TRADITIONAL AND INTEGRATIVE MEDICINE

Trad Integr Med, Volume 6, Issue 1, Winter 2021

Review

The Effect of Consuming Food Allergens on Immune System Function with the Focus on Infectious Lung Diseases (COVID-19)

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Received: 22 Jan 2021 **Revised:** 1 Mar 2021 **Accepteed:** 3 Mar 2021

Abstract

The pandemics of respiratory diseases are the most common ones comparing to other diseases. The latest pandemic is caused by COVID-19, for which no definitive cure has been found. Therefore, at present, strengthening the immune system is the only way to protect humans against this virus. Food is one of the factors assisting the immune system to function properly. Moreover, food plays an important role in strengthening the immune system against various pathogens. However, many popular sources of human food, including legumes, eggs, and nuts, contain anti-nutritional factors that can adversely affect the human immune system and increase inflammatory factors such as interleukin 4 and interleukin 6. A cytokine storm and increased secretion of interleukin 4 and 6 are among the most frequent causes of death in COVID-19 patients. Consequently, taking the COVID-19 patient's diets into account by considering the foods influencing their immune system can greatly reduce the disease's severity and mortality rate.

Keywords: COVID-19; Respiratory system; Food hypersensitivity

Introduction

A pandemic is an infectious disease on a large scale that significantly increases mortality in a large geographical area and causes much economic, social, and political damage. The probability of a pandemic's occurrence rises due to increased traveling and migration, urban sprawl, land-use changes, and greater exploitation of the natural environment. Pandemics are more likely to be detected on a geographic scale than the severity of the disease. Unlike the seasonal influenza epidemic, a new flu virus appears and

Citation: Kamalinejad M, Nabimeybodi R, Zareshahi R, Nabimeybodi N. **The Effect of Consuming Food Allergens on Immune System Function with the Focus on Infectious Lung Diseases (COVID-19).** Trad Integr Med 2021; 6(1): 55-69.

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spreads worldwide while many people are not immune to it. The flu virus is a pathogen that can cause most pandemics [1].

Severe acute respiratory syndrome 2 (SARS-CoV-2) is one of the agents that caused coronavirus 2019 (COVID-19), which spread from Wuhan in China to all around the world and quickly became a pandemic. It affected millions of people, caused more deaths than any other flu type, and had many economic consequences for the whole world [2]. Since December 2019, when the first report of the virus was published, several articles have examined the disease and worked on its various aspects. In this short period, no detailed study could suggest an effective treatment for this disease, but the clear point is the immune system's role in general that protects the body against infectious agents, such as bacteria, viruses, fungi, and parasites. The immune system comprises various cells distributed throughout the body and commute between their location, the lymph flow, and the blood flow. The immune system is always active, but specific immunity is activated against pathogens, so the immune system needs substrates and nutrients to have the vital energy to fight pathogens [3]. Therefore, food plays an important role in strengthening the body's immune system against various pathogens.

Food has played an important role in treating diseases, so scientists' attention has been drawn to functional foods. The American Institute of Nutrition and Medicinal Foods defines efficient foods as any kind of food or portion of food that can promote health in addition to its usual nutrients. These foods include carbohydrates, proteins, lipids, vitamins, minerals, and other groups. For example, Lycopene existed in tomatoes, can prevent prostate cancer and cardiovascular diseases. Moreover, soy isoflavones and lignans in flaxseed oil are very useful in reducing the risk of breast cancer and menopausal complications. Besides, consuming vegetables, fruits, and legumes can diminish cardiovascular disease risks (CVD), namely diabetes mellitus, hypertension, obesity, and metabolic syndrome [4].

However, some foods contain allergens that can stimulate the immune system and secrete inflammatory factors or contain anti-nutritional factors and natural or artificial substances. It should be mentioned that anti-nutritional factors may exist in the human diet or animal feed. They can have a negative effect on the immune system by preventing the absorption of nutrients from food. The anti-nutritional nature of a substance is not inherent but depends on the digestion in the digestive tract. For instance, trypsin inhibitors, which are anti-nutritional agents for monogastric animals, do not cause any side effects in ruminants because they can be broken down in their rumen [5].

There are anti-nutritional factors in many human food sources, including legumes, eggs, milk, seafood, fruits, and nuts. These substances are among the most widely consumed foods globally, so their side effects on the immune system can affect many people. It becomes even more severe when patients' diets consist of these anti-nutritional factors, especially in pandemics, which affect many people worldwide. Meanwhile, exceedance probability analysis shows

a 1% chance of having the flu pandemic each year, which could cause nearly 6 million people to die from pneumonia and influenza [1,6]. Therefore, this study aims to examine the relationship between food allergens and infectious lung diseases.

The immune system, cellular, and humoral immune systems

When the body defends microbes, first innate immunity reactions and then adaptive immune responses are created. Adaptive immunity is of two types: humoral and cellular, which act through different immune system components to eliminate different microbes types. Humoral immunity is created by mediating the molecules in the blood and secreting antibodies produced by cells called B lymphocytes. Antibodies detect microbial antigens, neutralize microbial infections, and finally kill them. Cell-mediated immunity, also named cellular immunity, is created by mediating cells called T lymphocytes. Intracellular microbes, such as viruses and several bacteria, survive and duplicate within phagocytes and host cells so that circulating antibodies cannot reach them. Therefore, defense against such infections is cell-mediated immunity, which destroys the microbes in the phagocytes or kills the infected cells, thereby eliminating the infection's reservoir [7]. Many human diseases are caused by immune responses toward environmental non-microbial antigens, in which T-helper cells (producing IL-4, IL-5, IL-3), mast cells, eosinophils, and IgE are involved. During the executive phase of these responses, mast cells and eosinophils are activated to rapidly release their mediators, increase vascular permeability, dilate blood vessels, and contract the lungs' smooth muscles viscera. This reaction is called Immediate Hypersensitivity. Following the immediate response, a slow-growing inflammatory response is produced, known as the delayed phase reaction, accompanied by the accumulation of neutrophils, eosinophils, and macrophages. These reactions are called allergies, and comorbidities occurring with these reactions are called atopic allergic diseases or immediate hypersensitivity. In multiple reactions, chronic allergic diseases are associated with damage and changes in tissue structure. Antigens causing immediate hypersensitivity are called allergens. Most allergens are common environmental proteins, animal, and chemical products that can alter their proteins[7]. Cytokines and chemokines play a key role in the origin, growth, differentiation, and immune cells' function. They compose a consistent and tunable communication channel that aims to keep the organism in a homeostasis state. Injuries, infections, and autoimmune reactions destroy this balance and lead to massive amounts of such highly reactive components [7]. Acute infectious diseases trigger the central nervous system's response and cause symptoms, such as fever, fatigue, drowsiness, social withdrawal, and negative moods, namely depression and anxiety, pain hypersensitivity, and decreased appetite. Fever and sickness behavior in response to infection or inflammatory diseases is caused by immune mediators, such as cytokines and prostaglandins, signaled to the brain [8].

The prevalence of sensitivity to food allergens

The global increase in the prevalence of asthma, allergic rhinitis, and atopic dermatitis has been accompanied by a rapid increase in food allergies called "the second wave of the allergy epidemic." Food allergy is an immediate hypersensitivity reaction to overeating, which leads to the release of mediators from the mast cells of the intestinal and the underside of the gastrointestinal tract mucosa. Clinical manifestations of food allergies include itching, tissue edema, increased intestinal peristaltic waves, increased epithelial fluid secretions, as well as symptoms associated with oropharyngeal edema, nausea, and diarrhea. Inflammation of the nasal mucosa, urticaria, and mild bowel contraction are also associated with allergic reactions to food[7]. Recently, animal proteins have been gradually replaced by plant proteins. Among plants, legumes are rich sources of protein and carbohydrates [9]. Chickpeas, beans, lentils, broad beans, and soybeans are among the most important and widely consumed legumes. The protein content of these substances is reported to be 17-43% [10].

The presence of compounds, such as protease inhibitors, phytic acid, lecithin, and oligosaccharides in legumes, can be very beneficial in treating variant diseases, but they can also cause food poisoning and food allergies [11]. Food allergies are adverse reactions to food and occur when the immune system reacts to one or more proteins in food, recognizes it as an external factor, and wants to neutralize it. Food allergies can vary from person to person, and a protein can cause allergies in one person while it is safe in another, so the pattern of food allergy prevalence in different parts of the world varies significantly. Evidence suggests that these allergies are spreading in developing countries, and in countries such as China and Africa, there is a similar pattern to western countries regarding this issue. Race plays an important role in the development of food allergies. In Australia, the prevalence of food allergies in infants with East Asian parents was three times higher than in infants with Caucasian parents. Indeed, the East Asian race has a higher risk of food allergies compared to the Caucasians when they have a similar westernized lifestyle. Studies in Asian countries, such as Thailand, show that the outbreak of food allergies in preschool children is 1%, whereas it is 5.3% in Korean infants, and in one-year-old and two-year-old Chinese children, it is 3.8% and 7.7%, respectively [12].

Food allergies are both widespread and costly for a country's health system. For instance, approximately 24.8 billion dollars was spent on the complications of food allergies by the USA health system annually. An epidemiological study of 33,200 children in the United States revealed that 6.7% of the children had food allergies. Between 1997 and 2007, the prevalence of allergies among children under 18 had increased by 18% and reached 3.9%. Another study in the United States investigated 34,480 children under 18 and reported an 8% prevalence of food allergies. They also stated that 40% of them had life-threatening allergic reactions, and 30% had multiple food allergies[13]. Anaphylactic shock is caused by food consumption in 6-8% of chil-

dren and 4% of adults. Annually, anaphylactic shock from food is reported in 3,100,000 people in Western countries. In the United States, 30,000 people go to the emergency room each year due to anaphylactic shock caused by food allergies. Peanuts, almonds, brazil nuts, cashew nuts, hazelnuts, macadamia nuts, pecans, pistachios, walnuts, tree nuts, fish, and shellfish were among the substances that caused the most allergic reactions. Meanwhile, high consumption of legumes has made these substances the fifth most common cause of food allergies in children under five [10].

Research conducted in the United States based on data from the National Health and Nutrition Examination Survey estimates that allergy towards peanuts is 7.6%, shrimp 5.9%, milk 4.8%, and eggs 4.3% in the population over the age of six, and the allergy towards peanuts is 6.8%, milk 21.8%, and eggs 14.2% in children aged 1-5 years [14].

Legumes cause allergies in 4.5% of Australian adults, from which 2.7% of allergies are related to peanuts and 0.1% to soybeans. Peanuts contain 2S albumin storage proteins, which can cause very severe allergies. Soy proteins (Gly m 5 and Gly m 6) are also associated with severe allergies. There is also a cross-allergy between legumes, i.e., in patients sensitive to peanuts, allergies are also observed in lupine, pea, and soy. Besides eating peanuts, other consumption methods, such as topical use or inhaling peanut powder, may cause allergies. They also make an allergic reaction to peanuts' first oral consumption, as sensitization is already caused by inhalation or topical use [15].

In Canada, the prevalence of food allergies among children is estimated at 7.1% and among adults at 6.6%, and according to the individuals' reports, cow's milk, peanuts, and tree nut are the most common food allergies. In Europe, the spread of food allergies is estimated to be 5.9%, considering people's reports [14].

A study conducted in Iran reported that 15.2% of children with asthma tested positive for a food allergen, among which allergies to cow's milk (26.6%), hazelnuts (25.3%), wheat flour (15.2%), and egg whites (12.6%) had the highest prevalence. It is worth noting that peanut consumption is not common in the Iranian diet, but there is a cross-sensitivity between hazelnuts and peanuts [16].

Hypersensitivity caused by food allergens

The role of food allergies in the pathology of many diseases has been proven recently. Although the intestinal epithelium acts as a membrane that restricts macromolecules' penetration, food allergens can cross the intestinal epithelium. The high stability of these molecules against stomach acid, digestive enzymes, and the presence of surfactants allow them to remain intact, stimulate the gastrointestinal tract and stimulate hypersensitivity through the immune system in sensitive individuals [17]. Hypersensitivity occurs in a variety of forms, including acute urticaria and angioedema, atopic eczema, gastrointestinal anaphylaxis associated with nausea, abdominal pain, abdominal cramps and vomiting, food protein-induced proctocolitis associated with dysentery and anemia caused

from it, and weight loss, which is usually caused by allergies to cow's milk, and food protein-induced enteropathy, which is more common in infants and is caused by inflammation of the small intestine and loss of integrity of the intestinal villi, leading to malabsorption syndrome. Another symptom of hypersensitivity is asthma occurrence. Besides, uncontrolled asthma is a risk factor for an anaphylactic shock from food allergens. Airway hyperactivity and controlled asthma activation have been reported in people exposed to food allergens. Ultimately, anaphylaxis, an IgE-dependent systemic reaction, will occur due to releasing target organ mast cells' mediators, such as cutaneous, respiratory system, gastrointestinal tract, and circulatory system [18]. Moverare et al. reported respiratory symptoms, such as respiratory distress and dyspnea, in 56% of participants after eating peanuts and even having skin contact and peanuts' inhalation. Studies have shown that food allergies are directly linked to asthma. Particularly, food allergies are considered a risk factor for asthma in children. Children who are allergic to eggs and tree nuts are significantly more likely to have asthma, and diagnosing food allergies in children is a predictor of future asthma[19].

The association of food allergens with brain complications, such as glioma, has also been reported. These allergens can cause hyperactivity in children [20,21], diseases of the nervous system, such as epilepsy, Parkinson's, schizophrenia, depression, memory disorders, and skin diseases, such as psoriasis [22-25]. Food allergens are also associated with mood swings and behavioral and cognitive functions. These allergens can alter the brain's inflammatory state and cause behavioral disorders, such as decreased motor activity and cognitive memory. Besides, food allergens increase the levels of antigen-specific immunoglobulins and mast cell markers in the brain. In particular, food allergies increase the total number of microglia and the percentage of active microglia in the cerebral cortex and the hippocampus of the CA1 region and increase TNF-a in the cerebral cortex [26]. A high prevalence of food allergies among children with epilepsy has also been reported [27]. Migraine is one of the most common pain syndromes for which a specific mechanism has not yet been suggested, but diet is one of the factors associated with migraine pain patterns. IgE-mediated mechanism and histamine can be useful in establishing this relationship [28].

The oral allergy syndrome (OAS) and the pollen-fruit-vegetable syndrome are mostly associated with fruit allergic reactions are frequently reported. Consuming fresh fruits or raw vegetables can easily lead to those syndromes[29]. Allergy reactions to kiwi were reported several times in adults, which is accompanied by oral symptoms. Some other generalized reactions such as respiratory reactions, vomiting, urticaria, and cardiovascular collapse were seen in some individuals. On the other hand, one of the most significant reasons for IgE-mediated hypersensitivity is fish and seafood. It occurs in countries in which people's career is mostly fishing, and fish plays a significant role in their diet [30].

Anti-inflammatory agents with anti-inflammatory effect

Abscisic acid

Plants, including legumes, contain a phytonutrient called abscisic acid (ABA), which plays a vital role in the plant's life cycle and also plays an anti-inflammatory role in the human body facing inflammatory factors. Abscisic acid is pro-inflammatory endogenous and is stimulated by activated granulocytes or nitric oxide produced by the inflammatory agent and acts through the Peroxisome proliferator-activated receptor (PPAR) [31]. Endogenously producing this hormone in the human body at nanomolar concentrations can act locally and increase beta-pancreatic cells' ability to secrete insulin. The hormone of PPARγ activates pre-adipocytes, while PPARγ deficiency in immune cells impairs ABA's ability to normalize blood sugar [32]. Studies have shown that prescribing ABA in the absence of PPARγ results in a net pro-inflammatory effect through PKA-dependent activation of NF-kb [32]. Disrupting these receptors' activity in the intestines of people with gastrointestinal diseases, such as inflammatory bowel disease (IBD), causes ulcers in the epithelial mucosa [31].

On the other hand, the number of abscisic acid increases in grains that have been stored for a long time[33]. High levels of abscisic acid enter the body through the patient's diet, but there are no PPAR receptors to activate them. In this case, not only does ABA have an anti-inflammatory effect, but also it can cause inflammation [34]. Given the link between gastrointestinal and pulmonary diseases on the one hand[35] and the fact that PPARs are also present in the lungs, studies have shown that ABA can improve the inflammation caused by the influenza virus in the lungs [36]. If a factor interrupts the function of these receptors, can abscisic acid cause inflammation in the lungs? Can eating grains with high levels of abscisic acid be harmful in inflammatory diseases of the lungs?

Phytic acid

Phytic acid is another controversial component of grains. Phytic acid is also recognized as inositol hexakisphosphate or phytate in the form of salt. This compound exists in a stable form of phosphate in many plant tissues, especially seeds and grains [37]. Humans cannot digest phytic acid, and although it has a beneficial nutritional effect as an antioxidant, it blocks the absorption of minerals, such as iron, calcium, and zinc, by chelating them [38]. The high amount of phytate in the diet is directly related to zinc and iron deficiency [39]. Phytic acid mostly tends to bind to zinc, so high levels of phytic acid in the diet can negatively affect health because minerals, including zinc, play a role in gastrointestinal infections and respiratory infections and simultaneously reduce the severity of these diseases [40]. Zinc can prevent the development of respiratory diseases by applying anti-inflammatory and antioxidant effects [41]. The question is whether the phytic acid plays a role in increasing inflammation and exacerbating lung inflammation in people with COVID-19 or not.

2S albumin

2S albumin is one of the most significant food allergens in legumes and tree nuts, namely hazelnuts, walnuts, peanut and cashew [42, 43]. This protein belongs to the family of prolamins. Prolamins are the main storage proteins in grains' seeds and are considered essential for humans. Prolamins are the main proteins in rice, wheat, corn, barley, and oats. Wheat prolamins are the main constituents of gluten, and their properties affect the quality of wheat flour [44]. 2S albumin is present in many edible grains and is highly considered in allergy-related research due to its allergenic nature[45, 46]. In addition to providing plant nutrients, 2S albumin can act as a defensive weapon against fungal attacks. This protein's resistance to the gastrointestinal tract's defense barriers leads to its absorption in its immunologically active forms. As a result, the immune system is easily exposed to this allergen and causes allergic reactions in sensitive individuals [47].

In addition to these proteins' inherent properties as food allergens, food matrices may contribute to their allergenic nature, either by facilitating the arrival of this protein to the immune system through the gastrointestinal tract mucous or by participating in the activation of immune cells. Some studies have shown that allergens alone cannot induce Ig E, but a complete food matrix must produce this response [47].

Reports regarding allergic reactions to 2S allergens are increasing. The severity of these allergic reactions has also been reported from mild irritation of the larynx, urticaria, respiratory symptoms, such as cough, wheezing, and asthma, to angioedema anaphylactic shock. The severity of these reactions from person to person is different, but its reason is not clear. However, the high resistance of 2S proteins to proteolytic attack and the cooking process can be a good reason for the stability of their allergenicity and the capability to induce an immune response. The severity of the symptoms depends on the amount of allergen absorbed, the matrix's effect, and the type or degree of the immune response [47].

Food allergy reactions occur through two mechanisms: symptoms caused by immunoglobulin and gastrointestinal symptoms that occur without immunoglobulin. These allergens can activate CD4 + lymphocytes[10]. Specific cytokines produced by the main subcategories of TCD4 +, IFN-γ cells for TH1, IL-4, IL-5, IL-13 cells for TH2 and IL-17, and IL-22 cells for TH17 cells (Abu al-Abbas). TH2 lymphocytes secrete interleukin 4 and 13, which trigger the release of immunoglobulin E and, subsequently, binding of Ig E antibodies with mast cells will occur. Re-entry of food allergens into the body causes a cross-linking to Ig E antibody, binding to mast cells, and releasing secondary mediators that trigger reactions, such as vasodilation, smooth muscle contraction, and mucus secretion. Ig E's indirect symptoms occur through eosinophils or inflammation caused by T cells, which triggers inflammatory mediators' release[10]. Interleukins 4 and 13 can stimulate interleukin 6 from human bronchial epithelial cells [48]. This issue gains more importance when studies reveal that interleukin 6 is also increased in patients with COVID-19. So, it may

be dangerous to consume foods containing 2S albumin by a patient with COVID-19 who is also allergic to this protein.

Egg allergy

One of the most common food allergies in Western countries is egg allergy, affecting about 2% of children. In Australia, 8.9% of 12-month-old babies suffer from this problem[49]. Egg allergy is associated with an increased risk of allergies to peanuts and other food allergies, atopic dermatitis, respiratory allergies, and asthma [50].

Ig E-mediated reactions are the most common type of allergic reaction to eggs. Clinical manifestations of this allergy in children occur with urticaria or angioedema within minutes to two hours after egg digestion. Coetaneous symptoms are also common. Immediate reactions to egg allergies include gastrointestinal or respiratory symptoms, and even life-threatening reactions may occur. Occupational asthma has been observed in bakery workers exposed to aerosolized eggs and people who work in egg processing factories. Egg allergies can also cause atopic dermatitis. The combination of sensitivity to egg and atopic dermatitis is a risk factor for asthma. A study found that 80% of children with both of these allergies have asthma. Eggs are the second leading cause of observing disease symptoms in eosinophilic esophagitis patients. This inflammatory disorder is characterized by a large number of eosinophils in the esophagus [51].

Egg whites contain several allergenic proteins, such as ovomucoid, ovalbumin, conalbumin, lysozyme, and ovomucin. Among these, albumin is the most abundant protein in egg whites [52]. Albumin can induce inflammation of the airways in laboratory animals. Increased mucosal adhesion in the airways associated with goblet cell hyperplasia and increased mucus secretion in the lumen of the airways in the mice and the progression of inflammation and narrowing of the smooth muscle layer in rats were observed as a result of this allergen [53]. Elevated levels of immunoglobulin E in response to allergens have also been reported in this animal model, which results in CD4 + and CD25 + cell depletion, increased eosinophils in the lungs, and an increase in interleukin 5 and 13, which play an important role in asthma occurrence [53].

In a study, Shen-Hao et al. compared the type of inherent immune system's response to the respiratory syncytial virus (RSV) and human metapneumovirus (HMPV) infection in two groups, namely mice sensitized to albumin and not sensitized to albumin. They reported a cytokine/chemokine response in both groups after a viral infection. However, a significant increase in the virus proliferation in animals' lungs sensitive to albumin was reported compared to animals insensitive to albumin because IFN1 secretes respond to cellular attacks to prevent the virus proliferation. However, albumin inhibits IFN1 secretion and causes the virus to duplicate more in mice's lungs[54]. Although albumin is the most abundant protein in egg whites, it is not heat resistant and is denatured, and its allergenicity will be reduced [52].

In the process of baking cakes, biscuits, and foods containing amylase or after long-term storage, Millard's reaction, which is a non-en-

zymatic reaction of amino acids with non-reduced sugar, will occur. During the reaction, ovalbumin reacts with Millard glycosylation to form advanced glycation end products (AGEs). The new antigens, created by Millard's reaction, are more resistant to digestion than primary proteins. Those created by Millard's reaction are more resistant to digestion than primary proteins. It stimulates the TH2 response more than unheated albumin and further induces an allergic reaction and secretion of interleukin 6 [55]. Many people who are allergic to eggs are not allergic to baked eggs, which can be due to the ovomucoid protein. Ovomucoid is another egg protein with unique properties, including its resistance toward heat and protein than other egg components and its strong allergenicity[52].

Although cooking and soaking can reduce the amount of these anti-nutrient compounds to some extent, the effect varies depending on the type of treatment used and the type of legume. The study by Shi et al. showed that these anti-nutritional factors' contents could be influenced significantly by the type and the treatment (soaking or cooking) of the legume and its type-by-treatment interaction. For instance, soaking soluble oxalates and lectins levels can be reduced by soaking, while it cannot affect phytic acid. Thus, it is more effective to cook the presoaked seeds. This way, the hemagglutinating activity will be reduced by more than 93%, and phytic acid content, except for common beans and soybean, will be decreased significantly. Moreover, cooking can diminish oxalate contents immediately while they do not change by the soaking treatment. However, phosphorus and potassium, which are useful contents, will be reduced in these culinary procedures [56-58].

Overview of Materia Medica

In the sources of Iranian traditional medicine (Persian Medicine), beans, such as chickpeas, broad beans, and mung beans, have been considered useful for various diseases, especially lung disorders. Using these beans has been recommended to cure coughs and lung inflammation. Among the mentioned beans, chickpeas are among the best food for healthy lungs, and their effect on the lungs has been more than other legumes [59]. Considering Iranian scholars' perspectives, the question is whether peas can be prescribed for all patients or not. Persian medicine scholars, including Avicenna (Ibn Sina), state that to maintain health and cure the disease, the patient should be given proper food and food to become a part of the body well-digested; the whole body must function in balance. To maintain this balance, they mentioned six necessary lifestyle principles (Asbab-e-Settah-e-Zaruriah), including air, body movement and relaxation, sleep and wakefulness, psychic movement and rest, food, drinks, and evacuation and retention. Therefore, Iranian scholars' dietary and medicinal recommendations have had to treat any disease are possible by considering these important principles. If the balance of each of these six principles is disturbed in the patient's body, his health will not be easily achieved [60].

Disbalance in any of these six principles can lead to disease. According to Ibn Sina, fresh air

is the basis of life energy for humans. According to him, polluted air can cause many disorders, such as itching, eye irritation, watery eyes, irritability, anxiety, and headaches. Besides, in the long run, it can cause heart and mental illness, depression, fatigue, and digestive disorders [61].

According to scholars of Iranian traditional medicine (Persian Medicine), sleeping is useful for improving general strength and brain function. The most important factor considering digestion is the stomach's heat, which acts on the food and causes digestion. According to Western medicine, the autonomic nervous system's function is different in various sleep stages. In the non-rapid eye movement (NREM) stage, the parasympathetic nervous system's activity increases. It reduces the peristalsis of the digestive system and increases the duration of mucosal contact with stomach acid. As the sympathetic and parasympathetic systems control the digestive system's function, the above factors will improve the digestive system's function [62].

Among these six principles, two principles are directly related to the digestive system, the first is the type of food, and the second is the excretion of waste from the body. Therefore, the gastrointestinal tract function is of utmost importance in preventing and treating diseases from Iranian medical scholars' perspectives. According to Persian medicine, food undergoes various stages of digestion before it reaches the tissue. Based on Ibn Sina's theory and many Persian medicine scholars, food digestion has four stages: gastric digestion, hepatic digestion, vascular digestion, and tissue digestion. These four steps must be performed on the food to be suitable for the body's use. During gastric digestion, food is converted to kilos and absorbed into the liver through mesenteric vessels for further digestion. Thus, according to Persian medicine, the stomach and liver must function properly so that the food that reaches the tissues is usable for the cell [63].

On the other hand, the liver is a key organ in maintaining immunity. It detects pathogens that enter the body through the gastrointestinal tract, as well as viruses and macromolecules. The liver has the largest set of phagocytic cells in the body. This organ is an important barrier between our bodies and our environment. In particular, portal vein blood transports a large number of foreign molecules, such as antigens. The liver has an anti-inflammatory function by default, but it may produce a rapid and severe immune response under certain conditions. Excessive inflammation in the absence of infection leads to liver damage, tissue damage, and remodeling [64].

Therefore, when choosing the right treatment for each patient, the health of other organs of the patient's body must be taken into consideration. For instance, while considering chickpeas to be useful for the lungs, Ibn Sina claims that the patient should not be given the kind of food that causes bloating in treating lung diseases. Also, while treating fever, it is suggested that the patient should be given soft food so that it can be easily digested and absorbed. Therefore, if a person has a lung disease and has a gastrointestinal disorder at the same time, that per-

son should not be given food causing bloating [59]. Considering Western medicine, this issue can be justified because the immunological connection between the lungs and the gastrointestinal tract causes a disordered immune response common to biological systems. For instance, in IBS patients, the number of mast cells activated in the gastrointestinal mucosa is associated with severe abdominal pain and bloating, directly related to the prevalence of gastrointestinal diseases in people with asthma to healthy individuals. Abdominal pain, bloating, nausea, anorexia, and lower gastrointestinal symptoms are among the gastrointestinal symptoms reported by people with asthma. A significant association between abdominal pain and allergic wheezing, as well as an increased prevalence of gastrointestinal symptoms in patients with rhinitis and allergic wheezing, have also been reported [35]. Disorders related to the smooth muscles in both the digestive tract and the respiratory tract may be linked to both systems' diseases. Gastric motility is maintained by the smooth muscle of the gastrointestinal tract. Studies have shown that in people with asthma, gastrointestinal emptying is significantly reduced compared to the control group [35,65].

The digestive system is the only organ in the body with its own nervous system, called the Enteric Neuron System (ENS). Intrinsic neurons of the gastrointestinal tract include motor and sensory neurons. ENS sensory neurons are the first intrinsic primary afferent neurons that respond to food changes in the gastrointestinal lumen. Subsequently, they send reflex signals during enteric interneurons and motor neurons to regulate gastrointestinal secretions [66]. Despite the potential independence of the ENS, the brain and gastrointestinal tract are interconnected and influenced by each other. In a healthy person, this interaction is well-established, but disorders germane to the central nervous system may have intestinal manifestations or even intestinal origin. In recent years, several disorders thought to have neurological origins, such as autism and Parkinson's, have finally been identified as having an intestine origin [31].

The relationship between food allergens and COVID-19 studies examining patients with COVID-19 have reported that mortality from COVID-19 is caused by cytokine storm syndrome, so elevated levels of cytokines can be a causative factor of COVID-19 virus mortality. Increases in TH2 cytokines, such as interleukin 6, have been reported in addition to cytokines, such as interleukin 4. An increase in interleukin 6 has been observed in critically ill patients, and the level of this interleukin is directly related to the patient's mortality [8]. On the other hand, as mentioned before, food allergens in legumes and eggs can make the immune system react and increase the level of immune mediators, such as interleukin 6 and interferon 1. Many studies have shown that released immune mediators against gastrointestinal inflammation are similar to the immune system's reaction to lung disease. Salar et al. indicated that even though SARS-Cov2 is sensitive to interferon 1 and can be used to treat and even prevent the virus, COVID-19 pathology includes pulmonary lesions with similar characteristics of interferonopathies. It suggests that COVID-19 triggers

a severe antiviral response through IFN1 and causes tissue damage[54]. According to Western medicine, after the skin, the respiratory system, gastrointestinal tract, and central nervous system are among the body organs affected by food allergens [67]. So, even if food allergens do not directly affect the lungs, they will affect the digestive tract. Given that Iranian medical practitioners paid special attention to liver and gastrointestinal modification as well as the type of food in the patient's diet in the treatment process; it is hypothesized that the consumption of foods containing allergens in patients with respiratory diseases, such as COVID-19, can delay the recovery or even worsen the disease.

Conclusion

Legumes, nuts, eggs, and fruits are important and vital foods for human beings, but they must be consumed properly and according to each person's nature. Since the freshness of food, especially legumes, has a great role in reducing their allergenicity[33], so if food labeling is not taken seriously and the time of harvesting and storage of legumes is not clear, legumes consumed by people, especially patients, might be harvested a long time ago and their complications for the body outweigh their benefits. Iranian scholars have also emphasized the importance of these foods' freshness when consumed in Iranian medicine sources.

Food allergens cause hypersensitivity in various forms in many human beings annually, some of which are very mild, but some are fatal. These allergens stimulate the immune system and secrete various inflammatory factors, especially those common in both inflammatory factors of COVID-19 and lung disease factors. Therefore, the presence of some foods that contain these allergens, including 2S albumin in legumes, peanuts, walnuts, and hazelnuts, ovalbumin in egg whites, and high amounts of abscisic acid and phytic acid (especially in patients with digestive disorders), in the diet of people with COVID-19 can slow the treatment process of the disease and can even worsen the disease. Therefore, it is recommended to make a proper diet for these patients while using foods containing allergens mentioned above.

When a person is exposed to the disease or at stage zero of COVID-19 or the test is positive, this hypothesis should be taken into consideration. It can have a preventing role at the beginning of the symptoms or reduce the disease symptoms.

In conclusion, considering the prevailing diet of the people living in the region, the conditions in which food is grown, harvested and stored, and according to each patient's nature and food allergens influencing the affected organ, an appropriate diet must be planned for the patient.

Conflict of Interest

None.

Acknowledgments

None.

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