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Review

Exploring the Ancient Persian/Unani Theory of Connection between Gastrointestinal and Respiratory Tracts: Current Evidence and Future Directions

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Abstract

The theory of connection between respiratory and gastrointestinal systems is a key topic in different types of traditional medicine. In this study, we discussed the history, main concepts of this theory along with related studies and its possible clinical applications. In this regard numerous scattered studies have shown a relationship between upper and lower respiratory disorders and gastrointestinal symptoms. Numerous epidemiologic, pathophysiologic and clinical evidence confirm the interrelationship and integrated functioning of the respiratory and gastrointestinal tracts. It seems that the holistic approach that emphasizes the link between the respiratory and gastrointestinal systems in traditional Persian medicine, is in line with the theory of united mucosa that has been considered in recent years. The interaction between the respiratory and gastrointestinal systems can occur through several mechanisms, including commonalities in embryonic sources, role of identical mediators and receptors, influence of common pathogens in the lungs and gut, similarity of microbiota patterns and changes, and same inflammatory and mucosal responses. We believe that this theory can provide new insight for the approaches to respiratory and gastrointestinal disorders in the light of holistic medical knowledge. Also, further research should be conducted to identify the exact paths and mechanisms of communication between respiratory and gastrointestinal systems.

Keywords: Respiratory system; Digestive system; Gut-Lung axis; Persian medicine; Complementary medicine

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Introduction

The respiratory tract consists of the upper and lower airways, which act as a synchronized unit. The connection between these structures has been noted both in health and disease. This concept points to the connection between inflammations in the bronchial and nasal mucosa in airway disorders such as rhinitis. This was first identified by Galen, an ancient Greek scientist, in the second century. In his work entitled “De usupartium," he observed the effect of the upper airway on the lower airway and described the nose as being a “respiratory instrument." Thenceforth, this concept was repeatedly emphasized by Persian scientists like Ibn Sina (popularly known as Avicenna in the Western world) for many years [1,2] . However, only in the last decade has the idea of an integrated system formed by the upper and lower respiratory structures been truly emphasized. This was initiated at the Allergic Rhinitis and its Impact on Asthma (ARIA) World Health Organization seminar [3,4].

The connection between the upper and lower structures has been confirmed through clinical, pathophysiological, and epidemiological research. While the correlation between upper and lower respiratory diseases has been extensively studied, many ambiguities still exist regarding the connection of these diseases with gastrointestinal (GI) system disorders [5].

There are numerous scattered studies on the relationship between airway disorders and upper and lower GI diseases. For example, it has been suggested that allergic rhinitis (AR) is not just a runny nose and is rarely found in isolation. It may occur with several comorbid conditions that are not limited to the respiratory system. Several studies have shown an association between AR and GI disorders. Prevalence of gastritis was observed among patients without nasal disturbances (14.8%) and those with rhinitis (19.9%), sinusitis (29.4%), or rhinosinusitis (29.7%) [6]. A similar pattern was noted regarding GERD, the prevalence of which was 14.1% in controls and 21.0%, 24.5%, and 31.3% in subjects with rhinitis, sinusitis, and rhinosinusitis, respectively [7]. Recent studies have also confirmed the strong association between gastritis/GERD and nasal disturbances, so that the combination of these two GI diseases was linked to a quadruple increase in the risk of non-allergic rhinitis and sinusitis [8]. Besides, the occurrence of irritable bowel syndrome (IBS) was significantly higher (2.67 times) in patients with seasonal AR [9]. There is compelling evidence suggesting that patients with asthma and AR experience more lower bowel symptoms [9-11] There is also a link between other respiratory diseases, such as sinusitis and asthma, and GI diseases, and vice versa. Some complementary schools of medicine, such as Chinese medicine, Persian medicine, Ayurveda, and Unani medicine (which have many concepts in common), emphasize the association of respiratory system disorders with GI tract disorders [12-15]. For example, Ibn Sina (Avicenna) has highlighted the relationship between respiratory and gastrointestinal disorders in his famous encyclopedia, “The Canon of Medicine." Based on his teachings, some of the gastrointestinal disorders, such as gastric pain, gastric ulcers, intestinal ulcers, diarrhea, and colic, can be the result of the persistence of *Zokam* (coryza) and *Nazleh* (catarrh) [16]. In this study, we hypothesized that there may be a link between the pathogenesis pathways and mechanisms of respiratory and GI disorders. In other words, the disease of one organ can lead to consequences in another.

From the Persian medical perspective, the transmission of disease from the respiratory system to the digestive system is elucidated through the theoretical framework known as *'Ensebab*.' *Ensebab* conceptualizes the purposeful movement of body fluids and chemicals across organs, positing a process wherein pathological influences are transferred from one anatomical site to another. In contemporary biomedical terms, this transmission could be understood as the systemic circulation of various bioactive substances, including inflammatory mediators and signaling molecules. According to Persian medical scholars, certain factors contribute to the susceptibility of specific organs to this transference. For instance, the weakened state of a recipient organ, stemming from trauma or chronic disease, is considered a predisposing factor. Additionally, the presence of pain at a particular anatomical site is believed to guide the direction of pathogenic humors, which can be likened to pathogenic biochemical complexes, toward that specific organ or site. This integrative perspective from Persian medicine prompts exploration into potential connections between organ vulnerability, systemic biochemical dynamics, and the manifestation of diseases in interconnected physiological systems [17-19].

As mentioned, since the question of how GI and airway disorders are associated is still unspecified, the association between GI disorders and airway disorders has not received due attention. This paper aims to review the compelling evidence in epidemiological, pathophysiological, clinical, and therapeutic studies that supports the connection existing between the GI and respiratory tracts and their possible mechanisms of interaction. By synthesizing traditional insights with modern biomedical concepts, the research hypothesizes a link in the pathogenesis pathways between these systems, offering a comprehensive understanding of potential shared mechanisms.

Methods

A comprehensive search was conducted across online

literature databases, including PubMed, Scopus, ISI, Cochrane Collaboration, and Google Scholar. The search employed a combination of medical subject search words or phrases: ("respiratory" OR "lung" OR "asthma" OR "rhinosinusitis" OR "rhinitis" OR "sinusitis" OR "catarrh") AND ("gastrointestinal" OR "intestinal" OR "constipation" OR "gastritis" OR "gastroesophageal reflux disease" OR "irritable bowel syndrome" OR "inflammatory bowel disease" OR "intestinal permeability" OR "leaky gut" OR "epithelial barrier"). There is no restriction on the timeframe, and all original studies are considered in this review. The evidence was categorized and expressed based on the underlying mechanisms and pathways involved in the relationship between the respiratory and gastrointestinal tracts.

On the other hand, we conducted a comprehensive review of four authoritative reference texts in Persian Medicine: "The Canon of Medicine" by Avicenna, "Khulasah al-Hikmah" by Aghili, "Tebb-e Akbari" by Arzani, and "Exir-e Azam" by Azam Khan. These texts are esteemed sources in Persian medicine schools in Iran [18-21]. Our research concentrated on the sections discussing Zokam and Nazleh, with the aim of identifying any documented connections between these respiratory conditions and gastrointestinal diseases. Relevant information was extracted and categorized by two independent researchers, and subsequently discussed in relation to the available contemporary evidence.

Results and Discussion

Two categories of evidence related to the link between airway and GI disorders were discussed: the prevalence of GI symptoms in airway disorders and vice versa, and the underlying mechanisms of these connections:

Prevalence of GI Symptoms in Airway Disorders

In airway disorders, GI symptoms are generally reported with a higher frequency. These symptoms include abdominal pain, diarrhea, and vomiting. Although less common, the following were also reported in great numbers of patients: eructation, constipation, gas, regurgitation, and distension of the abdomen [10].

Some GI diseases, such as gastroesophageal reflux disease (GERD), gastritis, duodenitis, peptic ulcer, irritable bowel syndrome (IBS), colitis, gastroenteritis, functional constipation, and other GI functional disorders, were significantly more common in patients with airway disorders as compared to the rest of the population [6,22].

Data from previous studies suggests a positive association between gastritis/GERD and nasal disorders. Individuals with rhinitis, sinusitis, or rhinosinusitis appear to have a higher prevalence of gastritis and GERD compared to those without nasal issues. Additionally, there's evidence linking seasonal allergic rhinitis to a significantly increased incidence of irritable bowel syndrome [9-11]. Furthermore, patients with respiratory tract disorders have been reported to have both histological and physiological abnormalities in their GI systems [10,23]. In individuals with AR, a biopsy of the small bowel revealed inflammatory reactions similar to those observed in their airways. The prevalence of GERD among patients with asthma ranges from 30% to 90% [24,25]. The existence of a relationship between GERD and asthma is, however, considered controversial. Some data support the idea that GERD treatment improves asthma patients' quality of life and may improve asthma exacerbations. Additionally, GERD treatment may cause small improvements in pulmonary function [26]. Nonetheless, there are articles emphasizing airway disorders in patients with GI disorders. In a prospective 10-year study, an association was established in children with severe infantile colic and airway disorders such as AR and asthma [27].

In patients with active IBD, there are more cases of pulmonary impairment compared to those in remission. There have been a number of case studies in patients with IBD that illustrate rapid and aggressive respiratory symptoms following colectomy. This is interesting as there is no direct anatomical link between the lungs and the primary inflammatory site in the bowels [28].

On the other hand, atopic conditions are more associated with functional GI disorders. For instance, studies have demonstrated a correlation between constipation [29], chronic and recurrent abdominal pain and allergic disorders like AR in the pediatric population. Specifically, it has been noted that children who are atopic are unlikely to acquire an oral tolerance to ingested food and, thus, are liable to experience symptoms of food allergies like GI symptoms. Additionally, their oral tolerance extends to the microorganisms often found in the GI tract. Atopic children have a measure of protection against enteric infections, as they are likely intolerant of such organisms in early childhood [10]. The development of AR is signaled in infancy via food allergies. Compared to controls, the frequency of food hypersensitivity is greater in patients suffering from chronic sinusitis with nasal polyps [30].

Underlying mechanisms of the Gut-Lung disorders connection:

Several mechanisms are involved in establishing a link between the gastrointestinal and respiratory tracts (Figure 1):

Common embryonic sources

There are many similarities between the lungs and

intestines. Interestingly, looking back to the development of the primitive gut, we are able to see that the GI system and the bronchial tree have a shared embryological origin. Goblet cells and submucosal lymphoid tissue are present in both the lungs and intestines. Additionally, they have defense molecules and submucosal lymphoid tissues, both of which contribute to innate and acquired immunity [28].

Common mediators and receptors

Taste receptors can be considered a prominent example of common receptors between the GI and respiratory systems. Initially, it was thought that taste receptors were solely present in the oral epithelium, but recently it has been shown that they are in fact extensively distributed. There is evidence that they are found in the respiratory tract, GI epithelium, thyroid, and brain. The discovery of these receptors in the nasal epithelium has led researchers to consider their role in innate immunity, like protecting the para-nasal sinuses from pathogens. Currently, we understand that extra oral taste receptors like the T2R38 bitter taste receptor and T1R2+3 sweet taste receptors play a role in innate respiratory defense. This paradigm also offers evidence that these and other taste receptors can be utilized in the management of chronic rhinosinusitis as therapeutic targets [31].

As a gut parasympathetic neurotransmitter, vasoactive intestinal peptide (VIP) seems to induce smooth muscle relaxation, stimulate bile and pancreatic secretion, and inhibit acid secretion. Some studies have described it as one of the parasympathetic neurotransmitters that is engaged in regulating airway mucus secretion. Compared with normal nasal mucosa, the expression levels of the VIP receptor mRNA and protein were significantly greater in AR patients [32].

Common microbiota pattern

The human microbiota comprises various microbial communities that reside in different regions of the body [33]. The greatest portion of them is located in the GI tract and plays a significant role in the maintenance of bodily health. Any changes in the gut microbiota homeostasis result in a number of maladies, including gut, lung, and respiratory tract disorders [34]. The patterns of microbiota in healthy GI and respiratory systems are similar, which include Proteobacteria, Actinobacteria, *Bacteroides*, and Firmicutes. As a result of viral or bacterial infections, allergic reactions, smoking, and antibiotic usage, Proteobactria and Firmicutes increase and Actinobacteria and *Bacteroides* decrease in both the gut and lungs [35]. Moreover, changes in the respiratory microbiota can affect the pattern of the gut microbiota as well. For instance, there are some studies that showed dysbiosis of the lung microbiota in mice after lipopolysaccharide (LPS) administration, which is associated with disruptions of the gut microbiota via bacteria moving from the lungs into their bloodstream [36]. One study showed that increased risk of AR was associated with reduced bacterial diversity of the infant's intestinal flora in the first 6 years of life, but asthma was spared. In addition, this relationship has been proven in adults with asthma in some other studies [30]. The mechanism of cross-reaction between the GI and respiratory systems usually occurs in two ways: bacterial seeding

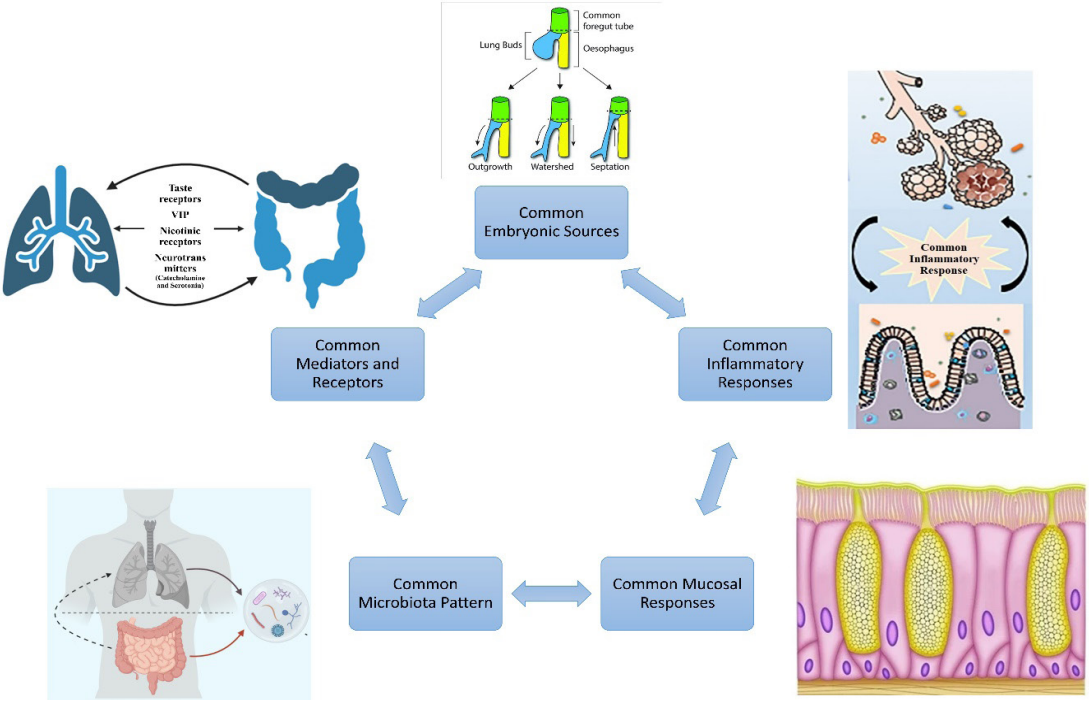

Figure 1. Possible mechanisms of interrelation between GI and respiratory tracts

and bacterial metabolite transfer.

Short-chain fatty acids (SCFAs) make up the majority of bacterial metabolites. The SCFAs that are made by the gut microbiota include butyrate, acetate, and propionate. These not only help recruit immune cells but also aid in their maturation, which eventually leads to a defense against an inflammatory response [37]. The SCFAs that are created in the GI tract are not only systemically distributed in the body, but they are also used as energy providers or signaling molecules [38]. There are studies indicating that hormone production by gut bacteria is induced by butyrate and propionate [39,40]. Greater levels of butyrate lead to improvements in epithelial integrity by increasing mucin production, which in turn decreases bacterial adhesion [41,42]. In this process, they sense metabolites and thus trigger the signaling pathways that lead to anti-inflammatory effects on the immune responses of the host [33]. In patients with cystic fibrosis, administering probiotics resulted in improved respiratory and GI clinical outcomes [43]. The decreased number of bacteria using pyruvate to make butyrate in both cystic fibrosis and asthma is in agreement with a comparable reduction seen in patients with allergic responses. The same bacteria can instead be administered as probiotics in the treatment of various lung disorders such as COPD, asthma, and respiratory allergies [44]. The importance of nutrition for lung health is highlighted by the fact that dietary fiber not only changes the microbiota in the intestines but also in the lungs. A diet rich in fiber leads to an increase in blood levels of SCFAs, which in turn provides a measure of protection against allergic inflammation in the lungs [45].

Mutual changes in response to a specific drug or pathogen

As it has been demonstrated, there is a correlation between dysbiosis in the gut microbiota and respiratory infections and lung disorders [41]. For instance, a reduction in Bifidobacteria and an increase in Clostridia in the intestines have been linked to early-life asthma [46]. There is evidence to suggest that a specific drug or pathogen's impact on the GI tract can lead to a reciprocal change in the respiratory tract, and vice versa. This is further exemplified in murine studies, which demonstrate that the use of antibiotics can deplete specific gut microbiota, thereby influencing allergic inflammation and lung disease [47]. In studies conducted on mice, researchers noticed an increased susceptibility to influenza virus infection in the lungs after removing sensitive gut bacteria by administering neomycin [48,49].

On the other hand, influenza virus infection in the respiratory system leads to an increase in Enterobacteriaceae, thus reducing *Lactococci* and *Lactobacilli* in the intestinal microbiota [49]. The presence of dysbiosis in the gut microbiome is correlated with both respiratory infections and lung disorders [49,50].

Common inflammatory responses

We are protected against toxic elements and infectious microbial diseases through a complex network of innate immunity, immune cells, and their specific derived mediators. In the GI, or respiratory tract, this system works efficiently by using epithelium cells. These cells are supported via adjacent cells and lymphoid tissue that work to protect their integrity. Disruptions in this integrity may result in inflammatory diseases or infections that can be incapacitating or even life-threatening. Currently, a great number of researchers are focusing on the mucosal immune system, including its impact on both health and disease [51]. *Staphylococcus* and Staphylococcal enterotoxin B are among the pathogens that can be swallowed through post-nasal drainage and lead to increased intestinal permeability and intestinal ulcers [52]. Small bowel biopsy samples taken from patients with asthma and AR show commonalities with the inflammatory reac-

Table 1. Underlying mechanisms of the Gut-Lung disorders connection

Mechanism	Description
Common embryonic sources	Both the respiratory and gastrointestinal systems develop from the endoderm in the early embryo, which may explain some similarities in their structure and function.
Common mediators and receptors	Both systems use many of the same chemical mediators and receptors, such as cytokines and toll-like receptors, to respond to pathogens and other stimuli.
Gut-lung axis and common microbiota pattern	There is growing evidence that the gut microbiota can influence the respiratory system and vice versa, possibly through shared immune and neural pathways. Both systems also have similar microbiota patterns, with a predominance of certain bacterial phyla.
Common inflammatory responses	Inflammation is a hallmark of many respiratory and gastrointestinal diseases, and there is significant overlap in the types of cells and molecules involved in the inflammatory response.
Common mucosal responses	Both systems have similar mucosal surfaces that are lined with mucus-secreting cells and contain various immune cells and antibodies to protect against pathogens. They also both produce a similar range of antimicrobial peptides.

tion seen in respiratory passages, along with a buildup of T-cells, eosinophils, mast cells, and macrophages, as well as an increase in the expression of proallergic cytokines like IL-4 and IL-5 [6,10,27]. In the same way, chronic inflammation in the GI tract could bring about pulmonary dysfunction and hyper reactivity. It has been shown that IBD patients, even with normal pulmonary function and without any bronchopulmonary symptoms, will have mild inflammation in their airways [28].

Common mucosal responses

As mentioned before, disruption of the intestinal microbial flora can lead to asthma and other respiratory diseases. There is growing body evidence for the effect of intestinal flora on mucosal immunity in other organs, such as the lungs. This effect is exerted by intestinal bacteria or their metabolites (i.e., SCFAs). Immune cells in the lamina propria and mesenteric lymph nodes neutralize most bacterial translocations and the remaining bacteria, and the carcasses of dead bacteria enter the bloodstream. In addition, bacterial metabolites (i.e., SCFAs) enter the systemic circulation through the lymphatic system.

Stimulated immune cells in the GI mucosa migrate to the target organs through the lymphatic system. Dendritic cells of the gastrointestinal mucosa that have antigen receptors are involved in the development of IgAs secreted from B lymphocytes [47,53-57]. Stimulated B lymphocytes and IgAs are distributed by the bloodstream and lymphatic system throughout the body, reach the lungs, and settle in the lamina propria, forming a defense barrier [33,54,57]. All the above-mentioned research confirms that the gut and the lungs are in fact interconnected and have the ability to impact their respective homeostasis.

According to this study, the possible interrelation between the respiratory and GI systems can occur through the following mechanisms: common embryonic sources, common mediators and receptors, mutual changes in response to specific external stimuli in both tracts, a common microbiota pattern, and common inflammatory responses through the mucosa. The possible underlying mechanisms of connection between the intestines and lungs are summarized in table 1.

Drawing parallels between modern findings and Persian medicine, it becomes evident that **Persian medicine** texts also offer intriguing perspectives on the interconnection between the respiratory and digestive systems.

For instance, Persian medicine scholars have posited that specific anatomical pathways are not necessarily required for inter-organ connections. Instead, they emphasized the significant role of fluid movements, a concept that aligns with the transfer facilitated by inflammatory mediators or biomedical signaling pathways in contemporary understanding. Trauma, or chronic disease, recognized in Persian medicine as predisposing factors, is believed to disrupt organ integrity, potentially leading to inflammatory diseases. The absence of explicit mention of microbiota in traditional concepts necessitates an adaptation to the traditional understanding. While microbiota is a recent finding in modern medicine, traditional perspectives emphasize the broader impact of chronic diseases on organ health. In this context, chronic diseases in the respiratory or digestive tracts, according to Persian medicine, can induce pathological changes, potentially affecting the biochemical balance within the organs.

In light of the above-discussed mechanisms, it becomes evident that these modern findings can align with and provide a scientific rationale for the principles proposed in Persian medicine regarding the transfer of substances and diseases between the respiratory and digestive systems.

Conclusion

Because of strong epidemiologic, pathophysiologic, and clinical evidence supporting an integrated view of GI disorders and respiratory disorders, the theory of the united mucosa is being emphasized in this review. The evidence presented in this study supports the hypothesis of a connection between the GI tract and respiratory system in physiology and pathology. To the best of our knowledge, the first description of this possible link was mentioned in the ancient Persian and Unani systems of medicine, where Avicenna reported this association between the GI and respiratory disorders. We believe that the currently available evidence supports this link, and it can provide a deeper insight into new aspects of diagnosis and treatment in respiratory and GI disorders. Persian medicine offers a rich array of therapeutic modalities. Future research should delve deeper into specific mechanistic pathways that mediate the transfer of substances and diseases between the respiratory and digestive systems and explore the efficacy of traditional interventions, such as herbal remedies, dietary approaches, or lifestyle modifications, in modulating the proposed mechanisms. This could open avenues for integrative and complementary treatment strategies for individuals with concurrent respiratory and digestive conditions.

Conflicts of Interests

None.

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