Advances in the Study of Cigar Smoke-Mediated Lung and Intestinal Injuries, Gut Microbiota Alterations, and Underlying Mechanisms

Lin Li[1], Jie Gao[1], Chunhuan Yuan[1], Yantiao Yang[1], Yunhan Huang[1], Wan Yang[1], Yuan He[2,*]

[1]College of Life Sciences, Zhengzhou Normal University, Zhengzhou, Henan, China

[2]Cigar Innovation Center, College of Tobacco Science and Engineering, Zhengzhou University of Light Industry, Zhengzhou, Henan, China

** Corresponding Author*

Abstract: This review discusses the mechanisms underlying cigar smoke-induced lung and intestinal injuries and associated alterations in gut microbiota. Cigar smoke, as a harmful environmental factor, exerts multifaceted effects on human health. In terms of pulmonary damage, harmful components within the smoke can trigger inflammation, oxidative stress responses, and lead to decline in lung function, thereby elevating the risk of respiratory diseases such as lung cancer. Regarding intestinal health, cigar smoke may affect intestinal function through systemic circulation pathways, resulting in mucosal damage and altered permeability. Moreover, cigar smoke significantly modifies the composition and structure of the gut microbiota. Evidence suggests that changes in gut microbiota could further exacerbate lung and intestinal injuries, forming a vicious cycle. The underlying mechanisms may involve immune response dysregulation and metabolic disturbances. This review provides an in-depth analysis of the pathways through which cigar smoke mediates pulmonary and intestinal damage, as well as alterations in gut microbiota, offering new insights and strategies for the prevention and treatment of related diseases.

Keywords: Cigar Smoke; Lung Injury; Intestinal Injury; Gut Microbiota

1. Introduction

In contemporary society, with the continuous improvement of living standards and the growing emphasis on health, unhealthy lifestyle habits have attracted increasing attention from researchers and the general public. Smoking, as one of the most prevalent unhealthy lifestyle habits globally, poses significant and far-reaching risks to human health. Among various tobacco products, cigars occupy a unique position in the field of tobacco consumption. Unlike cigarettes, cigars are typically larger, contain more tobacco, and are often smoked less frequently but for longer durations, releasing a complex mixture of smoke containing multiple harmful substances. Long-term exposure to cigar smoke, whether through active smoking or secondhand smoke, may have profound and detrimental effects on multiple systems of the human body.

In recent years, research on the health impacts of cigar smoke has gradually expanded beyond the traditionally recognized respiratory system to include the gastrointestinal system and the gut microbiota, which plays a crucial role in maintaining overall health. The exploration of the mechanisms underlying cigar smoke-induced lung and intestinal injuries, as well as the associated alterations in gut microbiota, is of great significance for conducting comprehensive health risk assessments of cigar smoking and developing targeted intervention strategies. This review synthesizes the current findings from relevant studies, systematically discussing the specific effects of cigar smoke on lung and intestinal damage, the changes in gut microbiota, and the complex interrelationships and mechanisms among these processes, with the aim of providing a valuable reference for future research and clinical practice in this field.

2. Composition and Hazards of Cigar Smoke

2.1 Cigar Smoke Components

Cigar smoke is a highly complex mixture containing thousands of chemical constituents, among which numerous harmful substances have

been identified. These include nicotine, tar, carbon monoxide, polycyclic aromatic hydrocarbons (PAHs), heavy metals (such as lead, cadmium, and arsenic), and various volatile organic compounds[1]. Nicotine, a well-known addictive compound, not only causes physical dependence but also can induce a series of adverse effects on the cardiovascular and nervous systems, such as increasing heart rate, elevating blood pressure, and disrupting neurotransmitter balance. Tar, a sticky substance formed during the combustion of tobacco, is a mixture of many carcinogens, including benzo[a] pyrene, which is recognized as a strong carcinogen that can damage DNA and increase the risk of cancer. Carbon monoxide, a colorless and odorless gas, has a high affinity for hemoglobin in the blood, forming carboxyhemoglobin, which impairs the oxygen-carrying capacity of the blood, leading to tissue hypoxia and affecting the normal function of various organs. PAHs and heavy metals also exhibit strong carcinogenic and toxic potentials, accumulating in the body over time and causing long-term damage to cells and tissues.

2.2 Health Hazards of Cigar Smoke

The health hazards of prolonged exposure to cigar smoke are widespread and severe, affecting multiple systems of the body. In the respiratory system, it significantly elevates the risks of developing lung cancer, chronic obstructive pulmonary disease (COPD), and other respiratory diseases. Lung cancer remains one of the leading causes of cancer-related deaths worldwide, and in China, its incidence and mortality have shown a continuous upward trend over the past few decades. The etiology of lung cancer is complex, involving multiple factors, but long-term smoking, including cigar smoking, is widely recognized as one of the most important high-risk factors[2]. COPD, a heterogeneous disease characterized by persistent airflow limitation, is mainly associated with smoking, although it is worth noting that less than a quarter of smokers develop COPD, and many cases have no clear identifiable cause, highlighting the complexity of the disease.

Beyond the respiratory system, cigar smoke also poses significant threats to other systems. For example, recent studies have pointed out a close relationship between gut microbiota, their metabolites, and cardiovascular diseases[3], suggesting that cigar smoke may indirectly affect cardiovascular health through its impact on the gut microbiota. In addition, a growing body of evidence indicates that cigar smoke can adversely influence gut health, inducing intestinal inflammation, causing mucosal damage, and disrupting the normal physiological function of the intestine, which in turn affects nutrient absorption and overall health.

3. Cigar Smoke-Mediated Lung Damage

3.1 Pathological Changes in Lung Tissue

Extensive research has demonstrated that cigar smoke can induce a series of pathological changes in lung tissues. Upon exposure to cigar smoke, the lung tissues initiate inflammatory responses, which over time can lead to structural alterations such as alveolar wall thickening and interstitial fibrosis[4]. These changes disrupt the normal architecture of the lung, reducing the surface area available for gas exchange and impairing lung function. Chronic exposure to cigar smoke can also lead to the development of emphysema[5], a condition characterized by the destruction of the alveoli, resulting in the loss of elastic recoil of the lung tissue and further deterioration of respiratory function. These histopathological alterations collectively contribute to the progressive decline in lung function and the development of various respiratory diseases. Moreover, cigar smoke–induced pulmonary histopathological changes may be closely related to airway remodeling. Similar to the effects of cigarette smoke, long-term exposure to cigar smoke may promote extracellular matrix deposition by activating abnormal proliferation and differentiation of pulmonary fibroblasts, thereby further aggravating the degree of lung tissue fibrosis[6]. Studies have shown that cigarette smoke extract can significantly promote the growth of rat pulmonary fibroblasts, whereas the higher concentrations of tar, polycyclic aromatic hydrocarbons (PAHs), and other deleterious constituents present in cigar smoke may exert a stronger effect by activating lung fibroblast–related signaling pathways, notably the TGF-β/Smad pathway, thus accelerating the progression of pulmonary interstitial fibrosis[6]. At the same time, in the context of pulmonary infection, cigar smoke exposure may also increase the risk of severe pneumonia. As Zeng et al. reported in cigarette smoke studies, smoke

constituents can suppress the ability of pulmonary immune cells to "lear pathogenic bacteria; if cigar smoke–exposed indi"iduals are concurrently infected with pathogens such as Klebsiella pneumoniae, this may, similar to the effect of cigarette smoke in combination with pathogens, further aggravate inflammatory injury in lung tissue, promote airway remodeling–related pathological changes, and form a vicious cycle of "smoke injury–infection aggravation–tissue remodeling."[7]

3.2 Imbalance of Cytokine Expression

Cigar smoke has been found to trigger dysregulation of cytokine expression within the lungs, which plays a crucial role in the pathogenesis of lung injury. Studies conducted by Rao et al. observed that exposure to cigar smoke leads to increased expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), while simultaneously decreasing the levels of anti-inflammatory cytokines like interleukin-10 (IL-10). This imbalance between pro-inflammatory and anti-inflammatory cytokines creates a pro-inflammatory microenvironment in the lungs, which exacerbates inflammatory responses, promotes the recruitment and activation of immune cells, and ultimately leads to further lung tissue injury. Notably, the cytokine imbalance induced by cigar smoke may also influence the progression of lung injury by regulating epigenetic modifications. Some studies have indicated that cigarette smoke can alter genome-wide DNA methylation levels, thereby affecting the expression of inflammation-related genes and modulating airway inflammatory responses[8]. It is hypothesized that cigar smoke may act through similar mechanisms, leading to decreased methylation in the promoter regions of pro-inflammatory cytokines (TNF-α, IL-1β, etc.) and thus upregulating their expression, while increasing methylation of the IL-10 promoter and suppressing its expression. This would further exacerbate cytokine imbalance and provide a molecular basis for the sustained progression of lung injury[8].

3.3 Oxidative Stress and Antioxidant Imbalance

Oxidative stress is another key mechanism through which cigar smoke mediates lung damage. According to research by Wiegmann et al., the harmful components in cigar smoke can induce oxidative stress in lung tissues, which is characterized by an increase in the production of reactive oxygen species (ROS) and a decrease in the activity of antioxidant enzymes. Reactive oxygen species (ROS) are highly reactive entities capable of causing direct damage to vital cellular structures, including DNA, proteins, and lipids, thereby resulting in impaired cell function and programmed cell death. The pulmonary antioxidant defense mechanisms—comprising enzymes like superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px)—are crucial for scavenging ROS and preserving the redox homeostasis essential for cellular integrity. However, cigar smoke can disrupt this balance, significantly reducing the activity of these antioxidant enzymes, thereby allowing excessive ROS to accumulate and cause oxidative damage to lung cells, further contributing to lung injury and the development of respiratory diseases.

3.4 Activation and Recruitment of Immune Cells

Emerging evidence suggests that cigar smoke can activate and recruit various immune cells in the lungs, which participate in the inflammatory process and contribute to lung damage. Upon exposure to cigar smoke, pulmonary immune cells such as macrophages and neutrophils are activated[7]. These activated immune cells migrate to the sites of injury in the lung tissues and secrete a variety of inflammatory mediators, including cytokines, chemokines, and reactive oxygen species, which further amplify the inflammatory response and cause damage to surrounding tissues. The continuous activation and infiltration of immune cells can lead to chronic inflammation, which is a key factor in the progression of many chronic lung diseases induced by cigar smoke. Further studies have found that immune cells activated by cigar smoke may also be involved in mediating lung injury through synergistic interactions with pathogen-associated molecular patterns (PAMPs). When exposure to cigar smoke is combined with a viral mimic such as poly(I:C), it may, similar to cigarette smoke in combination with poly(I:C), activate pulmonary immune cells (e.g., macrophages and neutrophils) to release greater amounts of inflammatory mediators, thereby not only exacerbating the inflammatory response but also potentially compromising the

integrity of the airway epithelial barrier. This would further promote immune cell infiltration and activation, create a cascade amplification effect, and accelerate the pathological progression of lung injury[9]. Meanwhile, these activated immune cells may also contribute to the degradation of the lung tissue extracellular matrix by releasing matrix metalloproteinases (MMPs) and other substances, participating in pathological changes such as emphysema and pulmonary fibrosis, thereby further highlighting the pivotal role of immune cells in cigar smoke–mediated lung injury[10].

4. Cigar Smoke-Mediated Intestinal Damage

4.1 Disruption of Intestinal Mucosal Barrier Function

The intestinal mucosal barrier is a critical defense mechanism that separates the intestinal lumen from the internal environment, preventing the entry of harmful substances such as bacteria, toxins, and undigested food particles into the systemic circulation. Cigar smoke has been shown to impair the integrity of this barrier, increasing intestinal mucosal permeability. This effect may be exerted through two main pathways: the direct toxic impact of smoke constituents on intestinal epithelial cells, causing damage to their structure and function; and indirect pathways involving alterations in the composition and function of the gut microbiota. Once the mucosal barrier is disrupted, harmful substances and bacteria can translocate into the bloodstream, triggering systemic inflammatory responses and causing tissue injury in various organs, including the lung. From a molecular mechanism perspective, the disruption of the intestinal mucosal barrier by cigar smoke may be closely related to abnormal expression of epithelial tight junction proteins. Similar to the effects of cigarette smoke on the airway epithelial barrier, harmful constituents in cigar smoke may reach the intestine via systemic circulation and suppress the expression of tight junction proteins in intestinal epithelial cells (such as occludin and ZO-1), thereby disrupting intercellular connections and increasing intestinal mucosal permeability[9]. In addition, cigar smoke may activate oxidative stress signaling pathways in intestinal epithelial cells, notably the Nrf2/HO-1 pathway. Although short-term activation may initiate cytoprotective mechanisms, prolonged exposure could lead to either excessive activation or inactivation of this pathway, further exacerbating intestinal epithelial cell injury, weakening mucosal barrier function, and creating favorable conditions for the translocation of harmful substances and bacteria, thereby indirectly exacerbating lung and other organ injuries[6].

4.2 Intestinal Inflammation and Gut Microbial Dysbiosis

Studies have demonstrated that cigar smoke can induce intestinal inflammation, which is characterized by mucosal hyperemia, edema, and infiltration of inflammatory cells such as neutrophils and lymphocytes. This inflammatory response impairs intestinal function, leading to the occurrence of symptoms such as diarrhea, abdominal pain, and malabsorption. Additionally, Gui et al. reported that cigar smoke can significantly affect the structure and function of the gut microbiota, leading to dysbiosis, which refers to an imbalance in the composition and relative abundance of the microbial community. This imbalance can further promote intestinal inflammation and injury, as the normal protective functions of the gut microbiota, such as inhibiting the growth of pathogenic bacteria and maintaining mucosal integrity, are compromised. The interaction between intestinal inflammation and gut microbial dysbiosis forms a mutually reinforcing cycle that exacerbates intestinal damage induced by cigar smoke.

5. Effects of Cigar Smoke on Gut Microbiota

5.1 Alterations in Microbial Composition

The gut microbiota is a complex and dynamic community of microorganisms that resides in the gastrointestinal tract and plays a crucial role in maintaining host health. Research has shown that exposure to cigar smoke can significantly alter the composition of the gut microbiota. Specifically, it reduces gut microbial diversity, which is generally considered an indicator of a healthy microbial ecosystem. In addition, cigar smoke exposure causes shifts in the abundance of specific bacterial populations. Studies by Chunxi et al. observed a decrease in the levels of beneficial bacteria such as Bifidobacterium and Lactobacillus, which are known for their roles in maintaining intestinal homeostasis, enhancing immune function, and producing beneficial metabolites. Conversely, there is an increased presence of potentially pathogenic bacteria like

Escherichia coli and Clostridium species, which can produce toxins, induce inflammation, and contribute to the development of various intestinal diseases.

5.2 Changes in Microbial Function

In addition to altering the composition of the gut microbiota, cigar smoke also impacts their metabolic activities and functional capabilities. The gut microbiota plays key roles in various metabolic processes, including the metabolism of carbohydrates, fats, and proteins, as well as the synthesis of vitamins and other bioactive substances. Exposure to cigar smoke may interfere with these metabolic pathways, leading to changes in the production of metabolites that are vital for intestinal and systemic health. For example, the production of short-chain fatty acids (SCFAs), which are important metabolites with anti-inflammatory, energy-providing, and barrier-protective functions, may be reduced. These changes in microbial function can further contribute to the development of intestinal dysfunction and systemic diseases associated with cigar smoke exposure.

6. Mechanisms Linking Gut Microbiota Alterations to Lung and Intestinal Damage Induced by Cigar Smoke

The interplay between cigar smoke-induced gut microbiota dysbiosis and organ damage involves intricate biological pathways, with the gut-lung axis serving as a central communication hub. This bidirectional network, combined with immune dysregulation and metabolic disturbances, creates a cascade that amplifies lung and intestinal injuries. Understanding these mechanisms is critical for unraveling the systemic impact of cigar smoke and developing targeted interventions.

6.1 Gut-Lung Axis

The gut-lung axis represents a dynamic bidirectional communication system that connects the intestinal microbiota to pulmonary health, mediated by immune, metabolic, and neuroendocrine pathways [. This axis ensures that changes in one organ's microbial community or physiological state can profoundly affect the other. In the context of cigar smoke exposure, this cross-talk becomes disrupted, exacerbating damage in both systems.

Cigar smoke-induced gut dysbiosis alters the balance of microbial species in the intestine, which in turn modulates immune cell activity and metabolite production. These changes can be transmitted to the lungs via systemic circulation. For instance, dysbiosis increases intestinal permeability—a phenomenon often referred to as "leaky gut"—allowing microbial components (such as lipopolysaccharides from gram-negative bacteria) and toxins to enter the bloodstream[13, 14]. Once in circulation, these substances trigger immune responses in the lung, activating resident macrophages and neutrophils, and inducing pro-inflammatory cytokine release. Over time, this leads to chronic pulmonary inflammation and tissue remodeling, such as interstitial fibrosis or emphysema.

Conversely, the lung can signal back to the gut. Inflammatory mediators released during pulmonary injury (e.g., TNF-α, IL-6) travel to the intestine via the bloodstream, where they disrupt epithelial barrier function and alter gut motility. This creates a feedback loop: lung damage worsens gut dysbiosis, which then further impairs lung health, perpetuating a cycle of injury. The gut-lung axis thus acts as a critical mediator through which cigar smoke's local effects on the gut amplify its destructive impact on the respiratory system.

6.2 Impact of Gut Microbiota on Pulmonary Health

The gut microbiota exerts direct and indirect influences on pulmonary health through the production of metabolites and modulation of immune responses. Beneficial bacteria, such as Bifidobacterium and Lactobacillus, produce short-chain fatty acids (SCFAs)—including acetate, propionate, and butyrate—via fermentation of dietary fiber[15, 16]. SCFAs play a pivotal role in maintaining pulmonary homeostasis: they strengthen the intestinal barrier, reduce systemic inflammation by inhibiting pro-inflammatory cytokine production, and enhance the activity of regulatory T cells, which suppress excessive immune responses in the lung.

In contrast, cigar smoke-induced dysbiosis reduces SCFA-producing bacteria, diminishing these protective effects. Simultaneously, the overgrowth of pathogenic species (e.g., Escherichia coli, Clostridium) leads to increased production of harmful metabolites, such as endotoxins and reactive oxygen species. These substances, when released into the bloodstream, promote oxidative stress and inflammation in the

lung. For example, endotoxins activate toll-like receptors on pulmonary immune cells, triggering a cascade that results in neutrophil infiltration and tissue damage. Over time, this chronic inflammatory state contributes to the development of respiratory diseases like COPD and lung cancer, where persistent immune activation drives tissue destruction and malignant transformation.

Additionally, gut microbiota metabolites can influence pulmonary epithelial cell function. SCFAs, for instance, support the integrity of the alveolar epithelium, enhancing its ability to resist oxidative damage from cigar smoke components. Their depletion, due to dysbiosis, weakens this defense, making the lung more susceptible to injury.

6.3 Bidirectional Influence of Pulmonary Damage on the Gut

While the gut-lung axis is often discussed in terms of gut-to-lung signaling, pulmonary damage can also significantly disrupt intestinal homeostasis, creating a reciprocal cycle. Lung diseases induced by cigar smoke—such as COPD—trigger systemic changes that directly impact the gut.

One key mechanism is hypoxia. COPD and advanced lung disease reduce oxygen exchange, leading to systemic hypoxia. This low-oxygen environment impairs intestinal blood flow and oxygenation, damaging the intestinal epithelium and altering the gut microbiota composition[17, 18]. Hypoxia also stimulates the release of stress hormones (e.g., cortisol) via the hypothalamic-pituitary-adrenal axis, which further disrupts gut motility and barrier function. For example, cortisol increases intestinal permeability and promotes the growth of pathogenic bacteria, exacerbating dysbiosis.

Pulmonary inflammation also contributes to gut dysfunction. Inflammatory mediators (e.g., TNF-α, IL-1β) released during lung injury enter the bloodstream and reach the intestine, where they induce mucosal inflammation, edema, and immune cell infiltration. This inflammation impairs nutrient absorption and reduces the production of protective mucus, creating an environment that favors pathogenic bacterial overgrowth.

Furthermore, the gut-brain axis—another arm of microbial communication—plays a role. Pulmonary damage activates neural pathways that signal to the central nervous system, which in turn modulates gut function via the vagus nerve. This neuroendocrine cross-talk can alter intestinal motility, secretion, and immune responses, further promoting dysbiosis and intestinal injury. Collectively, these processes demonstrate that pulmonary damage induced by cigar smoke is not isolated but propagates systemically, worsening gut health and reinforcing the cycle of organ injury.

6.4 Immune Regulation and Metabolite Effects

Gut microbiota are critical regulators of both innate and adaptive immunity, and their dysregulation under cigar smoke exposure disrupts immune homeostasis, amplifying tissue damage[19]. The microbiota educate immune cells (e.g., macrophages, dendritic cells, T cells) in the gut-associated lymphoid tissue, shaping their response to pathogens and environmental insults. In a healthy state, this education promotes tolerance to beneficial microbes while enabling robust responses to threats. However, cigar smoke-induced dysbiosis skews this balance, leading to either hyperactive or suppressed immune function.

For example, pathogenic bacteria overgrowth in the gut can prime macrophages to become pro-inflammatory. When these activated macrophages migrate to the lung (via circulation), they respond excessively to cigar smoke components, releasing high levels of ROS and cytokines that damage alveolar tissue. Conversely, reduced levels of beneficial bacteria (e.g., Lactobacillus) diminish the production of anti-inflammatory cytokines like IL-10, weakening immune regulatory mechanisms and allowing inflammation to persist.

Metabolites produced by the gut microbiota are equally influential. SCFAs, as noted, have anti-inflammatory effects, but their production is reduced in dysbiosis. Other metabolites, such as bile acids, are also disrupted. Gut bacteria metabolize primary bile acids into secondary bile acids, which regulate lipid metabolism and immune function. Cigar smoke exposure alters this process, leading to abnormal bile acid accumulation, which can induce oxidative stress in both the gut and lung.

Additionally, microbial metabolites influence the activity of immune cells in the intestinal mucosa. For instance, butyrate—a key SCFA—supports the proliferation of regulatory T cells in the gut, which help maintain barrier integrity. Its

depletion, due to dysbiosis, reduces this protection, allowing pathogens to translocate and trigger systemic inflammation. This interplay between immune dysfunction and metabolic imbalance underscores how cigar smoke-induced gut microbiota changes drive both local intestinal injury and distant pulmonary damage.

In summary, the mechanisms linking gut microbiota alterations to lung and intestinal damage induced by cigar smoke are multifaceted, centered on the gut-lung axis, immune dysregulation, and metabolic disturbances. These pathways create a self-perpetuating cycle: cigar smoke disrupts the gut microbiota, which impairs lung health via systemic signals, while pulmonary damage exacerbates gut dysfunction, further worsening microbial imbalance. Targeting these interconnected mechanisms may offer novel strategies to mitigate the harmful effects of cigar smoke on multiple organ systems.

7. Conclusion

This review comprehensively summarizes the current understanding of the deleterious effects of cigar smoke on the pulmonary and gastrointestinal systems, highlighting the key roles of oxidative stress, inflammation, mucosal barrier disruption, and gut microbiota dysbiosis in these processes. The harmful constituents in cigar smoke can directly affect lung cells, provoking inflammatory responses and causing tissue injury, while also impacting the integrity of the intestinal mucosal barrier and altering the composition and function of the gut microbiota. The gut microbiota and its metabolites, through the complex bidirectional communication of the gut-lung axis, further influence lung health, forming a network of interactions that exacerbate the damage caused by cigar smoke.

Understanding these mechanisms provides valuable insights for developing more targeted preventive and therapeutic strategies to mitigate the health risks associated with cigar smoking. Public health initiatives should continue to promote awareness of the harms of cigar smoking and encourage the reduction or cessation of cigar use. Future research endeavors should aim to further elucidate the specific pathways by which cigar smoke influences the lung and gut microbiota, identify key microbial species or metabolites involved in these processes, and explore the potential of targeting the gut microbiota for the prevention and treatment of cigar smoke-related diseases. Such research will contribute to improving our ability to protect public health from the adverse effects of cigar smoke.

Author Contributions

L.L. and J.G. conceptualized the structure and overall design of the manuscript. The initial draft was prepared collaboratively by J.G., C.Y., Y.Y., Y.H.H., and W.Y. Y.H. contributed valuable insights and suggestions throughout the writing process. All authors have reviewed and approved the final version of the manuscript.

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