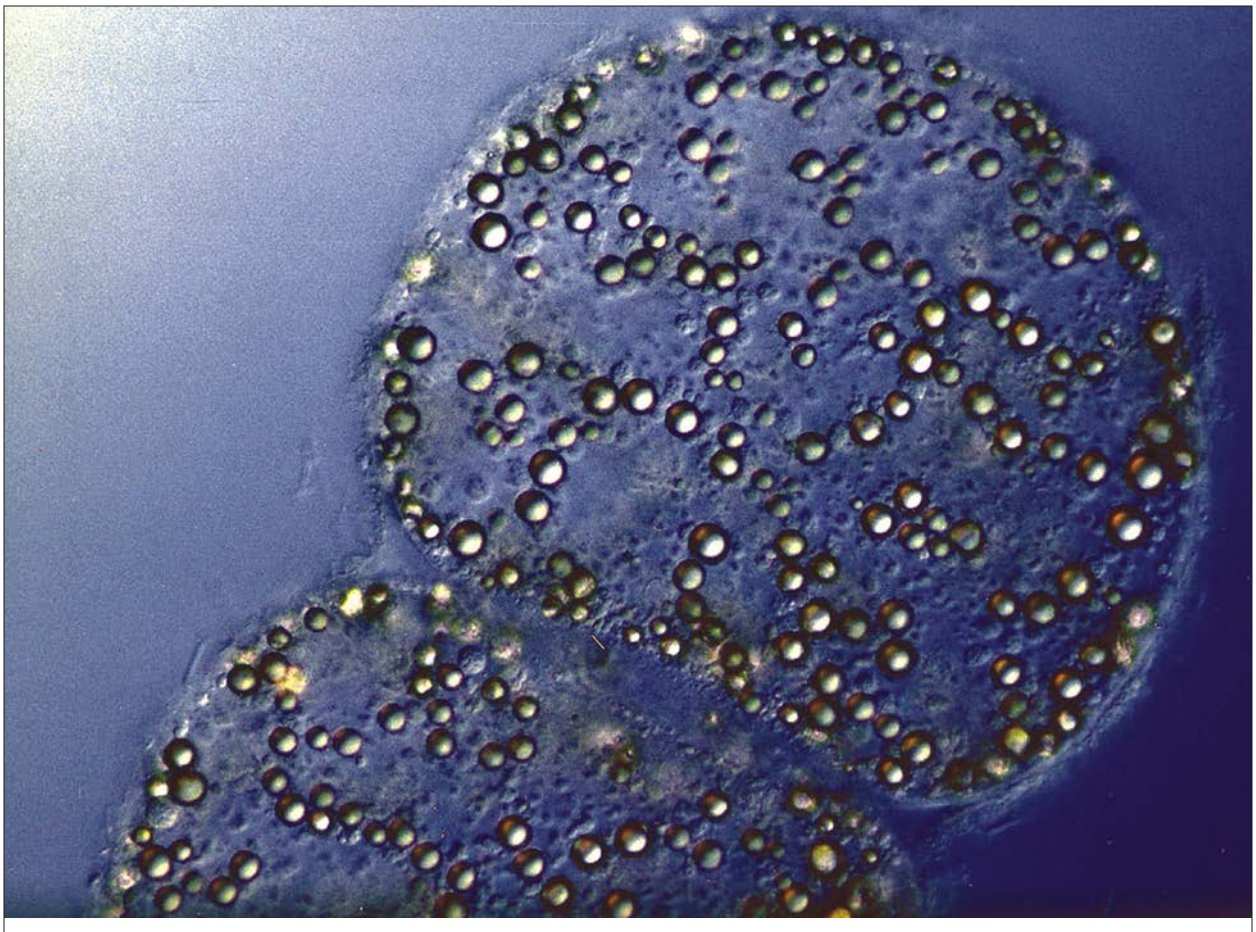

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Microbial Allergy with Special Focus on Saudi Arabia

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ABSTRACT

Asthma is a clinical syndrome that typically consists of increased airway hyper-responsiveness and recurrent episodes of airway obstruction and inflammation. Allergy is a heightened sensitivity to a foreign substance. The early interventions with anti-inflammatory agents have indicated that the inhalation of corticosteroids may be effective in the treatment of recurrent wheezing. Currently, long-term asthma control medicines have been prescribed to be taken by mouth in order to open the airways and prevent airway inflammation. Examples included inhaled long-acting B2-agonists (used with low-dose inhaled corticosteroids), leukotriene modifiers, cromolyn and nedocromil and theophylline. In future, the bronchial thermoplasty may become the first non-pharmaceutical treatment for asthma. Furthermore, there is an urgent need for new anti-asthma drugs, where there are millions of people suffering of severe asthma. New treatments have been attempted especially those involving plant and herbal extracts. Asthma and allergy updated knowledge have been highlighted in this review.

Key words: Asthma, allergy, microorganisms, plant extracts, treatment

INTRODUCTION

Asthma is a chronic inflammatory condition and evidence of inflammation can be observed in mild, moderate and severe disease forms. However, the relative magnitude, type of inflammatory cells and site of the inflammatory infiltrate may differ among patients. Many cells are involved in the immune and inflammatory responses to allergens in asthma, these include T-cells, eosinophils, mast cells, neutrophils and epithelial cells. The different clinical expressions of asthma involve varying environmental factors that interact with the airways to cause acute and chronic inflammation and the varying contributions of smooth muscle contraction, edema and remodeling of the formed elements of the airways. Although chronic (typically eosinophilic) airway inflammation and remodeling are pathological hallmarks of asthma, heterogeneity of clinical presentation, accompanying atopy, clinical severity, airway inflammation and genetic predispositions indicate that asthma is a syndrome rather than a single disease. Asthma is considered as a good example of gene-environment interactions, although no single gene or environmental factor accounts for the disease. The heterogeneity of asthma also relates to the different response to therapies (Hershenson *et al*., 2008). The histopathological changes in the bronchial and bronchiolar walls in asthma involve the mucosa (i.e., epithelium and lamina propria), submucosa with included Airway Smooth Muscle (ASM) and mucus-secreting glands and adventitia (the interface between airway and surrounding

lung parenchyma) (Hogg, 1993). The characteristic pathological features of asthma include the presence in the airway of inflammatory cells, plasma exudation, edema and smooth muscle hypertrophy, mucus plugging and shedding of the epithelium (British-Thoracic-Society). Asthma is one of the most common chronic diseases worldwide with a prevalence estimated at 5% of the population and is among the major health issues in developed countries with rising incidence and prevalence (Apter and Weiss, 2008). Reflecting its increased prevalence over the past 40 years in the developed world, almost 30 million Americans have asthma. The social and economic costs of asthma are staggering. It is the most common cause of missed school days by children and costs related to asthma care or to lost wages and productivity in the United States exceed $16 billion annually (Hogg, 1993). Despite effective therapies, the incidence of this disease and the frequency of its significant complications are increasing. However, new therapeutic approaches based on our understanding of the pathophysiology of asthma could have profound repercussions for the care of asthmatics and the health of the public in general. Herb and plant based preparations are a popular treatment for asthma, although there remain concerns as to their efficacy and safety.

Allergy is a global disease that is triggered or influenced, by allergens present in the indoor and outdoor environments. Microorganisms such as fungi for example differ in their metabolism from animals and plants in that they secrete enzymes into their surroundings and absorb the breakdown products of enzyme action. Some of these enzymes are well-known as allergens. Allergens vary from region to region and some could be indigenous to a particular geographical location. Air pollution is the addition of any harmful substance to the atmosphere. Due to industrialization and urbanization air pollution is becoming a major threat to human health and environment. Airborne particles are readily transferred from one environment to another as they are light weight. Air does not serve as a natural environment for them, it act as a transport environment in which microorganisms can be transported over considerable distance. The sampling and analysis of airborne microorganisms in indoor air has received attention in recent years (Kim and Kim, 2007; Huttunen *et al*., 2008; Stanley *et al*., 2008). Particulate matter of biological origin which include living organisms such as bacteria, virus, fungi and their metabolites, toxins or fragments is known as bioaerosols. Bioaerosols vary in size from 20 nm to 100 μm and composition depending on its source (Pillai and Ricke, 2002). It was found that several sources are responsible for emission of these bioaerosols in air. These sources include natural sites such as soil, water, plants and animals and human as well as anthropogenic like agricultural practices, healthcare units and industrial operations (Cullinan *et al*., 2001). Bioaerosols contribute to about 5-34% of indoor air pollution (http://www.pollutionissues.com/Ho-Li/Indoor).

FUNGAL ALLERGENS

Aspergillus species are ubiquitous, occur worldwide and are known to cause four distinct clinically recognizable forms of hypersensitivity respiratory disorders (i.e., allergic bronchopulmonary aspergillosis (ABPA), allergic *Aspergillus* sinusitis, IgE-mediated asthma and hypersensitivity pneumonitis) (Shah and Panjabi, 2002). We studied the experimental Hypersensitivity Pneumonitis Induced by *Fusarium kyushuense* in mice. The specific IgG anti-*F. kyushuense* levels in sera of the high freeze-dried *F. kyusuense* dose group were significantly higher than in the control group. Histologically, the lungs of both low and high dose groups showed signs of atelectasis with granulomatous lesions containing multinuclear giant cells and activated macrophages. This is the first report that mice developed HP induced by repeated exposure to freeze dried *F. kyushuense* (Harada *et al*., 2000). The ABPA is the most frequently recognized

manifestation of allergic aspergillosis is an indolent disease with a protracted course, occurring worldwide. The prevalence of ABPA is speculative as the few earlier studies that were performed adopted widely different diagnostic criteria (Eaton *et al*., 2000). In order to determine the incidence of ABPA, which is a disease predominantly of asthmatic subjects, it may be appropriate to study the frequency of sensitization to *Aspergillus* antigens in asthmatic subjects. Sensitization to *Aspergillus* conidia occurs in asthmatic subjects when the thick secretions, which are usually present in the airways, trap the fungal spores. This generally develops in atopic subjects and is sustained by the continuous in halation of *Aspergillus* antigens, resulting in acute asthma (Sugar and Olek, 1998). The prevalence of ABPA also varies from 1 to 11% in patients with asthma (Eaton *et al*., 2000; Al-Mobeireek *et al*., 2001) and from 25-28% in *Aspergillus* skin test-positive asthmatic subjects (Eaton *et al*., 2000). These variable prevalence rates probably reflect the lack of a single diagnostic criterion with a standardized test (Shah, 1994). Over the past few years, attention has been focused on the role of sensitization to fungi in asthmatic subjects as this is an important risk factor for the increasing severity of the disease (Zureik *et al*., 2002; Kauffman and van der Heide, 2003). A European Community respiratory health survey 18 in 30 centers demonstrated that the frequency of sensitization to *Alternaria alternata* and/or *Cladosporium herbarum* increased significantly with increasing asthma severity. The investigators recorded that a positive *Aspergillus* skin test result in patients with asthma was related to the severity of airway obstruction and stated that this was an unexpected finding. In the light of this situation, there was an attempt to as certain the frequency of sensitization to *Aspergillus* antigens in patients with asthma and its effect on the severity of the disease.

Sensitization to fungal allergens is shown in Fig. 1 (Hasnain *et al*., 2012). As can be seen sensitization to *Cladosporium* spp. varied from 0% in Abu Dhabi (UAE) and Khamis Mushait (KSA) to 42% in Khartoum (Sudan), sensitization to *Aspergillus fumigatus* from 0% in Khamis Mushait (KSA) to 40% in Khartoum (Sudan), sensitization to *Alternaria* from 0% in Khamis Mushait (KSA) to 38% in Khartoum (Sudan). Other molds, *Ulocladium* and *Penicillium* were less prevalent but also with big variations depending on the region studied (Fig. 1).

Burkard personal volumetric sampler was operated as volumetric 'Viable' spore traps at two different sites (Al-Batha, a more developed area in the south and Al-Ulia, a less developed area in the north) in Riyadh. Twice a week samplings were carried out over a period of 12 month. The seasonal fluctuations of the most frequent fungi were plotted as 'Major' components. The dominant species at the two sites were members of the genera *Alternaria*, *Aspergillus*, *Cladosporium*, *Penicillium* and *Ulocladium*. *Drechslera*, *Fusarium*, *Rhizopus* and *Stachybotrytis* species were

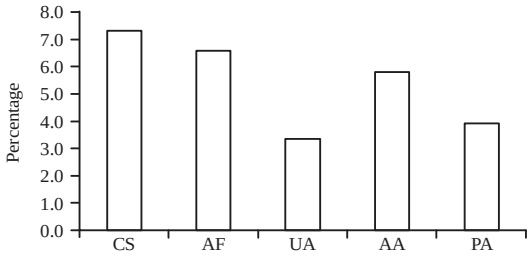

Fig. 1: Overall skin test sensitization rates to different mold species, CS: *Cladosporium* spp., AF: *Aspergillus fumigatus*, UA: *Ulocladiumatrum*, AA: *Alternaria alternata*, PS: *Penicillium* spp.

minor components or sporadic. Fungal colonies appeared with higher concentrations in the winter season and the lowest in summer. The Al-Batha site was always higher in spore concentrations than the Al-Ulia site. The results provide valuable information for the diagnosis and prophylaxis of allergic diseases due to airborne fungi found in very high concentrations. Alkhobar and Dammam are new, connected coastal cities with high humidity and temperatures (40.8-50.8°C) throughout the year. Several aerobiology studies have been conducted in Saudi Arabia, indicating the potential allergenicity of locally abundant species. These studies have confirmed that both local and imported florae were represented in air samples with Chenopodiaceae, *grasses* and *Ambrosia* spp. as the most common botanical groups. The airborne concentration of airborne mold spores have also been investigated. These studies concluded that *Alternaria* and several species of *Cladosporium* are of allergological importance in Saudi Arabia. *Cladosporium*, *Ustilago*, *Alternaria*, *Chaetomium* and *Ulocladium* are the main mold spores detected in the outdoor environment in this region. *Cladosporium* emerged to be the most prevalent genus in the outdoor environment constituting up to 25% of all fungal spores in the dry region and 37.1 and 41.2% in 2 coastal cities, respectively. Among the species, *Cladosporium sphaerospermum*, *C. macrocarpum*, *C. cladosporioides* and *C. herbarum* were the most relevant. Distinct seasonal fluctuations in mold spores were detected. The *in vitro* allergenicity of several of these species was also investigated, confirming the presence of the most important allergens.

Alternaria spp. is a potential allergic sensitizer in susceptible individuals and was thought to be a risk factor in sensitized individuals with symptoms of bronchial asthma and allergic rhihitis in Saudi Arabia (Hasnain *et al*., 1998). The spores of these fungi are known to be a major component in the outdoor environment with peaks in April and October, highest during summer (Hasnain *et al*., 1998; Cetinkaya *et al*., 2010).

Aspergillus niger is an agent of mold onychomycosis (Hilmioglu-Polat *et al*., 2005). It is also known to cause pulmonary intracavitary colonization, when associated with diabetes, the prognosis becomes generally poor due to acute oxalosis (Severo *et al*., 1997). *Aspergillus flavus* causes a spergilloma and chronic fibrosing pulmonary aspergillosis (Pasqualotto and Denning, 2008; Hedayati *et al*., 2007). It is also a major causative agent of endophthalmitis (Aydin *et al*., 2007) and induces keratolytic malignant glaucoma (Jain *et al*., 2007). Common clinical syndromes associated with *A. flavus* include chronic granulomatous sinusitis, keratitis, cutaneous aspergillosis, wound infections and osteomyelitis (Hedayati *et al*., 2007). *Rhizopus* spp. causes zygomycosis, an emerging increasingly important infection with high mortality especially in immunocompromised patients (Zaoutis *et al*., 2007). *Penicillium* spp. have been variably implicated in causing disease in patients with chronic granulomatous disease, severe combined immunodeficiency, chronic mucocutaneous candidiasis and considered as an indicator disease of AIDS (Antachopoulos *et al*., 2007; Devi *et al*., 2007). *Candida* spp. causes CNS infections either in the meninges or brain (Chakrabarti, 2007). *Cladosporium* spp. present in animal coats causes phaeohyphomycosis (Mariani *et al*., 2002). *Cunninghamella* spp. causes pulmonary mucormycosis and the very rare lung mucormycosis and nosocomial invasive infection exclusively in immunocompromised patients (Passos *et al*., 2006; Lassalle *et al*., 2007). *Rhodotorula* spp. can cause opportunistic mycoses in immunocompromised patients and meningitis in HIV infected patients (Pamidimukkala *et al*., 2007; Thakur *et al*., 2007). *Aspergillus terreus*, a less common pathogen causes aspergillosis with severe neutropenia (Tokimatsu *et al*., 2007).

The common genera of fungi frequently isolated from hospital air include *A. niger*, *Chaetomium* and *Alternaria*. Lukaszuk *et al*. (2006) isolated 9 fungal species from selected rooms of the

department of dermatology, venerology and allergology of medical university in Wroclaw. In another study, 6 fungal genera *Aspergillus*, *Rhizopus, Mucor, Penicillium, Verticillium* and *Candida* were isolated from two hospitals (Bhatia and Vishwakarma, 2010). *Aspergillus niger* was isolated throughout the year by Sudharsanam *et al*. (2012) from a hospital ward in a tropical setting.

To sum up, Hospitals are complex facilities designed to fight infections. There had been a tremendous increase in resistant infection specially hospital infections and also increasing awareness to control and improve outcome of infections. In this context bioaerosol monitoring in hospitals can serve as a useful tool to control Hospital Associated Infections (HAI). This will also increase awareness regarding the air quality of hospital environment and its impact on human health.

BACTERIA POLLUTION INDOOR OF HOSPITALS

Hospital indoor air contains a diverse range of bacteria such as *Bacillus subtilis*, *Bacillus* spp. and *Bacillus polymyxa*. *Staphylococcus epidermidis* has become the most important cause of nosocomial infections in recent years. Its pathogenicity is mainly due to the ability to form biofilms on indwelling medical devices. In a biofilm, *S. epidermidis* is protected against attacks from the immune system and against antibiotic treatment, making *S. epidermidis* infections difficult to eradicate (Vuong and Otto, 2002). *Corynebacterium* spp. (coryneform) have been in the focus of attention in recent years since cases of osteomyleitis, cerebrospinal meningitis, endocarditis, bacteremia, urinary tract infections and liver abscess were associated with this agent (Mikucka *et al*., 1997). *Pseudomonas aeruginosa* has become an important cause of infection, especially in patients with compromised host defense mechanisms. It is the most common pathogen isolated from patients who have been hospitalized longer than 1 week. It is a frequent cause of nosocomial infections such as pneumonia, Urinary Tract Infections (UTIs) and bacteremia. Pseudomonal infections are complicated and can be life threatening (Qarah *et al*., 2005). *Bacteroides* species are anaerobic bacteria that are predominant components of the bacterial florae of mucous membranes and therefore, are a common cause of endogenous infections. *Bacteroids* infections can occur in all body sites, including the CNS, the head, the neck, the chest, the abdomen, the pelvis, the skin and the soft tissues (Brook, 2006). Pathogenic species of the genus *Clostridium* may contaminate the materials used in the injection of drugs and under the right conditions may cause serious or life-threatening disease (Brazier *et al*., 2002; Alwakeel, 2008). *Staphylococcus aureus* is ubiquitous and may be a part of human flora, however, the organism may cause disease through invasion and toxin production such as abscess, pneumonia, *diarrhoea* and the most feared toxic shock syndrome (Tolan, 2007). The results of their study have several implications on the preference for floor carpeting. The presence of these fungal and bacterial pathogens poses risk for individuals. The result of the physiological effect of temperature on these fungi further showed that individuals are more at risk for opportunistic infection during summer months. This explains why most people experience a lot of respiratory symptoms from acute allergic rhinitis to pneumonia during climate changes especially during the summer months.

ASTHMA TREATMENT

The search for novel treatments for asthma has significantly advanced in recent years. Asthma treatments are more commonly used and many compounds were used. Almost all derived from

herbs or plants. Ginger, cayenne, Indian tobacco (*Lobelia inflata*), turmeric, skunk cabbage and goldenseal are supposed to hold promise for asthma sufferers. Several scientific studies in recent years suggested that some of these folklore medicines have significant effect in reducing the severity of respiratory disease symptoms and improving patient's quality of life. The alternative medicines, particularly plant extracts have shown acceptance by patients and physicians alike (Markham and Wilkinson, 2004). However, no detailed scientific studies have been conducted to further the understanding of anti-allergic mechanisms associated with these products. In spite of lack of information, a substantial interest has been shown to alternative and supplementary medicines. In addition, the side effects from long-term use of asthma drugs have prompted interest in complementary and alternative therapies such as Traditional Chinese Medicine (TCM) herbs. In a recent article, National Center for Complementary and Alternative Medicine (NCCAM) supported scientists from the Mount Sinai School of Medicine to review research evidence on TCM herbs for asthma, focusing on studies reported since 2005 (Li and Brown, 2009). Currently, closer to 2000 herbal products are available for the treatment of various ailments and the list is steadily increasing (Markham and Wilkinson, 2004). A number of herbs and herbal products have been used in the treatment of allergy and asthma in ancient traditional Chinese medicine, Indian Ayurvedic medicine and Japanese Kampo medicine. However, few scientific studies have been carried out to as certain their action and effectiveness (Kobayashi *et al*., 1997). Other Asthma therapies; Immunomodulation Asthma is thought to be mediated through the imbalance of Th2 and Th1 cell responses. Th2 lymphocytes are thought to play a key role in the pathogenesis of asthma. Out of the Th2 cytokines IL-5 is regarded as most important because its expression correlates with asthma severity and local eosinophil infiltration (Truyen *et al*., 2006). Therapeutic strategies directed towards inhibition of Th2 cytokines would thus seem to offer an attractive immunomodulatory strategy for asthma (Von Hertzen, 2002). The IL-10 is one of those cytokines that inhibits inflammation and cytokine therapy with IL-10 may have relevance as far as asthma is concerned. While it may not be possible to administer cytokines directly into patients, strategies may be developed to increase their release e.g., that of IL-10 release (Asadullah *et al*., 1998). IL-12 is produced by APCs and have role in the Th1 cell development, Th1 cells secrete IFN-gamma that may strongly inhibit Th2 cytokines (Shevach, 2000).

Acupuncture for Asthma: Acupuncture is a treatment originating from traditional Chinese medicine. It consists of the stimulation of defined points on the skin (mostly by insertion of needles). Acupuncture has traditionally been used to treat asthma in China and is used increasingly for this purpose internationally (McCarney *et al*., 2004). It is thought that such treatments can correct any imbalances in vital life energy (perhaps along the lung, spleen, or kidney system meridians) that may be triggering the breathing problems. A few small clinical trials showed that acupuncture may help improving asthma symptoms. But to date, the research is inconclusive, since no one has conducted either a review or a randomized controlled trial for the gold standards in proving a treatment successfully.

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