International Journal of Advanced Research in Medicine

E-ISSN: 2706-9575
P-ISSN: 2706-9567
IJARM 2022; 4(1): 120-131
Received: 12-01-2022
Accepted: 27-02-2022

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A review on the effect of fungi on patients with respiratory diseases

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DOI: https://doi.org/10.22271/27069567.2022.v4.i1b.358

Abstract
Respiratory diseases are considered chronic diseases that negatively affect the lives of patients, and recent research has focused on the relationship between respiratory diseases caused by inhaling parts of fungal strings or fungal blackboards. There are a few full reports that fully reveal the relationship of fungi to the events of a number of chronic diseases associated with the respiratory system, as well as the effect of toxins secreted by people exposed to these fungi and the characterization and purification of fungi from clinical specimens that included on sputum, wiping, parts of tissues from the lung and other samples such as the serum. As an immunological study. In this review, the authors searched through four scientific bases based on calligraphy data using the following keywords (fungi), (respiratory disease) and (production, synthesis, or synthesis). The scientific criteria were adopted in this review to classify the existing articles according to the degree (from 0 to 10). After Exclusion criteria, 62 articles were selected. None of them received a maximum of 10 points determined by the methodology, which indicates a lack of studies dealing simultaneously with respiratory diseases, isolation and fungi, purification of their toxins, and the study of the genetic makeup of these fungi and the extent of the effect of these toxins on the respiratory system directly to the patient. Among the fungi studied in these articles are *Penicillium* spp and *Aspirgillus* spp, which were the most frequent and closely related fungi species with respiratory diseases which were isolated by researchers in this review.

Keywords: Fungal genotypes, mycotoxins, respiratory tract disease

Introduction

Bronchial diseases such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF) are common, and are considered to be major respiratory diseases. Infection of the respiratory system can be caused by pulmonary fungi that exist in the environment, although clinical importance is unclear. The sensitivity of *Aspergillus* bronchopulmonary disease (ABPA) is known to cause severe complications of airway colonization associated with hypersensitivity reaction. *Aspergillus fumigatus* has been reported at a high rate in asthmatics (Pashley *et al*. 2012) [52], and cystic fibrosis patients (Kraemer *et al*. 2006) [38]. The fungal invasion may have a harmful effect without meeting all the criteria necessary for the diagnosis of the fungus. It is considered one of the most important risks and its strongest is causing the fungi to produce benign pulmonary tumors, fibrosis or pulmonary cyst and decreased lung function. However, it is not clear whether the fungi that invade the lung and the respiratory system in general may contribute to reducing lung function in most patients. (Sudfeld *et al*. 2010) [83] Some studies have focused on linking to the presence of fungi and association with most diseases such as pulmonary diseases, asthma and chronic obstruction and those that are found mostly from patients and suspected of having the fungus *A. fumigatus* which was isolated from sputum samples when most patients under study. (Pihet *et al*. 2009) [56].

In comparison with BAL, the sputum provides the advantage of being non-invasive to obtain, and is therefore more accessible and more available for repeatability in most measurements. (Pihet *et al*. 2009) [56].

The use of an induction protocol can result in samples obtained from more than three quarters of the normal and asthmatic who cannot produce sputum (Pavord *et al*. 1997) [54]. Most studies in the United States, Canada, and Australia have relied on several criteria for isolating fungi and studying their genetic makeup from clinical samples. For the respiratory system as well as conducting immunological studies through the use of the national standard

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method established by the Health Protection Agency (HPA) in BSOP57 (Standards Unit, Department For Evaluations 2009) [83]. Most recent studies that focused on immunological studies related to the study of antibodies such as IgE have found a link of *A. fumigatus* fungus associated with a reduction Lung function in the case of asthma. *A. Fumigatus* was detected in sputum of *A. Fumigatus*-IgE sitensized asthma. (Standards Unit, Department for Evaluations 2009) [83]. There were a number of differences in the methods used to study the various fungi and toxins they produced and their relationship to respiratory diseases, including samples, clinical methods, and other comparisons. The aim of this study was to directly methodological comparison of the reports collected, which concerned the relationship of fungi to respiratory diseases which included Comparisons on the methods of purification followed with the fungi and toxins they produce, as well as the extent to which genetic studies are used to determine the genetic patterns and mutations occurring in most of these fungi. Review. In this study, the fungal species that isolated the specific articles under review were identified, as well as the most frequent fungi in clinical samples, and it was noted the importance of conducting other studies based on the link between fungi and most respiratory diseases in humans.

Method

The first step in the research was to conduct electronics research at Scopus (http://www.scopus.com/), Science Direct (http://www.sciencedirect.com/), Elsevier https://elsevier.com/about/open-science/open-access/open-access-journals, SCIENCE OPEN https://scienceopen.com, and OXFORD ACADEMIC https://academic.oup.com/journals/pages/open_access. Using the following keywords: (fungi), (mycotoxins and fungi) and (producing mycotoxins and their effects on the respiratory system in Human) and (asthma). This procedure allowed the selection of papers published on the production of mycotoxins and the presence of fungi in the human environment. There were no restrictions on the year and date of publication, due to a lack of publications on this research. There were no restrictions on the methodology used, types of analysis, and outcome measurement. In addition, there were no restrictions on fungi, culture conditions and other checks, including measuring the proportion of toxins and fungal species present in the human environment, as well as how they relate to allergies in the respiratory system, nose, ear, and eye, as well as their association as a cause of some respiratory diseases such as asthma As a substrate. Criteria for selection of papers were determined to assess the wager conditions for the presence of fungi and their association with respiratory sensitivity, and the criteria adopted in this review were consistent with the criteria suggested by Greenhalgh. 40 parameters evaluated on scale: suitable (score: 2), partially appropriate (score: 1), insufficient (score: 0) or adequate (score: 1) and inappropriate (0). (Wanderley *et al*. 2017) [92].

Production process: The papers examined indicated the extent to which fungi and their presence in the environment surrounding the human being are associated with a group of respiratory-related diseases and the most important of these diseases is asthma which is a type of respiratory sensitivity affecting a person a number of reasons including genetic causes or causes related to the human environment and the presence of a group of the microorganisms, including fungi as a catalyst, the effect was irritation and respiratory sensitivity in some people, fungal species are described in most of these leaves as well as the production of mycotoxins.

Characterization of fungi and their association with allergy production: papers which describe how fungi have been associated with provoking allergies or causing respiratory diseases. Several tests, including a study of the genetic makeup of fungi producing fungi toxins, have a score of 2. Those that relied only on describing fungi and their fungal toxins in the human environment. Which did not have at least the basic values to explain the association of fungi mainly with respiratory diseases. On a degree 1. Papers that did not have at least these three factors in fungi associations and respiratory diseases were considered as the main cause of respiratory diseases and only indicated the fungi and toxins in general got a score of 0. (Wanderley *et al*. 2017) [92].

Quantitative method for mycotoxins: The method that was adopted on modern methods of measuring mycotoxins and their genetic makeup using ELISA and rtPCR as well as HPLC method she got a score of 2. Sheets with other quantitative methodologies, got a score of 1, and those that only kept a qualitative analysis activity for toxins, got a score of 0. There are many other things that were not recorded, but were taken into account in studying fungi and their association with production Respiratory sensitivity as well as studying some of the differences between mycotoxins and some toxins from other microorganisms such as bacteria, because they were associated with the subsequent discussion. The parameters recorded in the mentioned tables are summarized. The table was combined with a summary of selected data related to the criteria according to the criteria approved in the review, including some features such as studying the genetic makeup of fungi toxins as well as the extent of respiratory fungi and asthma diseases.

Results and discussion

Through the application of the search procedure, a total of 1,200 articles were found in the Science Direct database, 400 articles in the Scopes database, 500 articles, 269 books in Zlibrary articles, and 444 articles in Oxford,. Based on the specific inclusion and exclusion criteria, (62) articles were selected for this review, distributed as shown in Table (2), (18) articles scored a score of 5 (29.03% of all articles selected), 33 articles recorded a score of 4 (53.2%), and 24 articles recorded a score of 3 (38.7%), which indicates a decrease in study coefficients at the same time. Respiratory, by inhaling blackboards or parts of the fungal floss or toxins that produce and cause them to provoke an allergic respiratory-like asthma .There was no time lapse between these articles however, only 31 articles were published within 10 years. Of these 37 articles, only 15 have been published in the past five years, clearly indicating the need for more research related to linking fungi and respiratory disease.

Table 1: Score of selected parameters for critical evaluation of the systematic review.

Criteria for determining the scores	Pointing		
	2	1	0
A. Fungi and toxin by Genetic and other method	Purification and study of fungi and their toxin	Purfi by other method without genetic type	Only descript or review
B: Relation of fungi with respiratory diseases	complete description	partial description	no

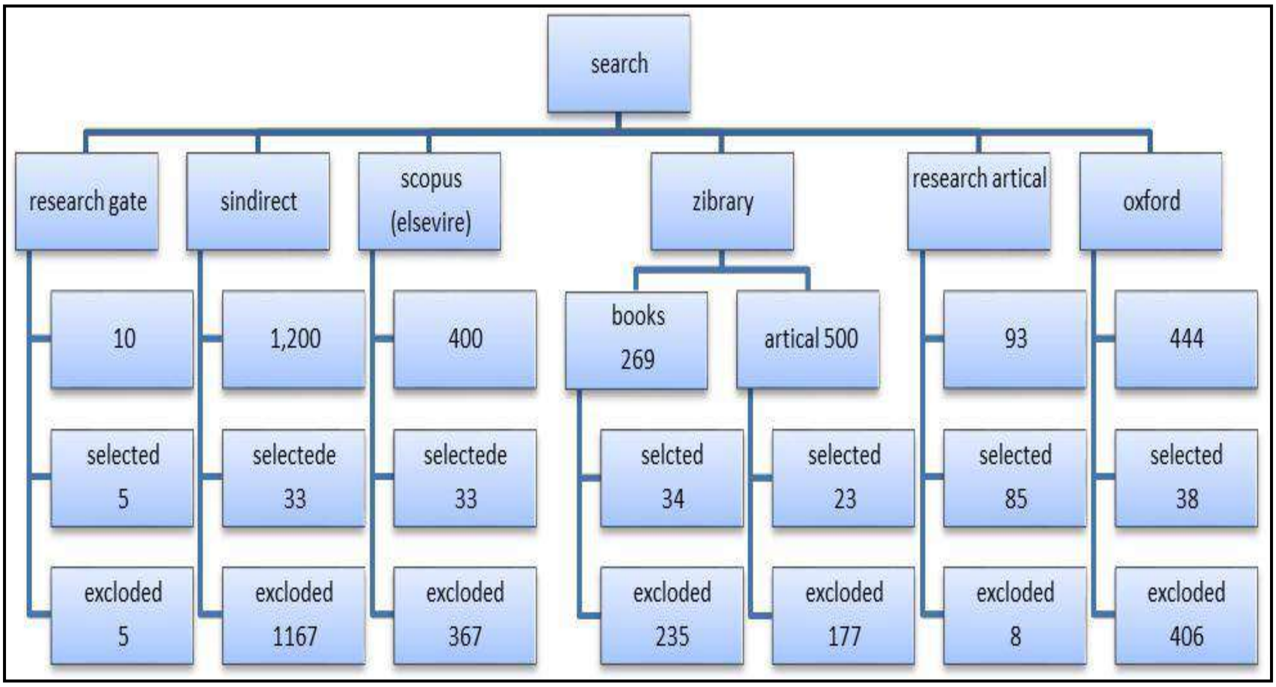

Fig 1: Total articles selected in four different databases using the described methodology:

Table 2: Scores distribution of selected articles.

Authors	A	B	C	D	E
(Pihet *et al*. 2009) [56]	2	0	0	2	5
(Porter *et al*. 2011) [57]	0	1	0	2	4
(Periselneris and Brown 2019) [55]	2	0	0	2	5
(Cole *et al*. 2004) [16]	2	0	0	2	5
(Borman *et al*. 2010) [8]	0	1	0	2	4
(Pashley *et al*. 2012) [52]	2	0	0	2	5
(Abliz *et al*. 2004) [2]	2	0	0	2	5
(Sharma *et al*. 2012) [79]	0	1	0	2	4
(Marchisio *et al*. 1999) [44]	0	1	0	2	4
(Couillin *et al*. 2012) [17]	0	1	0	2	4
(Leclair and Hogan 2010) [42]	2	0	0	2	5
(Gordon and Read 2002) [26]	0	1	0	2	4
(Roilides and Simitsopoulou 2010) [68]	0	1	0	2	4
(Richardson, Bowyer, and Sabino 2019) [67]	0	1	0	2	4
(Aberkane 2002) [1]	0	0	1	2	3
(Pryce *et al*. 2003) [59]	2	0	0	2	5
(Casadevall and Pirofski 2006) [14]	0	0	1	2	3
(Schwarz *et al*. 2018) [75]	2	0	0	2	5
(Wiszniewska *et al*. 2009) [96]	0	1	0	2	4
(Fong *et al*. 2017) [21]	0	0	1	2	3
(Kondori *et al*. 2015) [36]	2	0	0	2	5
(Irinyi *et al*. 2015) [32]	2	0	0	2	5
(Becker *et al*. 2014) [5]	2	0	0	2	5
(Zvezdanova *et al*. 2019) [100]	2	0	0	2	5
(Lagerström, *et al* 2004) [39]	2	0	0	2	5
(Casadevall and Pirofski 2006) [14]	0	0	1	2	3
(Paugam *et al*. 2010) [53]	0	1	0	2	4
(Siqueira *et al*. 2018) [81]	2	0	0	2	5
(Wang, Hearon, and Phillips 2020) [93]	0	0	1	2	3
(Venkatesh and Keller 2019) [91]	0	1	0	2	4
(Hooper *et al*. 2009) [31]	0	1	1	2	4

(Zain 2011) [99]	0	0	1	2	3
(Cai *et al*. 2011) [13]	2	0	0	2	5
(Reverberi *et al*. 2010) [66]	0	1	0	2	4
(Sherif, *et al*. 2009) [80]	0	0	1	2	3
(Terčelj *et al*. 2011) [87]	0	1	0	2	4
(Park and Cox-Ganser 2011) [51]	0	1	0	2	4
(Fisk, Eliseeva, and Mendell 2010) [20]	0	0	1	2	3
(Tanaka *et al*. 2000) [86]	0	1	0	2	4
(Sengun, Yaman, and Gonul 2008) [76]	0	0	1	2	3
(Schulz, Senkpiel, and Ohgke 2004) [73]	0	1	0	2	4
(Marinas *et al*. 2010) [45]	0	1	0	2	4
(Proietti *et al*. 2013) [58]	0	1	0	2	4
(MYERS 1947) [49]	0	1	0	2	4
(Hassan, Sand, and El-Kadi 2012) [30]	0	1	0	2	4
(Varga *et al*. 2013) [90]	0	1	0	2	4
(Boonzaaijer *et al*. 2008) [7]	0	1	0	2	4
(Rosenbaum *et al*. 2010) [69]	0	1	0	2	4
(Puel *et al*. 2007) [60]	0	1	0	2	4
(Ganguly 2014) [25]	0	1	0	2	4
(Frisvad, Filtenborg, and Thrane 1989) [22]	0	1	0	2	4
(Winck *et al*. 2004) [95]	0	1	0	2	4
(Molina, Zón, and Fernández 2002) [48]	0	1	0	2	4
(Bisht *et al*. 2002) [6]	0	1	0	2	4
(Jang *et al*. 2019) [35]	2	0	0	2	5
(West and Palu 2008) [94]	2	0	0	2	5
(Mokubedi *et al*. 2019) [46]	2	0	0	2	5
(Pashley *et al*. 2012) [52]	0	1	0	2	4
(Chevallier 2019) [15]	0	1	0	2	4
(Schütze *et al*. 2010) [74]	0	1	0	2	4

*A: Purification and study of toxin fungi by physical, chemical and genetic methods. *B: Purification by chemical and physical methods only.* C: Study review only.* D: Microorganism, fungi and toxins.

Fungi

Were selected based on this systematic review. A number of fungal species were diagnosed in these articles that included the diagnosis of various types of filamentous fungi, including *Penicillium, Aspergillus, Alternaria, Monacrosporium, Trichophyton, Fusarium, Microsporum mucor, phialophora, fonsecaea, stemphylum, acromonium, histoplasma, oidiodinometes, cladosporium, Exophiala, soedosporium*, and *Rhizopus*). It has also been noted from previous articles that the highest proportion of fungi that are closely related to most respiratory diseases are *Aspergillus* and *Penicillium* fungi, if the frequency of *Aspergillus* fungi is about 30% and *Penicillium* fungi have a frequency of 24%, while the rest of the fungi isolated with different fungi differed depending on On the articles selected in this review. It is interesting that about 33% of the fungi mentioned in the selected articles are described as one of the most common pathogens and production of mycotoxins that were closely related to respiratory diseases. Pathogenic species associated with the production of mycotoxins were *Aspergillus, Penicillium* SP and *fusarium*. Among the most important toxins isolated in most of these articles are: AFLB1, AFLAB2, AFLAG1, AFLAG2, AFLAM, OTA, DON, ZEN, T-2 - toxins, fusidic acid, and others. (Puel *et al*. 2007; Ganguly. 2014; Chevallier. 2019) [60, 25, 15] We compared a set of results from studies that were conducted to link potential respiratory diseases and their relationship to the presence of fungi in patient-inhabited environments. (Pina-Vaz. 2004) [61] The source also indicated, through his study that he relied on the study design or method of analysis: age, gender, and some other measurements, as a relationship between the presence of mold in damp places, respiratory infections, and bronchitis. (Pina-Vaz. 2004) [61]. There is insufficient evidence to document the relationship between humidity factors with respiratory infections, but this evidence is still specific for airway inflammation, and is consistent with WHO findings regarding respiratory infections, which strongly suggest that moisture and mold are closely related to bronchitis. (Pina-Vaz, *et al*. 2004) [61]. Respiratory infections include lower, upper and middle respiratory infections and otitis media. While upper respiratory infections include colds, sinus infections and pharyngitis (sore throats). Most of these infections are caused by microorganisms such as viruses, although some cases are caused by bacteria (Pina-Vaz. 2004) [61]. Otitis media, inflammation of the middle ear is often caused by a previous infection of the upper respiratory tract, which can be bacterial or viral in origin (Barbosa JM, *et al*. 2008) [9]. A marked increase in respiratory infections can occur with mold and increased humidity, or more serious infections may occur and become clinically apparent; or they may be caused by weakened immune defenses. (William J Fisk el at. 2010; Álvarez-Barrientos *et al*. 2000) [97, 20, 3] Although it has not been shown that exposure to microbial toxins in pathogenic or wet fungal homes can reduce the human immune response, potential mechanisms may be suggested that inflammatory responses, whether in the laboratory or in specific microorganisms present in buildings Humid [Barbosa JM, *et al*. 2008; Bornehag. G. *et al*. 2004] [9, 11], and that this study concluded conclusions related to linking moisture to bronchitis. It referred to the IOM audit in 2004. (Barbosa JM, *et al*. 2008) [10]. It was the last WHO review. In 2009, which linked moisture or mold to respiratory infections or bronchitis, he said: "Healthy people who are exposed to moisture or rot in indoor environments are more likely to develop respiratory infections. (Bornehag G. *et al*. 2004) [11]. As shown by conducting a skin examination test For a number of patients through a skin test, which is injected extract of different types of fungi identified in the researcher's study, where almost 82% of patients with respiratory sensitivity have a positive test, and the researcher also used the ELISA test to confirm the relationship between the presence of Fungi and mold in Humid environments and their relationship to respiratory sensitivity and through antibody study. (Institute of Medicine. 2004) [33], (IgE) Tocheck for thepresence of Cross-active -proteinsin), studies of inhibition with patients were performed, mutual interaction between IgG between EN, C. lunata, A was evaluated. Alternata, and C. herbarum by examining EN spots using antibodies against these fungi. Both antibodies to fungi were discovered and found to be in high levels. (Institute of Medicine. 2004) [33].

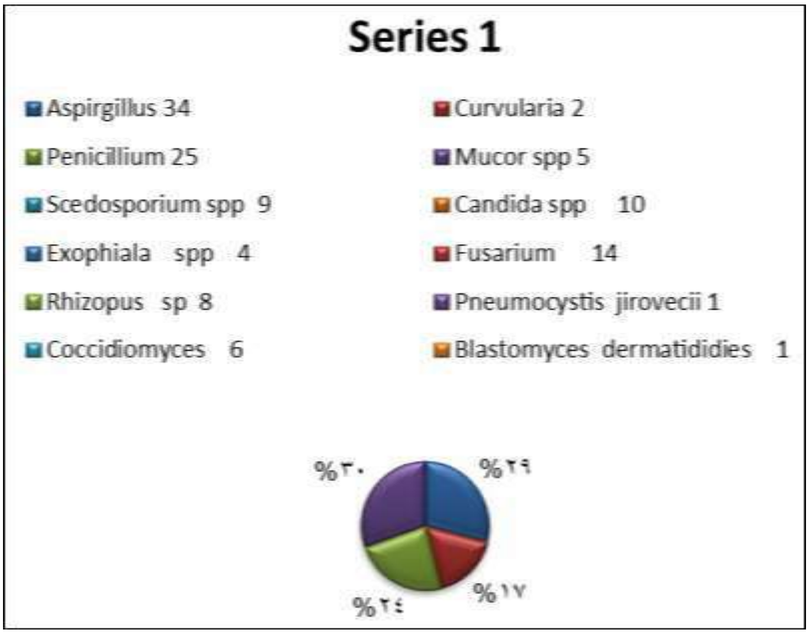

Fig 3: Summary of the percentage of fungi isolated from the pathological samples of the selected research group and approved in the review of the group.

Fungal toxins

Mycotoxins are toxic compounds and known byproduct metabolites that are mainly produced by various large and fungal species of *Aspergillus*, *Fusarium*, *Penicillium*, and alternative genera. (Greco, M.V.; *et al*. 2014; Njobeh, P.B. *et al*. 2012] [27, 50]. Although these substances can be found in foods and other products generally low levels with toxicological data, their health risks cannot be completely excluded and their effects on the immune and reproductive system in humans and other animals are noticed, (Fraeyman, S, *et al*. 2017) [23]. Among the most important of these toxins are the following:

1. **Aflatoxin:** The first poison found in the late 1950's was aflatoxin, from *Aspergillus flavus* (+ toxin), and many other fungal species from which aflatoxin was isolated. These toxins are named aflatoxin including B1 (the toxin has a visible blue spot) and G1 (contains a gray spot) according to the fungi from which toxins were first isolated from. There are 4 types of aflatoxin toxins, which are B1, B2, G1, G2 in addition to Type M, which is the metabolism type of toxins. Aflatoxin B1 is almost three times more toxic than aflatoxin G1. Aflatoxins are primarily produced by *A. flavus* and *A. parasiticus*, although aflatoxins are also produced by other fungi. Toxins of the type aflatoxins are highly toxic and their target organ is the liver. Aflatoxin B1 is considered the most potent spacta-carcinogen (carcinogen in the liver). Given the level of toxicity and carcinogenicity, the effect of aflatoxin on human food or lactating dairy mammals was about 20 ppb shortly after it was determined in 1957; this number decreased to 1 ppm today according to the World Health Organization. A person consumes 0.002 ppm aflatoxin daily (often corn products), or 0.02 ppm in the southeastern United States, which is ten times higher. A lethal dose for humans from aflatoxin is about 400 ppm of aflatoxin. (Ranjit Bordoloi and G.Subha, 2014) [65].
2. **Stigmatiocysteine:** Another type of toxin, produced by *Aspergillus versicolor* and some strains of *A. flavus* and A. parasiticus, and is considered a synthetic biological precursor to aflatoxin, and contains a di-dihydrofurofuran carcinogen, the target organ is the liver. (Ranjit Bordoloi and G.Subha. 2014) [65].
3. **Ochratoxin:** Toxin is produced by *Aspergillus ocraceus* and *Penicillium viridicatum*. Ochratoxin Type A (OA) is combined with aflatoxin to make it more toxic and has been shown to be a carcinogen for humans. Ochratoxin is preferred in cold temperatures below 50 Fahrenheit and can grow in cheese cake. Ochratoxin A is stored in edible tissues in pigs, and the USDA sets work limits for Ochratoxin in feed and pig tissue. The target organ of Ochratoxin A is the kidney, followed by the liver. Ochratoxin B is non-toxic. (Ranjit Bordoloi and G.Subha. 2014) [65].
4. **Alternatives:** The toxins produced by the types of alternatives, which are one of the most common fungal spores that are encountered because they can grow on cement, plaster of tiles, a variety of foods, and wallpaper. (Ranjit Bordoloi and G.Subha. 2014) [65].
5. **Trichothecenes:** These are toxic chemicals produced by *Fusarium*, *Stachybotrys*, *Trichoderma* and other less common fungi. Trichothecenes is divided into four categories: T-1, T-2, T-3, and T-4. Mycotoxins T-1 are extremely rare and toxic. The first of them is T-2, and it

has a history dating back to 1912 in Russia, where it was associated with dietary leukemia (ATA). T-2 is very toxic and contact with it leads to cellular death, ulceration and necrosis at the site of contact. (Ranjit Bordoloi and G.Subha. 2014) [65]. and with bacterial infections, wounds and burns resulting from contact with this type of toxin, which may lead to death. According to classified documents, the T-2 is the only one used as a biological weapon. Mycotoxins are generally resistant to high temperatures because they have high thermal stability as well as resistance to UV stabilization and these properties are very important when considering their use as a biological weapon during biological warfare. (Ranjit Bordoloi and G.Subha. 2014) [65].

6. **Diacetoxicerpenol (DAS):** known as angidine, TI is a less toxic type of tricyclic known as T-3 and is produced by *fusarium.* The importance of this type of toxins lies in its ability to interact with other types of toxins, which makes it more effective. (Ranjit Bordoloi and G.Subha. 2014) [65].
7. **Deoxynivalenol (DON):** The least toxic trioxine known as T-4, DON is the most easily detectable tri-triethoxine. Since all four classes of tri-tyrosine are found together, DON is an sentiment because of the presence of other more powerful triethoxine. (Ranjit Bordoloi and G.Subha. 2014) [65].
8. **Zearalenone:** One of the very strong fungal toxins that *Fusarium* produces and is associated with prolapse of the uterus, breast development in males and testicular atrophy, as it is considered to have an effect on reproductive characteristics. Many countries have already established work levels for zearalenone. (Ranjit Bordoloi and G.Subha. 2014) [65].
9. **Fumonisin-(Fumonisin B1):** This mycotoxin is produced by *Fusarium moniliforme*. Fumonisin and This type of toxin is a formidable subject because suspected as a carcinogen. (Ranjit Bordoloi and G.Subha. 2014) [65].

Diseases related to fungi and their mycotoxins

There are many diseases that may result as a result of the presence of fungal toxins in the environment in which a person is present. Among these diseases are:

1. Asthma and Lower respiratory symptoms

Often in some patients, asthma may not be diagnosed in many people who have asthma-like symptoms such as shortness of breath, coughing, wheezing, chest tightness, or Difficulty breathing at night if they have asthma. In a population study of a group of adolescents, Searsted and his colleagues, (1998) reported that a third of the asthma cases identified were not diagnosed as asthma diseases (Guerra S, *et al*. 2002) [28]. As it was found in this study that cough is the most common symptom in patients, this study has linked the health effects of humid indoor environments to both building-related symptoms and diagnostic diseases that reflect the fact that this type of disease is associated with the presence of fungi in buildings, and this indicates that the ratio Certain occupants with symptoms of water-damaged buildings may suffer from asthma (Guerra S, *et al*. 2002) [28].

2. Rhinitis/sinusitis

Rhinitis is one of the most common diseases characterized by stuffy nose, gonorrhea, itchy nose and sneezing. There are two different types of rhinitis, allergic rhinitis and non-allergic inflammation. Allergic rhinitis is diagnosed through a combination of characteristic symptoms and a positive SPT or a specific serum IgE for airway allergens, while the diagnosis of non-allergic rhinitis is by symptoms of the nose, as there is no known cause of allergy, and negative SPT, and there is no specific serum IgE (Togias A, 2003; Abbas AK, *et al*. 1996) [88, 4]. Non-allergic rhinitis has been defined by a set of other terms such as permanent, non-infectious, internal, and idiopathic rhinitis (Sokol CL, *et al*. 2008) [85]. The incidence of rhinitis is about 20-40% of people in western countries (Sokol CL, *et al*. 2008) [85] and about 20% of the US population have allergic rhinitis (Shen HH, *et al*. 2003; Ponikau JU, *et al*. 1999) [84, 63]. As for sinusitis, which is often associated concurrently with nasal airway inflammation in most cases and may be preceded by a set of symptoms of rhinitis (Bourke SJ, *et al*. 2001) [12]. As a result, a new term for sinusitis has been defined as inflammatory disorders of the nasal mucosa and paranasal sinuses (Lacasse Y, *et al*. 2008) [40]. Allergic sinusitis is a type of chronic sinusitis (CRS) (Selman M, *et al*. 1993) [77]. If more than 30 million sinusitis cases are diagnosed in the United States annually (Bourke SJ, *et al*. 2001) [12]. Asthma is often associated with sinusitis or otitis media Bourke SJ, *et al*. 2001) [12]. Most occupational asthma or patients with symptoms of asthma in wet buildings may also have work-related rhinitis symptoms. (Seuri M, *et al*. 2000) [78]. In the past decade, nasal sinusitis has been diagnosed as one of the independent risk factors contributing to the development of asthma. Further research on the association of measures of exposure to rot, development of sinusitis and other low respiratory diseases among wet building occupants is warranted

3. Allergic rhinitis

It is a type I response to hypersensitivity. Inhaled fungal allergens are treated by giving antigen cells, which activate Th2 cells and produce Th2 cytokines such as IL-4 and IL-5 (Togias A. 2003) [88]. IL-4 stimulates B cells to produce specific IgE binding to mast cells and basal cells that migrate to the nasal mucosa, which reflects sensitivity to fungal allergens (Cragin LA, *et al*. 2009) [29]. IL-5 has been causally associated with allergic rhinitis (Laney AS, *et al*. 2009) [41]. This allergy mechanism is guaranteed through chronic exposure to allergens produced by fungi that can lead to allergic rhinitis. On the other hand, the mechanisms that cause non-allergic rhinitis are not well understood and may suggest neurological and inflammatory mechanisms as their main cause. However, many other causes of non-allergic rhinitis may be shared by a number of different mechanisms that are not yet known (Young SH, *et al*. 2008) [98].

4. Hypersensitivity pneumonia (HP)

Also called exogenous allergic alveolitis, it is a granulomatous pulmonary disease caused by repeated inhalation of a sensitive antigen in people exposed, and is characterized by a group of frequent symptoms that include fever, sweating, chills, shortness of breath, cough and fatigue. (Iriarte MJ *et al*. 2001; Ramachandran G, *et al*. 2014) [34, 64]. In HP, sensitivity, antigen properties, and interactions between the environment and genes are among the most important factors that work together to develop allergic pneumonia (Iriarte MJ *et al*. 2001) [34]. Since not all inhaled antigens stimulate HP, potential HP antigens may have a certain set of properties such as specific volumes, the ability to produce an inflammatory response and melting as well as cellular immune responses. Although a large number of exposed people may be aware (either humoral or cellular) of HP provoking antigens, only 5-15% of people exposed to them develop HP. This pattern indicates that genetic susceptibility and hematological factors are also an important factor. Acute and subacute clinical forms may develop from HP to chronic HP with continued exposure, although low levels of exposure may also indirectly lead to a transition to chronic form of inflammation (Iriarte MJ *et al*. 2001; Ramachandran G, *et al*. 2014) [34, 64]. Repeated cases of HP and chronic HP may lead to pulmonary fibrosis or emphysema, and chronic HP has progressive shortness of breath when exerting effort, increasing coughing, weight loss and fatigue. (Romero HS, Iregui CA. 2010) [70]. The disease progression can be more complex than described above, which mainly depends on the interaction between exposure and host response (Iriarte MJ *et al*. 2001; Ramachandran G, *et al*. 2014) [34, 64]. It has been suggested that increased exposure to microbes, including fungi and their products, may primarily cause HP in occupants prone to mold-contaminated buildings. (Ramachandran G, *et al*. 2014) [64].

5. Sarcoidosis

Sarcoidosis is a type of granulomatous disease that includes multiple organs, including the lung, and which represents the most affected organ. They are characterized by non-destructive granulomas that consist of epithelial cells, giant Langerhans cells, lymphocytes, and fibroblasts (Todar K, 2017; Fraser A, 2017). Currently, there is no precise definition of sarcoid disease, nor are there medical tests that determine the definitive diagnosis of sarcoidosis. The annual incidence of sarcoid disease is 35.5 cases/100,000 in America and Africa and 10.9 cases/100,000 Caucasian (Morris WE. 2009; Ehling-Schulz M, *et al*. 2006) [47, 19]. A recent study of sarcoid prevalence in Vermont, USA, reported 66.1 cases/100,000, which is much higher than previous estimates (Morris WE. 2009) [47]. The peak of infection in this disease occurs between the ages of 30 and 39 years, and the disease often develops before the age of 50 years, although the infection varies greatly throughout the world. The International Organization for Migration and the World Health Organization have not evaluated sarcoid disease as a possible health outcome of exposure to internal rot). Until now, epidemiological evidence of a correlation between exposure to mold Sarcoid disease is rare (Morris WE. 2009) [47]. However, even with the possibility of misdiagnosis, all results indicate that sarcoidosis may occur as a result of exposure to naps in occupants affected by water or other microbial factors and that disease in such groups deserves greater attention from physicians, toxicologists, epidemiologists, and health professional. (Ehling-Schulz M, *et al*. 2006) [19].

6. Other respiratory diseases

Infections: Infections that may occur in occupants of wet/rotting environments, which often complain of increased infection including colds, bronchitis, sinus infections and ear infections. The IOM report discussed respiratory infections that may be associated with moisture or mold, in which WHO indicated that people who are deficient or weak in the immune system are the most dangerous for fungal colonialism or opportunistic infections. The 2009 WHO report found definitive evidence of a link between mold, moisture, and respiratory infection. Seven studies of children also found that the odds ratio ranged from 0.65 to 5.10. In addition, there is limited evidence of an association between moisture/internal mold, respiratory tract and airways, (Ehling-Schulz M, *et al*. 2006) [19].

Purification

1. Eliza

Interactional studies by enzyme-linked immunosorbent assay (ELISA) and immunoassay inhibition using serum antigen-antigen-aggregated sera from patient-positive EN test. (Dressler D, *et al*. 2005) [18].

2. HPLC

An important method used to determine the amount of toxins present in pathological samples, which depends in this method on the use of pure chemical solutions such as chloroform. (Massimo reverberi. 2010) [66].

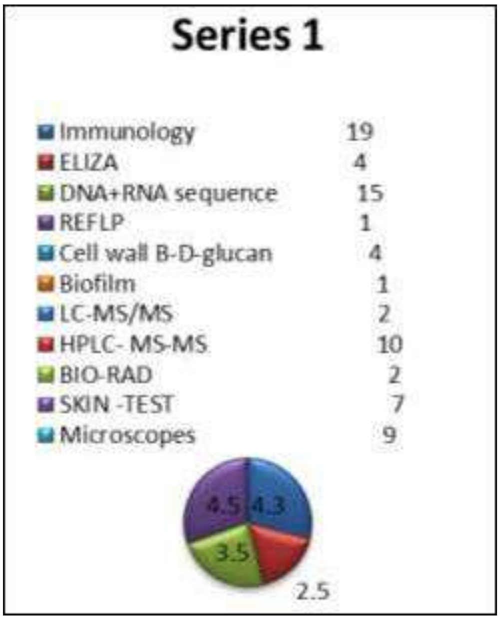

Fig 2: Summary of methods used to detect fungi and mycotoxins to group for selected materials according to the standards approved in the review.

3. Analysis of Fungal Gene by Real Time Quantitative PCR

Real-time quantitative PCR (qPCR) method is essential in determining the size of gene expression as well as other applications. The main advantages of qPCR are the high sensitivity of this method, the use of small amounts of mold and the ability to detect products during the reaction. After selecting qPCR among other options (Northern Blot, Para-

Quantitative PCR), several factors should be considered. (Dressler D. 2005) [18]. The decisive first step in qPCR for fungi is to choose an appropriate growth medium for the fungus to be cheaper and RNA extraction method, avoiding the accumulation of inhibitors. Syber Green tincture is preferred to detect accumulated product, it is also possible to consider other detection techniques, such as hybridization sensors. The precise qPCR analysis with Syber Green is mainly based on the optimized PCR reaction, and design of prefixes is also very important in avoiding formation of interfering structures. It is possible to perform a relative analysis or to measure the absolute quantity of the mold in the sample. In the proportional analysis method, the expression of the gene of interest is compared with the expression of the reference gene. Accordingly, it is recommended that at least three reference genes be used in order to obtain more reliable results. (Dressler D. 2005) [18].

4. Evaluation of antifungal sensitivity using flow cytometry and antibiotic test tablets Cytometry has wide applications in many fields such as hematology and immunology, and also offers great potential in studying microorganisms such as fungi. (Lindbäck T, *et al*. 2006) [43]. The susceptibility range of pathogenic isolates of fungi and malignant cocci of antifungal compounds can be measured by measuring flow cytometry using fluorescent sensors such as FUN-1 and propidium iodide one or two hours after incubation, depending on the antifungal compound or for 48 hours of classical methods that rely on tablets For antibiotic testing, it is possible to identify different allergy profiles. In addition, it can provide information about working mechanisms and resistance mechanisms. (Lindbäck T, *et al*. 2006; Kubista M, *et al*. 2006; Álvarez-Barrientos, *et al*. 2000) [43, 37, 3].

Conclusions

Of 62 selected papers, 37 have been published in the past ten years and only 12 in the past five years. According to the criteria for exploration methodology, only 18 studies showed a score = 5. This paper summarized the main findings on the association of fungi and fungal respiratory diseases and included filtration methods on physical and chemical methods in addition to genetic methods for detecting the amino acid infiltration of fungi isolated in those studies. Only 33 articles reported on the association of fungi with diseases of the psychological system, which included purification methods on an immunological, physical and chemical path only only without addressing the detection of the genetic sequence of isolated fungi, and studied several fungi that were isolated directly from clinical samples, while only 24 articles were included on a study General for fungi and review studies for respiratory diseases resulting from the association of fungi with respiratory diseases in humans. In this review, I identified the most important fungi that were characterized by the highest frequency in these articles, which were isolated from clinical samples and found that the highest frequency was for the fungus *Aspirgillus, Penicillium***,** They are among the most frequent filamentous fungi and produce a large mycotoxin. Articles of better grade did not undergo a suitable purification process. It was possible to notice a gap in the literature on the association of fungi with diseases of the respiratory system and bronchial allergies that result from ingestion or inhalation of fungal parts or blackboards as a result of the presence of these fungi in the environment inhabited by these patients, as well as their relationship to increased pathogenic fungi with high humidity inside buildings and their characterization, which increases the need for more studies, to identify asthma diseases of genetic origin or asthma resulting from exposure to microorganisms, including fungi in humid environments and old buildings inhabited by the most expensive people in the countries of the world. It was also noted that the studied fungi fungi offer promising and competitive properties for biotechnology when comparing toxins and diseases they cause with bacterial toxins that are associated with food poisoning events in people exposed to ingestion of food contaminated with these toxins.

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