Review Article

A Review of the Role of Indoor Fungi in Sick Building Syndrome

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ABSTRACT

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Sick building syndrome (SBS) is a group of non-specific symptoms associated with the built environment, including mucosal symptoms in the eyes, nose, throat, and skin, and general symptoms such as headache and fatigue. Currently, more attention has been paid to the impact of buildings on the health and well-being of occupants, so SBS has become a global concern. Indoor microbial agents such as fungi are important in causing this syndrome. Fungi are eukaryotic microorganisms that occur in indoor air. Among the fungi, *Cladosporium*, *Aspergillus*, *Stachybotrys*, and *Penicillium* have a significant role in causing SBS. Fungi can contribute to this syndrome in different ways. Thus, this review article attempts to investigate the role of fungi and how to intervene in these microorganisms in SBS. To this end, keywords such as: "air," "indoor," "fungi," and "sick building syndrome" were searched. Articles published in scientific databases, such as Google Scholar, PubMed/MEDLINE, Elsevier, and Scopus were used.

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Introduction

Recently, people, especially children and older people, have usually spent 90% of their time indoors (at home, schools, offices, markets, vehicles, and other closed environments) [1]. Due to the global corona virus disease 2019 (COVID-19) pandemic, people are advised to stay home more often to reduce the risk of infection [2]. As people spend more time indoors, they are more likely to be exposed to indoor air pollutants affecting indoor air quality [1]. One of the diseases due to bad indoor air quality is sick building syndrome (SBS) [3]. SBS became a household name in 1985 when it was associated with Legionnaires' disease (a type of pneumonia first discovered in an air conditioning system in a Philadelphia hotel during a conference) [4]. SBS is defined as non-specific symptoms that occur when living or working in a particular building but disappear after moving away from the environment [5]. These symptoms can include panting, fever, joint pain, nausea, dizziness, itching, nose irritation, eyes, skin, and throat, dry cough, sensitivity to odors, headache, and fatigue (Table 1) [4, 6]. These symptoms' occurrence depends on environmental and individual characteristics [6]. Environmental characteristics include volatile organic compounds (toluene, benzene, ethyl benzene, xylene, chloroethylene, trichloroethylene, formaldehyde), biological airborne contaminants (bacteria, fungi, viruses), inorganic chemical pollutants (Carbon dioxide, Carbon monoxide, Methane, Sulfur dioxide, Sulfur trioxide, Nitrogen oxides, Nitrogen dioxide, and Ozone), building characteristics (inadequate ventilation or dampness, construction materials, lighting, noise, temperature), Electromagnetic radiation and smoke either from tobacco or incomplete combustion of fuel [4, 6, 7]. Individual characteristics include gender, age, activities of occupants, education level, history of allergies, and psychosocial work stress (Table 2) [6]. Among the biological agents, fungi can play an essential role in SBS [2]. People who live or work in moldy buildings complain of various health problems [8]. This review was conducted to help improve awareness and knowledge about the role of fungi, how to intervene in these microorganisms in SBS, and how to solve this problem.

Table 1. The symptoms of sick building syndrome

Central nervous system	Headache, fatigue, difficulty in concentration, lethargy, nervousness, depression, dizziness, mood swings and memory
Skin and mucous membranes	Skin itching and irritation, dry skin, itching and inflammation of the eyes, nose and throat
Respiratory symptoms	Asthma-like symptoms, complaints of odors
Gastrointestinal symptoms	Diarrhea, gas, and bloating
General symptoms	Drowsiness, pain in the muscles of the arm or hand, cold feeling in hands or feet, feeling heavy air, chest pain, back pain, neck pain, visual impairment

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An overview of the characteristics of fungi

Fungi are eukaryotic, heterotrophic, and chlorophyll-free microorganisms that exist as natural flora in the human body or the surrounding environment in air, water, soil, sewage, plants, and others [9-14]. Fungi are highly diverse microorganisms that inhabit all known ecosystems [15]. It has been estimated that approximately 25% of Earth's biomass is made up of fungi [12]. Estimates suggest that there are probably more than 2×10^6 species, and analysis of typical fungal genomes suggests that they contain an average of about 50 biosynthetic gene clusters [15]. Fungi have developed diverse relationships with plants and other organisms and can be divided into functional guilds such as mycorrhiza, pathogens, mycoparasites, and saprotrophs [16]. These fungal functional guilds are recognized by various traits, including genetic, enzymatic, morphological, and physiological criteria [17]. Many fungi are opportunistic and change their lifestyle depending on environmental conditions [16]. Some fungi can produce numerous secondary metabolites and hybrid compounds. A number of them are very useful in medicine, such as the 'classic' special metabolites penicillins, cephalosporins, statins, and mycophenolic acid, and new antimicrobial agents such as the enfumafungin and pleuromutilins that overcome certain patterns of resistance [15]. Fungi can play a role in threatening human health by causing various infections and allergies, as well as causing or aggravating cancer and suppressing the immune system through various mycotoxins [18-20].

Role of fungi in SBS

SBS is commonly associated with poor indoor air quality [21]. A World Health Organization (WHO) report shows that up to 30% of buildings worldwide are the subject of indoor air quality complaints [22]. Airborne fungi are becoming increasingly important due to health hazards [21]. In the presence of moisture, fungi can grow on many building materials, such as brick, wood, cement, wallpaper, carpet, and edible materials. Sexual and asexual spores and metabolites of fungi are easily spread in the air and surrounding environment. Fungal spores are also abundant in the air outside the building. Trees, plants, animals, organic matter in nature, and others are the sources of fungi in the air outside the building [10]. On the other hand, the spores of outside air and indoor air are exchanged. Microorganisms can enter the building during the ventilation of rooms or through various cracks. Many fungi often colonize air conditioning equipment's air filters, and then it will be a direct source of air pollution [22]. Spores and other fungal structures can enter the human body through the mouth, nose, or skin. *Cladosporium*, *Aspergillus*, *Stachybotrys*, and *Penicillium* are among the fungi studies that have pointed to their role in SBS [23]. Fungi play a role in SBS by producing volatile organic compounds (VOCs), mycotoxins, spores, and fragments [22-30].

VOCs

VOCs are organic substances that are volatile, colorless, odorous, and with medium water solubility and low molecular weight that can vaporize and enter the gas phase at normal

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atmospheric temperatures and pressure [24, 25]. It is well known that fungi can secrete many VOCs such as ethylhexanol, 1-octanol, 2-octanol, methylbutanol, methylfuranes, 2-pentanone, 2-hexanone, 2-heptanone, 3-octanone, α-pinene, β-pinene, limonene, camphene, cyclohexane and benzene. Secretion of these VOCs occurs, especially when molds grow in closed, poorly ventilated rooms with high relative humidity. The type of molds-VOC produced depends on the strain and species of fungus and the nature of the substrate on which it grows. Symptoms associated with releasing VOC fungi manifest as lack of comfort, headaches, eye pain, pharyngitis, dry cough, dizziness, blurred vision, lack of concentration, sensitivity to smell, fatigue, apathy, and a greater tendency to catch a cold [22].

Spores or conidia and cellular fragments

Fungi reproduce and propagate by producing conidia or sexual and asexual spores [10]. Spores are thick-walled, dormant structures that retain the genetic content of the microorganism. Fungal sporulation or conidiation refers to the formation of spores or conidia from vegetative cells, and it is influenced by environmental and endogenous biological factors. Light, temperature, humidity, carbon dioxide, nitrogen, nutrient levels, and host substrate are the main environmental factors affecting sporulation [26]. Most fungi are mesophilic, and the optimum temperature for sporulating fungi is 20 to 25 °C. Incidentally, this temperature range corresponds to human comfort indoors, where fungi thrive in workplaces. Inadequate ventilation, humidity control, and dirt management can cause microbial growth and spore production inside the building. Spores and cellular fragments of fungi can spread in the air [23]. Spores and small fragments during inhalation can penetrate the alveolar region and enter the circulatory system by escaping phagocytosis by macrophages, whereas large spores and other fragments are deposited in the nasopharynx. Based on microscopic sample analysis, it has been revealed that hyphal fragments represent 6 to 56% of the total number of fungal particles in field samples [27]. It was shown that the number of released fragments was always up to 500 times greater than the number of intact spores.

Moreover, the number of spores and fragments were not correlated. Smaller fragments have a longer lifespan in the air than larger spores and can penetrate deep into the alveolar region when inhaled. Fungal fragments contain fungal antigens, mycotoxins, and (1→3)-β-D-glucan that may potentially contribute to adverse health effects [27].

Mycotoxins

Mycotoxins are low molecular weight, thermoresistant compounds that can be synthesized by some filamentous fungi [28]. These secondary metabolites are produced by several genera of fungi, such as *Aspergillus*, *Penicillium*, *Fusarium*, *Alternaria*, and others (Table 3) [29]. Mycotoxins can enter the body through fungal spores [30]. Mycotoxins can also be isolated from construction materials contaminated with fungi and house dust. Production of mycotoxins by indoor fungi growing in building materials is usually lower than *in vitro* production in building materials [23]. Some mycotoxins can have mutagenic or teratogenic effects by affecting DNA replication. Mycotoxins exposure can disrupt metabolic, nutritional, endocrine, immune, hepatic, and reproductive systems. Among the acute effects of mycotoxin poisoning, we can mention the deterioration of liver or kidney function, which can potentially lead to death. Some mycotoxins can interfere with protein synthesis and, depending on the exposure dose, cause disorders ranging from skin sensitivity or necrosis to immunodeficiency. Some mycotoxins have neurotoxic effects and cause symptoms ranging from tremors to brain damage. Aflatoxins, trichothecenes, T-2, HT-2, deoxynivalenol, nivalenol, diacetoxyscirpenol, satratoxin, trichoverrol, verrucarol, and ochratoxins are common mycotoxins in indoor environments [31].

Some effects of indoor fungi on human health

People are constantly exposed to airborne fungi, and this contact sometimes causes adverse effects in humans, especially related to respiratory diseases [32]. Fungi can affect human health in different ways, such as allergy, infection, etc.

Table 2. Risk factors of sick building syndrome

Physical	Temperature, building ventilation, noise, vibrations, daylight, electromagnetic fields, ions, ergonomic issues, universal design
Chemical	Formaldehyde, phthalates, volatile organic compounds, odors, environmental tobacco smoke, biocides
Biological	Bacteria, molds, viruses, animal dander, cat saliva, house dust, mites, cockroaches, pollen
Psychosocial, personal	Gender, health condition, stress, individual characteristics, feelings of loneliness and helplessness, working position, social status

Table 3. Some important fungi involved in the sick building syndrome

Fungus	**Allergens/Antigens**	**Toxins and metabolites**
Alternaria	Alt a 1(30 kD), Alt a 2(450 kD), Alt a 3(85 kD), Alt a 4(63 kD), Alt a 5(30 kD), Alt a 6(11 kD), Alt a 7(22 kD), Alt a 8(39 kD), Alt a 9(42 kD), Alt a 10(53 kD),	Alternariol, alternariol monomethyl ether, tenuazonic acid, altenuene, iso-altenuene, tentoxin, altertoxin-I, AAL toxins TA1 and TA2
Cladosporium	Cl a h1(30 kD), Cl a h1(45 kD), Cl a h1(53 kD), Cl a h1(11 kD), Cl a h1(22 kD), Cl a h1(48 kD), Cl a h1(42 kD), Cl a h1(110 kD), Cl a h1(100 kD),	azaphilones, benzofluoranthenones, coumarins, isocumarins, lactones, naphthalenones, macrolides, perylenequinones
Aspergillus	Asp f1(17kD), Asp f2(37kD), Asp f3(18 kD), Asp f4(30 kD), Asp f5(42 kD), Asp f6(23 kD), Asp f7(12 kD), Asp f8(11 kD), Asp f9(34 kD), Asp f10(34 kD), Asp f11(24 kD), Asp f12(47 kD), Asp f13(34 kD), Asp f14(105 kD), Asp f15(- kD), Asp f16(43 kD), Asp f17(- kD), Asp f18(34 kD),	Ochratoxin, aflatoxin, gliotoxins, helvolic acid, verruclogen, fumagillin, fumitremorgin A–C
Penicillium	Pen c1(70 kD), Pen c1(18 kD), Pen c1(33 kD), Pen c1(33kD), Pen c1(34 kD), Pen c1(32 kD), Pen c1(34 kD), Pen c1(68 kD), Pen c1(70 kD),	Ochratoxin A, patulin, citrinin, penicillic acid, penitrem A, PR-toxin, roquefortine, rugulosin, xanthomegnin, viridicarumtoxin, verruculogen
Fusarium	Fus c 1(11 kD), Fus c 2(13 kD), Fus p 4(37.5 kD)	Zearalenone, fumonisins, moniliformin, trichothecenes
Stachybotrys	Sta c 3(21 kD), SchS34(34 kD)	Trichothecenes

Allergy

Allergy is a high sIgE level to some allergens, which is associated with allergic clinical symptoms and affects 10% of children and adults in some countries [33, 34]. Genetic predisposition and geographical and cultural factors effectively affect the prevalence of allergies [31, 35]. All fungi may be allergenic depending on exposure and dose [36]. Allergy is perhaps the most common human reaction to airborne fungi, and the rate of allergy to fungi is reported to be more than 2% [31]. Fungal spores are the known cause of allergic diseases and are recognized as one of the major indoor allergens [31, 37]. *Alternaria*, *Cladosporium*, *Aspergillus*, *Penicillium*, and *Mucor* were reported to be the most allergenic fungi [31, 38]. Allergens initiate a specific immune response by associating those allergens with IgE antibodies [39]. Fungi are potent sources of allergenic molecules that cover various molecular structures, including toxins, enzymes, cell wall components, and highly phylogenetically conserved cross-reactive proteins [40]. The number of fungal proteins capable of binding IgE is about 200; according to some authors, this number is very real [41]. Many fungal allergens are strongly associated with asthma [39, 41]. Atopic diseases, rhinitis, and allergic alveolitis are other allergic diseases that fungi can cause or aggravate [42]. The clinical spectrum of hypersensitivity reactions caused by fungi is very broad and, in addition to IgE-mediated type I allergy, includes types II, III, and IV reactions. Although the classification into types I to IV is very broad in clinical practice, it should be noted that the reality is more complicated because several mechanisms often act together in the pathogenesis of hypersensitivity reactions, which is especially true in the case of reactions to fungi [40].

Mycotoxicosis

Mycotoxin production in buildings appears to occur when a_w (Water activity is defined as the ratio of water vapor pressure in a material to the vapor pressure of pure water at the same temperature) at the surface of building materials exceeds 0.9. However, significant toxin production does not begin until it reaches 0.95. Therefore, the worst-case scenario for an indoor mold problem involves a series of water intrusion events that allow large amounts of biomass and mycotoxins to build up, then a drying period disperses spores, mycotoxins, and colony fragments [43]. Exposure to mycotoxins via consumption, inhalation, and skin contact may lead to various diseases called mycotoxicosis [44]. Mycotoxins can cause acute or chronic symptoms depending on the type and dose of the mycotoxin [45]. Usually, the dose of mycotoxin received in the indoor environment cannot approach the levels that cause an acute toxic response due to the requirement for extremely high airborne spore levels [46]. However, the acute effects of mycotoxin can include headache, nausea, vomiting, abdominal pain, dizziness, and fever [47]. Mycotoxins' most important chronic effect is to induce cancer development, especially in liver and kidney tissues, and suppression of immunity [48, 49]. Many mold-

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toxic metabolites are produced by a diverse range of molds in domestic damp houses [50]. One fungi involved in the SBS is *Stachybotrys chartarum*, which is the flagship for mycotoxin-producing molds in indoor environments and can grow on wallpaper and wet plaster. A low concentration of Satratoxin H produced by *Stachybotrys chartarum* can cause necrosis and haemorrhage in many organs [48]. *Penicillium* and *Aspergillus* species are common and important molds in the human environment, and some of the carcinogenic effects of inhaling the spores of some have been confirmed [51].

Fungal infections

The human respiratory tract is exposed to airborne fungi daily. Various species of fungi are inhaled; some can survive at body temperature and escape the host defense of healthy people [18]. Several factors, such as mucociliary clearance, activation of alveolar macrophages, neutrophilic granulocytes, T-cell-mediated immune functions, and humoral immunity can influence the host's specific immunity to fungal spores can influence the host's specific immunity to fungal spores [52]. Some fungi, namely *Histoplasma* spp, *Blastomyces dermatitidis*, *Coccidioides* spp, and *Paracoccidioides brasiliensis*, are true pathogens and can cause infection [18]. Some fungi, such as *Cryptococcus* spp and *Aspergillus* spp, are saprophytes and can cause infection when inhaled in substantial quantities or compromised by the immune system [18]. True pathogens are limited geographically and do not exist in all countries, especially in Iran, whereas saprophytic fungi occur worldwide, and some affect a broad range of patients [18, 53]. The most common fungal diseases of the upper and lower airways in nonimmunocompromised patients include chronic invasive or granulomatous fungal rhinosinusitis, fungal ball, allergic fungal rhinosinusitis, community-acquired Aspergillus pneumonia, chronic pulmonary aspergillosis, pulmonary histoplasmosis, pulmonary coccidioidomycosis, pulmonary paracoccidioidomycosis, pulmonary blastomycosis, cryptococcal pneumonia and Aspergillus bronchitis which can be diagnosed by clinical, laboratory and radiological presentation [18, 54-56].

Discussion

Fungi can damage building materials and affect residents' health by causing SBS. Lack of moisture control, improper ventilation system, and lack of proper cleaning can cause the growth of microbial agents in the building. SBS is also seen in modern high-rise buildings because these buildings are designed so that the windows are sealed, natural ventilation and the entry of fresh air and light into the building are limited due to the reduction of energy consumption [23]. The surface of the respiratory tract is one of the biggest interfaces between humans and the environment, constantly in contact with suspended particles [57]. The size of the particles, flow rate, age, gender, and anatomical and physiological characteristics of the respiratory system of people determine the amount of inhalation of particles [58]. Fungi in buildings are constant sources of risk of allergy, infections, and other respiratory tract diseases [59, 60]. It has been shown that fungally contaminated buildings do not improve by themselves and require remediation to restore a healthy environment. Some fungi involved in SBS cannot grow on inorganic materials [61]; therefore, using inorganic materials in the construction industry may be a way to improve indoor air. It has been reported that fungal VOCs are associated with SBS, but compared to bacterial VOCs, they have been relatively less studied. More than 300 distinct VOCs have been identified from fungi [25]. Octen can be mentioned among fungal VOCs. Results show that a low concentration of 1-octen-3-ol causes a decrease in dopamine levels dopaminergic neuron degeneration and causes Parkinson's symptoms [62]. However, it seems that more studies are required on the role of fungal VOCs in the disease. Allergy is one of the problems that residents may experience. Among all described types of allergic reactions caused by fungi, the most common is type I hypersensitivity, which is also called anaphylactic and clinically appears as asthma, rhinitis, sinusitis, urticaria, swelling of blood vessels or bronchial obstruction. In this case, fungal allergens induce IgE production, which opsonizes mast cells and basophils [22]. *Aspergillus* species are a continuous source of allergens, antigens, complex proteins, and enzymes for the environment. *A. fumigatus, A. flavus*, and *A. niger* are known causes of type I and III allergic reactions in humans. *A. fumigatus* produces multifunctional enzymes and toxins that facilitate adhesion and hydrolysis of host cell components and complex allergens that cause severe allergic reactions [63]. Type II reactions are less frequent and are usually caused by the mannan antigen present in the cell walls of *Aspergillus* and *Candida* [22]. Type III sensitization to fungal antigens can be seen in the cases of allergic alveolitis and bronchopulmonary aspergillosis, which is usually associated with immune complexes consisting of fungal antigens and antibodies [64-66]. Type IV hypersensitivity reaction occurs 24-48 hours after antigen contact with Th1 sensitive lymphocytes, which may manifest as contact dermatitis or urticaria [67, 68]. Another danger that threatens residents is fungal toxins, which can enter through inhalation of spores, conidia, phialides, conidiophores, and fragments of mycelium [22]. Mycotoxin production depends on the fungal strain, genotype, growth stage, humidity, temperature, and substrate composition [69, 70]. Among the environment's most essential and common mycotoxins, we can mention ochratoxin A, aflatoxins, zearalenone, trichothecenes, and fumonisins [69]. The significant increase in cancer incidence in people living in moldy rooms is undoubtedly related to long-term exposure to mycotoxins [71, 72]. In Poland, a quarter of the houses are damp, and 24% of residents are at risk of mycotoxins and allergens secreted by fungi [22]. Infection is another problem that may afflict residents. Lungs or airways can be infected by some fungi that can be diagnosed by sampling from blood, sputum, induced sputum, or bronchial specimens and several tests, such as direct microscopy, fungal culture, galactomannan antigen, and polymerase chain reaction. Probable risk factors of this disease include environmental exposure, genetic factors, and pulmonary structural risk factors

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that need further study. Antifungal treatment is indicated in approximately all patients with chronic cavitary pulmonary infections, chronic invasive and granulomatous rhinosinusitis, and Aspergillus bronchitis. Drug resistance, drug interactions, and adverse reactions may be seen in some infections [18].

Conclusion

Airborne fungi can cause a wide range of diseases, such as allergy, intoxication, and infections systemically or in the lung and upper and lower airways. Some of these diseases are acute, and some are chronic. In addition to the immune system and genetic factors, environmental factors play an important role in causing these diseases. Building design, materials used in construction, temperature, humidity, and ventilation are among the environmental factors that influence the growth of airborne fungi and, as a result, sick building syndrome. Indoor building spaces must have continuous access to fresh air for residents' health, well-being, and performance. Clean, breathing air can be achieved by removing visible fungi from the interior of a building and adequate outdoor air exchange through ventilation. A dynamic assessment method for indoor air quality and SBS should be developed to provide a clean environment for building users. The essence of indoor air quality evaluation or monitoring is to identify trends and problem areas and then take corrective action.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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