		Hematologic cancers, such as lymphoma, leukemia	human	28	79
let-7d-3p, miR-1227-5p, miR-1587, miR-3135b, miR-3940-5p, miR-4530, miR-485-3p, miR-494, miR-572,	Healthy young adult smokers and middle-aged smokers	Down regulation	-	Hematologic cancers, such as lymphoma, leukemia	human	28	79

MicroRNA	Target group	Expression	Target gene	Function	Model	Sample size /cell line	Citation
miR-574-3p, miR-6068							
Mir-146a	Cells stimulated by CS extract	Down regulation	IL-8, FAF-2, monocyte chemotactic protein-1	Decrease the expression of inflammatory factors	In vitro	A549	80
miR-101-3p	Esophageal squamous cell carcinoma	Down regulation	COX-2	Cell proliferation,	In vitro	Eca109	81
miR-217	HBE cells induced by CS extract	Up regulation	lncRNA MALAT1	Inhibits the epithelial mesenchymal transition in the malignant transformation of HBE cells	In vitro	HBE	82
miR-217	Esophageal Adenocarcinogenesis	Down regulation	kallikrein 7 (KLK7)	Increased proliferation, invasion and tumorigenicity of EACC	In vivo		83
miR-154-5p, let-7i-3p	CS and Lung Cancer	Down regulation	NSCLC		human	20	84
miR-218	CS extract	Down regulation	EZH2-mediated H3K27 trimethylation	Inhibits the CSE-induced acquisition of CSC-like properties and neoplastic transformation of HBE cells	In vitro	HBE cells	85
Mir-1, mir-138, mir153	lung adenocarcinoma	Down regulation, down regulation, and up regulation respectively		survival	human	94	19
miR-338-3p, miR-145-5p, and miR-3620-3p	COPD	Up regulation		Inflammatory mediators, regulation of proliferation and oxidative stress	Human	19	86
OTR mRNA expression	CS in pregnant women	Up regulation	Oxytocin receptors	Increases oxytocin sensitivity of pregnant myometrium by increasing OTR levels	Human	6	87
Mir-21	Esophageal cancer cells	Up regulation	EMT	Oncogenic roles	In vitro	EC9706	88
miR-146a	lung fibroblasts	Up regulation	Cox2	Attenuates inflammation in response to respiratory toxicants	In vitro	Relb+/+and Relb-/−	89

MicroRNA	Target group	Expression	Target gene	Function	Model	Sample size /cell line	Citation
miR-200c	CS Extract	Down regulation	NF-κB	Blocking NF-κB and enhancement of IL-6	In vitro	HBE cells	90
miR-331-3p, miR-374b, miR-221, let-7e, let-7g, miR-301a, miR-30c, miR-335, miR-26a, miR-185, miR-30b, miR-374a, let-7b, miR-451, miR-27a, miR-29a, miR-26b, miR-191, miR-199a-3p, miR-223, miR-425, miR-328, miR-21, let-7d, miR-19b, miR-19a, miR-106b, miR-186, miR-93, miR-454, miR-17, miR-345, miR-20b, miR-16, miR-20a, miR-24, miR-106a, miR-126, miR-25, miR-126,miR-923, miR-188-5p miR-195, miR-92a,	Smokers and non-smokers	Up regulation	-	-	Human	11	91
microRNA-135b	CS–induced Inflammation	Up regulation	IL-1R1	Activation of Caspase-1, the IL-1R1 downstream activator of IL-1b leading to suppressed synthesis of the active	In vivo		92
miR-487b	Pulmonary carcinogenesis	down regulation	SUZ12, BMI1, WNT5A, MYC, KRAS	DNA methylation, de novo nucleosome occupancy, and decreased H2AZ ,TCF1 levels	Human	51	93
miR-145	CS condensate	Down regulation	MMP-2	Promoting a phenotype that enhance oral cancer migration and sheds new light	In vitro	fibroblast cells	94

MicroRNA	Target group	Expression	Target gene	Function	Model	Sample size /cell line	Citation
miR-452	Human Alveolar Macrophages	Up regulation	MMP12	Reduced expression	Human	16	95
hsa-miR-7, hsa-miR-18b, hsa-miR-137, hsa-miR-30d, hsa-miR-505, hsa-miR-374b, hsa-miR-543, hsamiR-1305, hsa-miR-3198, hsa-miR-1914, hsa-miR-1973, hsa-miR-3659	CS	Up regulation		Healing delay in CS	In vitro	Human mesenchymal stem cells and periodontal ligament derived stem cells	16
hsa-miR-210, hsa-miR-762, hsa-miR-1915, and hsa-miR-4281	CS	Down regulation		Stem cell-associated healing delay in CS	In vitro	Human mesenchymal stem cells and periodontal ligament-derived stem cells	16
miR-92b, miR-700 , miR-668	Interstitial fibrosis	Up regulation		Response to toxin/drug,' 'oxidoreductase activity,' 'inflammatory response,' 'cell adhesion.' 'extracellular matrix organization' and 'fibroblast proliferation	C57 mice	-	96
let-7e, miR-350, miR-142-5p, miR191, miR-19a	Interstitial fibrosis	Down regulation		Response to toxin/drug,' 'oxidoreductase activity,' 'inflammatory response,' 'cell adhesion.' 'extracellular matrix organization' and 'fibroblast proliferation	C57 mice	-	96
miR-128, miR-125b-5p, miR-30e, miR-20b	Smoking-related interstitial fibrosis	Up regulation			C57 mice	-	97
miR-365, miR-1267, miR-944, miR-340, let-7a-2-3p, miR-4513,	Smoking induces in human spermatozoa	Up regulation	-	Harmful phenotypes can be induced in progeny of	Human	6	98

MicroRNA	Target group	Expression	Target gene	Function	Model	Sample size /cell line	Citation
miR-1246, miR-576-3p, miR-576-5p, miR-30c, miR-933, miR-7, miR-1270, miR-1285, miR-509-5p, miR-146b-3p, miR-519d, miR-3145-3p, miR-4748, miR-550a, miR-550b, miR-574-5p, miR-3145-5p, miR-146b-5p, miR-634, miR-129-3p, miR-652, miR-4723-5p				smokers			
mir-34b, mir-345, mir-466, mir-421, mir-450b, mir-469	CS in mouse lung	Down regulated		Trigger the CS-related carcinogenesis process	Mice	-	8
let-7 family	CS in mouse lung	Down regulation		Oncogene activation, inhibition of oncosuppressor genes, recruitment of undifferentiated stem cells, inflammation, inhibition of gap-junctional intercellular communications, angiogenesis, invasiveness, and metastatization	In vitro	-	99
miR-16, miR-146a, miR-21	Maternal CS during pregnancy	Down regulated	TCL-1	Elicit some of its downstream effects via alteration of miRNA expression	Human	25	100

MicroRNA	Target group	Expression	Target gene	Function	Model	Sample size /cell line	Citation
mir-218	Smoking-induced in human airway epithelium	Down regulated	MAFG	Modulate the airway epithelial gene expression response to CS	Human	10	101

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extended periods are urgently needed. Third, the heterogeneity of smoking-related diseases necessitatesthe identification of context-dependent miRNA signatures; for instance, distinguishing between the roles of the same miRNA in different tissues (e.g., miR-124's opposing effects in the gut versus the liver) is crucial for developing safe targeted therapies. Fourth, sex-specific responses to CS exposure, as exemplified by the differential expression of the miR-199a/214 cluster in female versus male brains following nicotine self-administration, highlight the need for stratified approaches in both biomarker development and therapeutic interventions. Fifth, the interplay between smoking-induced miRNA dysregulation and other epigenetic layers (e.g., DNA methylation, histone modifications, and long non-coding RNAs) remains an underexplored area with significant potential for uncovering novel regulatory networks. Finally, advances in delivery technologies particularly nanoparticle-based systems and cell-specific targeting moieties will be pivotal in translating the therapeutic promise of miRNA modulation into clinical practice. Addressing these unanswered questions through well-designed preclinical and clinical studies will not only deepen our understanding of miRNA-mediated pathophysiology but also pave the way for personalized preventive and therapeutic strategies to mitigate the devastating health consequences of tobacco use

Conclusion

This comprehensive review establishes miRNAs as critical molecular intermediaries in the pathogenic cascade initiated by CS exposure. The evidence unequivocally demonstrates that CS induces profound and tissue-specific alterations in the miRNome through multiple mechanisms, including oxidative stress, direct DNA damage, and epigenetic reprogramming. These alterations are not merely epiphenomena but actively contribute to disease pathogenesis. Notably, the downregulation of miR-1 via a VEGF-driven pathway in pulmonary endothelial cells promotes angiogenic activation and field cancerization, establishing a direct mechanistic link to lung cancer, which accounts for approximately 85% of smoking-related malignancies. Similarly, the miR-124/STAT3 axis mediates the dichotomous effects of nicotine in inflammatory bowel diseases ,protective in ulcerative colitis (Th2-dominant) yet exacerbating in Crohn's disease (Th1-dominant), while dysregulation of miR-128-3p and miR-19a-3p implicates miRNA networks in smoking-associated psychiatric disorders, including depression and suicidal ideation. Furthermore, systemic consequences are evident in cardiovascular diseases (miR-34a, miR-126-3p), dermatological conditions (ferroptosis regulation by 17 miRNAs), and chronic respiratory diseases such as COPD and IPF, where smoke-induced shifts in alveolar macrophage miRNA signatures (e.g., miR-34a-5p, miR-16-5p, and miR-223-5p) toward pathological profiles highlight their role as risk factors and disease modifiers. The recognition that CS induces a reproducible and partially reversible miRNA signature (as demonstrated by the Rotterdam Study) has substantial translational implications. Circulating miRNAs hold promise as non-invasive biomarkers for early detection, risk stratification, and monitoring of treatment response or smoking cessation efficacy. Concurrently, preclinical evidence supports the therapeutic potential of miRNA mimics or inhibitors (antimiRs) in ameliorating smoke-induced pathology; however, several critical challenges impede their clinical translation. These include the lack of standardized protocols for miRNA isolation and quantification, poor tissue specificity and immunogenicity of current delivery systems, and the inherent complexity of miRNA-mRNA networks, wherein a single miRNA can modulate hundreds of targets, increasing the risk of off-target effects.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this manuscript. All authors contributed to the manuscript and approved the final version.

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