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Review Article

Status of Research in Respiratory Pharmacology in India During the Last Five Years (2012-2017)

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Research in the area of respiratory pharmacology and toxicologyis very exciting and vital for the development of new drugs with more efficacy and safety. Several medicinal plants from the Ayurveda and Unani systems of medicine are being evaluated for their efficacy and safety by using modern medical techniques;with an aim to bring them to the mainstream of the health care system. Effects of yogic intervention on pulmonary functions, cellular and molecular markers and quality of life in patients of bronchial asthma are also being assessed. Further, a lot of work is also going on novel aspects of immunotherapy and nanomedicine in the management of respiratory disorders. This review also highlights the relevance and pharmacoeconomic impact of nutraceuticals in prevention and treatment of respiratory diseases. Many clinical trials are being conducted to compare the efficacy and safety of already marketed individual drugs and combination therapy. Pharmacovigilance studies are being conducted to monitor the ADRs during pharmacotherapy of respiratory diseases, assess the causal relationship and find ways to prevent the ADRs to rationalize the therapy. However, more translational research is needed to bring scientific advances and knowledge into clinical practice; and there is a great need to find effective ways for collaboration between various research disciplines. There should be a focus on earlier and more specific diagnosis of respiratory diseases as well as better targeted and personalized treatments which may save cost, reduce adverse effects and improve disease outcomes and quality of life.

Keywords: Respiratory Disorders; Traditional Medicine; Immunotherapy; Ayurveda; Unani; Clinical Pharmacology; Yoga; Nutraceuticals

Introduction

Respiratory diseases are a major health problem worldwide which affect people of all ages and are by far one of the leading causes of morbidity and mortality. It is estimated that more than 1 billion persons suffer from chronic respiratory conditions and 4 million people die prematurely each year from chronic respiratory diseases (European Respiratory Society publications, 2013). Thus, healthcare costs for respiratory diseases are an increasing burden on the economies of all countries.

Respiratory disorders mainly involve the air passages, including nasal passages, small and large airways (bronchioles and bronchi), and the lungs. Their etiopathology could be infectious, allergic, inflammatory, neoplastic and traumatic. Respiratory disorders (acute and chronic) are one of the most prevalent causes of hospital visits or hospital admissions globally. Bronchial asthma, chronic obstructive pulmonary disease (COPD), pneumonia, pulmonary tuberculosis, pneumoconiosis, cystic fibrosis, lung cancers are some of the most commonly observed respiratory conditions. A large variety of pharmacological treatment strategies are widely practiced in these diseases, and they mainly involve bronchodilators, anti-inflammatory agents, anti-allergics, mucolytics, antibiotics and anti-neoplastics.

Obstructive lung disease is a respiratory disease characterized by narrowing of the smaller bronchi and larger bronchioles, inflamed and easily collapsible airways and obstruction to airflow. Types of

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obstructive lung disease include asthma, bronchiectasis, bronchitis and COPD. Although COPD shares similar characteristics as asthma but the airway obstruction in bronchial asthma is reversible whereas in COPD it is irreversible, in which environmental factors such as smoke inhalation play an important role (Barnes, 2008; Blease and Raymon, 2003). Bronchial asthma is a heterogeneous chronic airway disease characterized by obstructive airflow, bronchial hypersensitivity as well as airways inflammation. It is defined by the history of respiratory symptoms like wheeze, shortness of breath, chest tightness, cough that varies over time and in intensity, together with variable expiratory airflow obstructions. These variations are often triggered by different stimuli, including exercise, viral infections (cold), allergen exposure, irritants like car exhaust fumes, smoke or strong smells and changes in weather. Asthma is generally associated with airway hyper reactivity to direct or indirect stimuli, and with chronic airway inflammation. These features usually persist, even when symptoms are absent or lung function is normal, but may normalize with treatment (GINA, 2015). Bronchial asthma is aninflammatory disorder and the inflammatory symptoms start with T helper-2 and dendritic cells, followed by infiltration of inflammatory cells mainly eosinophilic cells and mast cells sensitization, resulting in the release of several kinds of inflammatory mediators such as leukotrienes, histamine etc. that promote bronchial hyper responsiveness, airway inflammation and mucus hypersecretion (Lemanske and Busse, 2010). COPD is caused by long term inhalation of lung toxins and irritants such as chemical fumes and industrial dusts etc., which results in chronic inflammation of airways and structural injury to the alveolus of the lungs. This condition finally results in chronic bronchiolitis,chronic bronchitis, and emphysema. It is slowly progressive and largely irreversible, characterized by cough, airway obstruction, increased secretion of sputum, and shortness of breath etc. (Lanzetti *et al.*, 2008; Yoshida and Tuder, 2007). Chronic airway inflammation leads to tissue injury followed by abnormal healing which results in structural alterations in the airway walls of asthmatic patients collectively called as airway remodeling. Structural changes include subepithelial fibrosis, accumulation of collagens, tenascin and laminin that contributes to airway wall thickening. Enhanced growth and proliferation of fibroblasts results in increased airway smooth muscle mass. Goblet cell hyperplasia causes mucus hypersecretion and further lead to occlusion of the airways. Airway remodeling contributes to permanent or not fully reversible airflow obstruction with accelerated and progressive decline of lung function. Remodeling is observed in almost each tissue of the airway wall in fatal asthma. Remodeling occurs in the entire bronchial tree, but large membranous and small cartilaginous airways are the most affected (Lloyd and Robinson, 2007; Shifren *et al.*, 2012).

The complexity of chronic asthma is a great challenge for developing interventions with a broad spectrum of pharmacological actions to counter the pathogenic changes during asthma and COPD. The current goal of pharmacotherapy of asthma and COPD is primarily targeted toward controlling airway inflammation with anti-inflammatory agents (inhaled corticosteroids) and relieving bronchoconstriction with bronchodilatory agents (β_2-agonists) (Mullane, 2011). Increasing complexities in the pathophysiology of infectious diseases such as tuberculosis and pneumonia caused by microorganisms, have led to constant changes in antimicrobial therapy. Interestingly, it has been found that several lifestyle factors like toxic chemicals, smoking, infectious agents, stress, and radiation also play a crucial role in promoting chronic inflammation by modulation of pro-inflammatory mediators like cytokines, chemokines, enzymes, transcription factors, and others. Several transcription factors such as NF-κB, AP-1, STAT-3, Nrf2, HIF-1 etc. are found to play a vital role in the pathogenesis of chronic inflammation. The incidence rate of lung cancer is increasing today, and early detection and immediate treatment are the order of the day. Cystic fibrosis remains to be an enigma, and therapeutic strategies for treatment are still far from expectations. In view of the higher rates of respiratory illness, there is a pressing need of extensive research to identify the possible targets or mechanisms involved and develop therapeutic strategies in this field (Gulati *et al*., 2016). In view of this, a lot of research on various aspects of respiratory disease has been going on in India and this review is an effort to give an overview of the same during the last five years in India.

Clinical Pharmacological Studies in Respiratory Disorders

The academicians or clinicians are the pillars of any medical college, hospital, or university as they perform multiple responsibilities of patient care, teaching, research and administration. Clinicians often carry out research that is mainly on the basis of observations in clinical practice or according to their patient's needs. Good clinical research provides evidence-based medicine and thus improves patient care with an ultimate goal of health promotion (Gogtay *et al*., 2017).

Obstructive Airway Diseases

The pharmacotherapy of bronchial asthma consists of mainly inhaled corticosteroids in combination with long acting inhaled β2-agonists, low dose theophylline, or anti-leukotrienes. Rani *et al.* (2017) studied the efficacy and safety of formoterol vs montelukast as add on therapy in moderate persistent asthma. Out of 60 OPD patients, 30 (group A) received inhaled budesonide 400μg and formoterol fumarate 6μg twice daily and the other 30 (group B) received oral montelukast 10 mg once daily along with inhaled budesonide 400μg twice daily for eight weeks. In Group A, both day and night time cough/wheeze score reduced after 8 weeks of treatment whereas in Group B only day time cough/wheeze score reduced from 4 weeks to 8 weeks. Modified Borg's dyspnoea score also reduced significantly in both Group A and Group B at the end of 8 weeks and decrease was comparable in both groups. Statistically there was no difference between two treatments as far as safety assessment was concerned. Most common ADRs reported were headache, asthenia and abdominal pain concluded that the addition of leukotriene antagonist in asthmatic patients whose symptoms remain uncontrolled with inhaled budesonide is as effective as addition of formoterol in improving modified Borg's dyspnoea score, lung functions, and need for rescue medications. They also suggested that use of montelukast is an alternative and reasonable therapeutic option in asthmatic patients as add on to inhaled corticosteroids.

Magazine *et al.* (2016) compared the effects of leukotrienes receptor inhibitors montelukast with 5-lipoxygenase inhibitor zileuton, after oral administration in acute asthma. The study was conducted in 120 asthmatic patients and the results showed that zileuton is better than montelukast as an additional drug in acute asthma and resulted in significant improvement in lung function, and reduction in the need for rescue medications.

In another study, Margay *et al*. (2015) compared the safety and efficacy of two methylxanthines drugs, theophylline and doxofylline which are prescribed to relieve bronchospasm in asthmatic patients. The study was conducted in 100 patients; they were divided into two groups. Group I received theophylline 300 mg twice a day orally for 6 weeks and Group II received doxofylline 400 mg twice a day orally for 6 weeks. The spirometric values of FEV1, FVC and FEV1/FVCshowed a statistically significant improvement over base line by the use of both methylxanthines, and intergroup comparison showed no significant difference in their efficacy parameters. However, treatment with doxofylline for six months showed a better safety profile as adverse effects were observed in greater proportion in patients treated with theophylline. They concluded that although the two drugs are equally efficacious, doxofylline has better safety profile.

Lal *et al.* (2015) also compared the safety and efficacy of theophylline and doxofylline in asthma and COPD patients. The study was conducted as per GCP guidelines and a total of 60 patients, 30 patients each with bronchial asthma and COPD were enrolled for the study. Patients of both groups received standard drug treatment for asthma and COPD. Asthma and COPD groups were again divided into two subgroupsof 15 patients each and treated with either theophylline or doxofylline in addition to standard therapy for 2 months. In each patient, efficacy parameters were assessed by using pulmonary function test (PFT), clinical symptoms and safety were assessed by recording adverse drug reactions. Both methylxanthines drugs showed increase in PFT in both asthma and COPD patients and maximum beneficial effects were seen after 6 weeks and 8 weeks of treatment by both drugs respectively. They concluded that doxofylline was more safe and efficacious in comparison to theophylline as evidenced by improvement in PFT and clinical symptoms; and decreased incidence of adverse effects.

In another study, Akhtar *et al*. (2016) evaluated the therapeutic efficacy of ascorbic acid, an anti-

oxidant drug in bronchial asthma patients. A total of 86 patients of bronchial asthma were enrolled for the study and finally 50 patients were used for primary analysis. They were divided into two groups. Group I patients received inhaled fluticasone+salmeterol and oral theophylline. Group II patients received oral ascorbic acid along with inhaled fluticasone+salmeterol and oral theophylline. Each patient was followed up for the assessment of efficacy parameters by using PFT, clinical symptoms and emergency drug use. Oxidative stress parameters were also assessed by estimating malondialdehyde (MDA) and superoxide dismutase levels in blood samples of both group patients. The results of the study showed significant improvement in PFT, clinical symptoms and emergency drug use in both groups after 4 weeks of treatment but no significant difference was observed in between the two groups. The MDA levels were significantly reduced and superoxide dismutase levels were increased in Group II patients vs Group I patients after 2 weeks and 4 weeks of treatment. This study concluded that although ascorbic acid did not affect the efficacy of the conventional treatment but had significant effect in reducing the oxidative stress parameters observed during treatment with theophylline.

Theophylline, although effective is considered as the third-line therapy in the treatment of bronchial asthma due to the drug's frequent side effects. The low-dose of theophylline in moderate childhood asthma is safe and well tolerated (Suessmuth, 2003). At low doses, the drug is easier to use, side effects are uncommon and the problems of drug interaction are less of an issue, thus making the clinical use of theophylline less complicated. Narrow therapeutic index of theophylline, its adverse effect profile and the fact that its serum levels correlate well with both therapeutic and toxic effects, necessitates its therapeutic drug monitoring. Bhatia (2012) used two different dosage of theophylline i.e. 200 mg (low dose) and 400 mg (high dose) administered orally, in addition to the standard treatment (salbutamol + fluticasone inhalation) to assess their efficacy, safety and adverse effect profile along with monitoring of serum drug concentration by HPLC. This was a prospective, open label, randomized, parallel design study to compare the efficacy and safety of two doses of theophylline. A total of 60 patients were enrolled and divided into three groups with 20 patients in each group. Group I patients received salbutamol + fluticasone (control group); Group II patients received salbutamol + fluticasone + 200 mg theophylline and Group III patients received salbutamol + fluticasone + 400 mg theophylline. Patients were followed up weekly for 4 consecutive weeks and assessment of safety and efficacy was done. Efficacy assessment was done using pulmonary function test parameters (FVC, FEV1 and FEV1/FVC ratio), clinical symptoms (cough, sputum and dypnoea) and emergency drug (SOS levo-salbutamol) use while safety was assessed by recording ADRs in the standard prescribed format. All three treatments produced continuous improvement in FVC, FEV1 and FEV1/FVC ratio at different time intervals. Improvements in all three groups were comparable. The maximum beneficial effects were seen after 1 week of treatment in control and high dose theophylline (400 mg) groups whereas for low dose theophylline (200 mg) group maximal effect was seen after 3 weeks of therapy. All three treatments produced comparable improvement in symptoms (cough, dyspnoea and sputum), again maximal effect of low dose theophylline was seen after 3 weeks of therapy. Short acting beta agonist, levo-salbutamol, was used as emergency medication to relieve asthma attack during maintenance therapy. It was found that minimal frequency of levo-salbutamol usage was required in patients consuming low dose theophylline, followed by high dose theophylline group and maximal usage was seen in control group. Assessment of safety parameters revealed that the ADR profile included dyspepsia, nausea, tremors, dizziness, anxiety and headache. These adverse effects were seen in patients taking theophylline (groups II & III) and out of all adverse effects, nausea and dyspepsia appeared to be the most common. Among groups II and III, adverse effects were more common in group III (400 mg). As far as control group is concerned, only one or two patients complained of adverse effects like tremors and dyspepsia. They concluded that low dose theophylline was comparatively better than other two groups in preventing asthma attacks. High dose theophylline was frequently associated with adverse effects like nausea and dyspepsia and therefore it was recommended that low dose should be preferred as add on therapy over high dose in mild to moderate asthma as it has same efficacy with less side effects.

The right technique and correct use of inhalers

effectively delivers the drugs to the lungs and thus affects the disease control. So, it is of vital importance to educate asthmatic patients about the disease and train them to use inhaler in a correct way to increase the treatment outcome. Chogtu *et al.* (2017) assessed the association of inhaler technique with asthma control and quality of life (QoL) of patients. It was an observational, prospective, cross-sectional study conducted on asthmatic patients. The history of patients was recorded and was asked to use inhaler in the presence of an investigator and the technique was scored. Asthma control and QoL of patients were evaluated using asthma control questionnaire and mini asthma QoL questionnaire. Surprisingly, they observed that about 36.6% of the patients performed the steps incorrectly. Breathing normally for 30-60 minutes post-inhaler use was the most common step done incorrectly. Patients with poorly controlled asthma and those with predicted forced expiratory volume at 1 second (FEV1), less than 70% performed the steps erroneously. Thus, they concluded that incorrect use of inhaler can lessen the delivery of required amount of drug to the lungs. This in turn can minimize the effectiveness of drug and can be one of the reasons for therapeutic failure. Thus, all patients, especially those above 40 years, should be given proper instructions regarding use of inhaler to obtain therapeutic advantage.

Tuberculosis

Tuberculosis (TB) is a highly infectious disease and remains a global epidemic with about 2 billion people harboring latent infection and more than 9 million new cases, of which 500,000 are multidrug-resistant and approximately 2 million deaths occur every year. A study published in September 2012 in The Lancet showed that approximately 44% of TB patients in countries like Peru, Russia and Thailand were found resistant to atleast one second-line drug. Treatment of drug-resistant TB can take years and also cost 200 times as much as treating the ordinary form of the disease. As a result, there is always a search for newer drugs with novel mechanisms of action, not only to shorten the duration of therapy of drug-sensitive TB, but also for the treatment of multi drug resistant TB. In 2016, the Ministry of Health and Family Welfare had launched bedaquiline drug for the treatment of drug resistant TB for 600 patients across India. It was made available in Delhi, Mumbai, Chennai, Ahmedabad and Guwahati. The unique and specific anti-mycobacterial activity of bedaquiline depends on proton pump inhibition of mycobacterial ATP synthase enzyme, which is a crucial enzyme in the ATP synthesis of Mycobacterium tuberculosis. Bedaquiline binding to the oligomeric and proteolipic subunit-c of mycobacterial ATP synthase results in the inhibition of ATP synthesis, which subsequently leads to bacterial death. The safety and efficacy of bedaquiline were confirmed in 440 patients in two phase-2 clinical trials. First trial patients were randomly assigned to be treated with bedaquiline + other drugs used in the treatment of TB, or a placebo + other drugs used for TB. All patients in the second trial were treated with bedaquiline + other drugs used in TB. Both studies were designed to determine the time taken for a patient's sputum to be free of Mycobacterium tuberculosis, called as sputum culture conversion. The results of the first trial indicated that those patients who received bedaquiline combination therapy achieved sputum culture conversion in a median time of 83 days as compared to 125 days in patients who received placebo combination therapy. The results of the second trial showed that the median time to sputum culture conversion was 57 days, supporting the efficacy results of the first trial. The common side effects found in the clinical trials was nausea, joint pain and headache (Mahajan, 2013).

Recently, in August 2017, DCGI gave approval to market delamanid, a new class of anti-TB drug discovered to specifically treat Multi Drug Resistant TB by Mylan Inc., an Indian unit of US drug maker. Like bedaquiline, delamanid's treatment is "limited" to those patients who have stopped responding to most of first and second line of treatment. The drug billed as "wonder drug" will be rolled out in government-run-TB programme. The new drug Delamanid 50 mg could benefit large number of people suffering from the multi drug resistant and extensively drug resistant TB. Dr. Soumya Swaminathan, Director General, Indian Council of Medical Research and clinical scientist known for her work in TB said that Delamanid is indicated for the treatment of pulmonary TB due to multi-drug resistant Mycobacterium TB for which presently there are not many effective therapies available in India. Swaminathan also suggested that clinical trials using bedaquiline + delamanid combination be conducted. The trial protocol has been approved by the DCGI with an aim to decrease the

duration of the therapy from current 30 months to 6-9 months. DCGI recently recommended "waiver of local clinical trials at this stage" and approved the drug with a restriction that "it shall be approved for use under government run Revised National TB Control Programme (RNTCP)" and for conditional access for treatment of multi drug resistant-TB patients only (Thacker, 2017).

Pneumonia

Pneumonia is an inflammatory disease of the lung and is also associated with lung parenchyma/alveolar inflammation and abnormal alveolar filling with fluid. Pneumonia can affect just one lobe of the right or left lung, a whole lung or both lungs. When the germs that cause pneumonia reach the lungs, the alveoli become infected and inflamed. The infected lungs leak fluid and shed dead cells, which clog up the air sacs, make them less elastic; and make it difficult for lungs to do their work of getting oxygen into the blood or in eliminating carbon dioxide from the blood efficiently. As a result, the lungs have to work harder to meet the body's need for oxygen. The symptoms of pneumonia are cough, chill, fever and difficulty in breathing. Pneumonia can result from variety of causes such as viruses, bacteria, other microorganisms like fungi and parasites, certain drugs and other conditions like autoimmune diseases. Bacteria, viruses or fungi that live in mouth, nose, sinuses or the surrounding environment can enter the lungs and causes infection. One can also get virus or bacteria from person infected with them. Viruses are the most common cause of pneumonia in children whereas bacteria are the casual factor in adults (Gupta and Gupta, 2014).

Durairajan *et al*. (2014) studied the cost effective analysis of several antibiotics in Community-acquired pneumonia (CAP) treatment in adult population. This retrospective study analyzed the case sheets of 50 CAP patients admitted in Sri Ramachandra Medical Centre from January, 2010 to December, 2011 who were administered antibiotics such as amoxicillin-clavulanate, levofloxacin, cefuroxime, ampicillin-sulbactam and azithromycin. The cost-effectiveness was compared between the group of patients who had received only i.v. antibiotics during the entire duration of treatment and the group of patients who had received the switch therapy i.e. the i.v. antibiotics used at the starting of treatment but shifted to oral antibiotics after improvement. Antibiotics administered i.v. showed better improvement in comparison to oral antibiotics. So, the cost effective analysis of antibiotics and a pharmacoeconomic evaluation was done. The cost effectiveness co-efficient was determined as the ratio of antibiotics price to number of asymptomatic days in a month. The cost effectiveness coefficient ratio showed that continuous i.v. administration of antibiotic is more costly than the switch therapy. The study concluded that timely switch from i. vantibiotics to oral antibiotics in an appropriate patient is an efficient way to safeguard against undesirable expenses.

Kotwani *et al*., 2015 determined the patterns and frequency of antimicrobial drug use among hospitalized patients with CAP. This retrospective study analyzed the case sheets of 261 CAP diagnosed patients of two public hospitals in Delhi from April 2007 to March 2012. The results showed that over the 5 years, 82% (2007-08), 78.6% (2008-09), 59.5% (2009-10), 64.7% (2010-11) and 67.8% (2011-12) CAP patients were prescribed two antimicrobials. In the last two study-years, the proportion of patients receiving three antimicrobials increased (from 2% to 26.5% and 28.8%), while the proportion of patients receiving monotherapy decreased (from 16.0% to 8.8% and 3.4%). According to guidelines, β lactams and macrolides were the two most frequently prescribed antimicrobials (34.1%). A total of 37 patients were given combination of β lactam tazobactam preparations. Overall, β lactams constituted more than 40% of prescriptions while macrolides were the second most prescribed. Cephalosporin prescriptions significantly increased and aminoglycoside prescription ranged from 9.7% to 16.4%, over five years. The group commented that reasons for giving three antibiotics, or higher end/ reserve antibiotics were not described in the medical records and there were no specific guidelines from the hospital for physicians to follow the treatment of CAP. They suggested the need for implementing antimicrobial treatment guidelines and an antimicrobial stewardship programme which may offer the most comprehensive solution for appropriate use of antimicrobials.

In another study, Kumar *et al*., 2015 studied the antibiotic prescribing habits of physicians in117 CAP

patients. A medicine consultant or a pulmonologist supervised and treated 45 (38%) patients. Out of 45 patients, 7 patients (16%) were prescribed macrolide, 12 patients (26%) were prescribed β-lactam antibiotics, 14 patients (31%) were prescribed β-lactam + macrolide, and 12 patients (26%) were prescribed a combination of more than one antibiotics. 72 patients (62%) were supervised by other specialists, out of which 5 patients (6%) were prescribed macrolide, 35 patients (48%) were prescribed β-lactam antibiotics, 4 patients (6%) were prescribed β-lactam + macrolide, 2 patients (3%) were prescribed quinolones, and 26 patients (36%) were prescribed various combinations. In 47 out of 117 patients, therapy was modified, which included 12 patients who underwent step-down switch. Patients who underwent step-down switch had a hospital stay of 7 days, whereas those who did not have any modification in the therapy stayed for 10 days in the hospital. The result of the study showed that β-lactam antibiotic was more commonly used, approx. 3.8 times more than a macrolide. Other combinations of antibiotics were prescribed in 28%, 68%, and 44% of patients treated by a medicine specialist, pulmonologist, and other specialties, respectively. These data concluded that in spite of the advances of knowledge in the management of CAP, there exists variability in the prescribing habits of the attending physicians.

Newer Biomarkers in Respiratory Disorders

Many novel tools are now being used or are under development for improved diagnosis and better measurement of the evolution of diseases. *In-vitro* biomarkers assessment can help in early diagnosis, improved patient care, contribute to protecting consumer health; and help to limit healthcare spending, which is a major economic issue in every country throughout the world. Studies were performed to evaluate new markers to assess the severity as well as outcome of therapy in asthma patients. Bronchial epithelium produces Nitric oxide and its fraction in exhaled air (FeNO) is a non-invasive marker of eosinophilic airway inflammation. Neelamegan *et al.* (2016) estimated the levels of Fractional exhaled nitric oxide (FeNO) in Tamilian asthmatic patients to predict the disease severity and response to inhaled corticosteroids. The study was a prospective cohort and a total of 102 persistent asthmatic patients completed the follow up periods of 8 weeks. FeNO analyzer was used for measuring NO levels in expired air. Treatment with inhaled corticosteroids (Beclomethasone dipropionate + salbutamol) reduced the mean FeNO levels in mild, moderate and severe asthmatic patients as compared to similar baseline FeNO levels. The reduction in the levels of FeNO in response to inhaled corticosteroid treatment, favored its clinical utility in monitoring the ongoing airway inflammation and assessing treatment response rate.

Further, Bhargava *et al.* (2015) evaluated the effect of systemic corticosteroids on a new serum apoptotic markers, Survivin and M30 apoptosense in asthmatic patients. The study was conducted in 60 patients with acute exacerbation of bronchial asthma and treated with systemic corticosteroids. Baculoviral inhibitor of apoptosis repeat containing 5-mRNA (also known as Survivin) is an important anti-apoptotic protein that has been involved in many types of cancer, and present day many studies showed its role in controlling inflammatory diseases, such as bronchial asthma. M30 apoptosense is a unique tool for quantitative measurement of apoptosis of keratin 18-positive cells. This cytokeratin 18 has been especially recognized as a bronchial epithelial antigen related with non-allergic asthma. Apoptotic markers, such as Survivin and M30 apoptosense and QoL were analyzed, before and after treatment with oral prednisolone. The levels of Survivin and M30 apoptosense in blood were significantly reduced after one week of oral prednisolone treatment. QoL scores and peak expiratory flow rate % were also significantly improved in the patients of asthma. The results of the present study suggested that administration of systemic corticosteroids reduces the survival of inflammatory cells and improves the quality of life in patients of bronchial asthma with acute exacerbation.

Studies on Traditional Systems of Medicine in Respiratory Disorders

Indian traditional systems of medicine *viz*., Ayurveda, Unani, Siddha and Homeopathic systems use natural products mainly derived from plant sources. These systems of medicine have been widely accepted throughout most of the countries and referred as Complementary and Alternative Medicine (CAM) (Hussain *et al.*, 2009). The World Health Organization also encourages, recommends and promotes

traditional or herbal drugs in National Health Care Programmes because of their easy availability, low cost, safety and the faith of people in such remedies. Scientific validation of several medicinal plant species has proved the efficacy of the plants in reducing respiratory symptoms (Mukherjee and Wahile, 2006) and the immense potential of such herbal agents have been recognized. Many drugs currently used in asthma and COPD *viz*., β_2-agonists, methylxanthines, anticholinergics and cromones have herbal source of origins. There is a large archive regarding usage of herbal preparations in many cultures for the treatment of respiratory disorders. The complimentary therapeutic approaches have been considered as having minimal of adverse effects and are being used as the adjunct therapy for many diseases (Huntley and Ernst, 2000; Lin *et al.*, 2015). In India, Golden Triangle Partnership (GTP) has given a boost to the research on traditional medicine with an aim to bring it to the mainstream of health care system of our country.

Studies with Monoherbal Ayurvedic Medicines in Respiratory Disorders

Several essential oils obtained from medicinal plants have been used traditionally in respiratory tract infections. Inhalation of essential oil vapors have shown anti-inflammatory effect on bronchial airways and attenuated bronchial asthma. Recently, Sharma *et al*. (2017b) investigated the effect of *Angelica glauca* essential oil on allergic airway changes induced by histamine and ovalbumin in experimental animals. The *A. glauca* essential oil was administered in the dose of 200µl/kg orally for 7 days. It was observed that both the doses of *A. glauca* essential oil significantly enhanced the pre-convulsive dyspnoea time in histamine induced bronchospasm in guinea pigs. It also reduced absolute blood eosinophil counts, serum IgE levels and the number of eosinophil and neutrophil cells in bronchoalveolar lavage fluid (BALF). Histopathological analysis of lung sections of mice exposed to ovalbumin led to significant inflammatory changes in peribronchial and perivascular areas, increased thickness of bronchial muscles and epithelial hyperplasia, which was markedly reversed by treatment with *A. glauca* oil. Thus, the authors concluded that *A. glauca* essential oil has bronchodilating and immunosuppressant activity in experimental animals.

Sharma *et al.* (2017c) also evaluated the activity of the essential oil of *Mentha arvensis* L. on histamine and ovalbumin induced bronchoconstriction in experimental animals. *M. arvensis* oil significantly reduced the histamine induced bronchospasm in guinea pigs as compared to that in control groups. It also decreased the serum IgE levels and the number of eosinophil and neutrophil cells in BALF. Histopathological analysis of lungs showed that the changes observed in the control group were markedly suppressed by treatment with *M. arvensis* oil. This study provided evidence that *M. arvensis* essential oil suppressed airway changes in experimental animals which may contribute to its efficacy in bronchial asthma.

Earlier, Sunita *et al*. (2012) studied the bronchodilatory and mast cell stabilizing activity of ethyl acetate and methanolic fractions of *Cressa cretica* L. in experimental model of asthma. Both fractions of *C. cretica* L. showed protection against histamine and acetylcholine induced bronchospasm in guinea pigs. The concentration dependent relaxant effects of both fractions were observed in guinea pig tracheal chain pre-contracted with carbachol (CCh), K^+ and histamine. It also significantly inhibited egg albumin induced mast cell degranulation in rats. The bronchodilatory and mast cell stabilizing property suggested the therapeutic potential of *C. cretica* L. in bronchial asthma.

Sagar and Sahoo (2012) also evaluated the anti-asthmatic activity of ethanolic extract of *Elephantopus scaber* L. leaves. Treatment with ethanolic extract of *E. scaber* significantly decreased the acetylcholine and histamine induced bronchospasm in guinea pigs. It reversed the histamine induced constriction of isolated guinea pig tracheal chain and also inhibited mast cell degranulation in rats. The bronchorelaxant and mast cell stabilizing property suggested the anti-asthmatic activity of ethanolic extract of *E. scaber* in experimental animals.

In another study, the effects of *Ephedra gerardiana* in an experimental mouse model of asthma were investigated by Chaitanya *et al.* (2014). Pre-treatment with ethanolic extract of *E. gerardiana* decreased the total number of cells, eosinophils, IL-4, IL-13 in BALF and total serum IgE levels as compared to control group of mouse. Histological analysis

showed that *E. gerardiana* treated group prevented the tissue edema, infiltration of inflammatory cell, epithelial cell hypertrophy and airway lumen plugging as compared to control group. The authors suggested that *E. gerardiana* possesses significant anti-asthmatic activity.

Recently, Chaudhary *et al.* (2016) evaluated the effects of *Solanum xanthocarpum* on airway inflammation and hyperresponsiveness in ovalbumin induced allergic asthma in rats. Rats were sensitized intraperitoneally with ovalbumin and aluminium hydroxide on day 1 and challenged with 1% aerosolized ovalbumin from day 15 to 22. Standardized aqueous extracts of *S. xanthocarpum* at a dose of 50, 100 and 200 mg/kg/day was administered orally for 22 days in different treatment groups. After 24 h of last ovalbumin challenge, blood and BALF were collected for the assay of ovalbumin specific IgE levels, cytokines (TNF-α, IL-6, IL-4 and IFN-γ) and oxidative stress parameters (MDA and reduced glutathione). Rats (vehicle treated) immunized and challenged with ovalbumin, resulted in increased levels of ovalbumin specific IgE, TNF-α, IL-6 and IL-4, whereas rats pretreated with *S. xanthocarpum* showed reduction in levels of IgE, TNF-α, IL-6 and IL-4 in both blood and BALF and these results were comparable with the standard drug prednisolone. Administration of *S. xanthocarpum* elevated the levels of IFN-γ in both blood and BALF as compared to control group of rats. It also reduced the levels of MDA, NOx and elevated the levels of GSH and SOD in both blood and BALF as compared to control (OVA) group of rats. In the experimental model of bronchial hyperresponsiveness, the values of Penh (a marker of airway resistance) was increased in control(OVA) group of rats in response to increasing concentration of methacholine (3.0-20.0 mg/ml) as compared to normal rats. This increase in the value of Penh was reduced after treatment with *S. xanthocarpum* - thus indicating reversal of bronchial hyperreactivity and airflow obstruction to increasing concentration of methacholine. The results of the study showed anti-inflammatory, immunomodulatory and anti-spasmodic effects of aqueous extract of *S. xanthocarpum*, which is accompanied with reduction in oxidative stress.

Arora *et al.* (2016) investigated the anti-asthmatic potential of alcoholic extract of *Vitis vinifera* fruits (grapes) in ovalbumin immunized and challenged Wistar rats. They observed that administration of *V. vinifera* for 28 days reduced the levels of IgE, IL-4, IL-5, TNF-α, IL-1β, LTD_4 and inflammatory cell counts in both blood and BALF as compared to ovalbumin sensitized control group. It also decreased the total nitric oxide and nitrite levels in both biological fluids and improved the lung function parameters (respiratory rate, tidal volume). In addition, *V. vinifera* reduced histamine levels in lung tissue homogenate and exhibited protection against airway inflammation in lung histology. The results of the study suggested that *V. vinifera* fruit extract might play an important role in the management of bronchial asthma.

Studies with Polyherbal Ayurvedic Medicines in Respiratory Disorders

The Ayurvedic literature, Sarangdhar Samhita highlighted the concept of polyherbalism to achieve greater therapeutic efficacy. The active phytochemical constituents of single plants are not enough to achieve the desired therapeutic effects. In polyherbal preparation, the combination of multiple herbs in a particular ratio provides a better therapeutic efficacy and also reduces the toxicity (Parasuraman *et al.*, 2014). Kanakasava is a polyherbal Ayurvedic formulation containing the following ingredients: Datura (*Datura metel*), Vasaca (*Adhatoda vasica*), Dhataki (*Woodfordia fruticosa*) and Grape (*Vitis vinifera*). Arora *et al.* (2017) evaluated the anti-asthmatic potential of Kanakasava in ovalbumin-induced bronchial asthma in rats. Treatment with Kanakasava decreased the number of inflammatory cells and the levels of IgE, IL-4, IL-5, TNF-α, IL-1β, LTD4, total nitric oxide and nitrite in blood and BALF as compared to ovalbumin sensitized control group. In addition, polyherbal preparation also inhibited the mast cell degranulation and improved the lung functions.Taken together, the findings of this study showed the protective effect of Kanakasava in allergen induced bronchial asthma,which validates its traditional use in Ayurveda.

Earlier, in a study by Rafiq *et al.* (2013) evaluated the effects of Bresol® – a polyherbal formulation in an experimental model of cigarette smoke-induced chronic obstructive pulmonary disease (COPD) in rats. Rats were exposed to cigarette smoke for 7 weeks for 10 minutes duration daily.

Pretreatment with Bresol® (250 and 500 mg/kg,p.o.) showed dose-dependent anti-inflammatory effects against cigarette smoke-induced lung abnormalities by reducing the levels of TNF-α and total protein in the bronchoalveolar lavage fluid (BALF) in comparison to untreated control group animals. Further, histopathological studies showed normal cyto-architecture of the lungs and trachea in Bresol®-treated animals. This group of workers concluded that Bresol® is a useful healing agent which may help to decelerate the progression of COPD, and reduce the exacerbations in patients.

Chelidonic acid is a secondary metabolite present in several plants that contain alkaloids such as *Chelidonium majus* and many others of a Papavar species. One preliminary study showed that chelidonic acid was as potent in preventing histamine release as disodium cromoglycate, a mast cell stabilizer used in the treatment of bronchial asthma and other allergic diseases. Singh *et al.* (2016) evaluated the effects of chelidonic acid on mast cell degranulation and adaptive immunity in rats sensitized and challenged with ovalbumin. They showed that OVA challenge resulted in mast cell degranulation, and treatment of rats with chelidonic acid (1, 3 and 10 mg/kg, i.p.) for 14 days significantly prevented mast cell degranulation and these effects were comparable with prednisolone. Further, there were reductions in the serum IgE levels after chelidonic acid treatment in a dose dependent manner. Chelidonic acid also suppressed histamine release from isolated rat peritoneal mast cells, with maximum inhibition of 65% at a dose of 10 mg/ml. To evaluate the immunomodulatory effects of Chelidonic acid, rats were immunized with sheep red blood cells (SRBC) and markers of adaptive immunity were assessed. Administration of different doses of chelidonic acid differentially inhibited the plaque forming cell count in rat splenic cells,anti-SRBC antibody titre and footpad thickness in the delayed type hypersensitivity reactions and all these effects were comparable with the standard drug, prednisolone. The results of the study proposed the possible therapeutic potential of chelidonic acid in allergic diseases.

Studies with Unani Medicines in Respiratory Disorders

UNIM-352 is a polyherbal Unani preparation which contains a mixture of following ingredients: *Linum usitatissimum* L., *Trigonella foenum-graecum* L., *Allium sativum* L., *Strychnos potatorum* L., *Caesalpiniabonducella* Fleming and *Pongamia glabra* Vent. Gulati *et al.* (2012) clinically evaluated the efficacy and safety of UNIM-352 in patients of bronchial asthma. It was a single blind, randomized, placebo controlled, parallel design and prospective study. The study was approved by Institutional Ethics Committee and was conducted as per GCP guidelines. 40 patients were enrolled for the study: there were 5 drop outs and 35 patients completed the study.The patients were randomly divided into two groups;16 were in placebo group (Group I) and 19 were in UNIM-352 group (Group II). Group I patients received formoterol (6 µg) + budesonide (200 µg) + placebo majoon (10 g) – BD and Group II patients received formoterol (6 µg) + budesonide (200 µg) + UNIM-352 majoon (10 g) – BD for 3 months. Levo-salbutamol (100 µg, SOS) inhaler was advised as an emergency medication and was considered as a parameter of exacerbations of asthma. The clinical symptoms, like breathlessness, tightness of chest, spirometry parameters like FEV1, FVC, FEV1/FVC ratio, frequency of use of emergency bronchodilator (levo-salbutamol) were assessed to determine the efficacy of the polyherbal drug UNIM-352. Analysis of the data showed that there was improvement in clinical symptoms like tightness in chest, wheezing, cough and difficulty in breathing in the patients receiving the test drug as compared to that of the placebo treated group. Spirometry data showed that the FEV1, FVC and FEV1/FVC ratio was significantly greater in the UNIM-352 treated group than that of the placebo.The frequency of use of emergency bronchodilators was appreciably lower in the UNIM-352 treated group as compared to the placebo group. The biochemical assay of blood samples showed that liver function test (SGOT, SGPT, bilirubin, alkaline phosphatase) and kidney function tests (urea and creatinine) were not significantly different in UNIM-352 and placebo treated groups. No other general parameters, like body weight, food intake, body temperature, etc. were influenced to any appreciable extent by UNIM-352 or placebo treated asthma patients. These results are of great significance, particularly in view of the fact that UNIM-352 has good potential to act as a useful adjunct in bronchial asthma. Gulati and coworkers proposed that this drug

could help to reduce the frequency of emergency bronchodilator usage and may also reduce the dose and duration of glucocorticoid therapy thus leading to rationalization and optimization of the therapy.

In the pre-clinical study, Guhathakurta *et al.* (2012) studied the mast cell stabilizing and bronchorelaxant properties of this Unani preparation, UNIM-352, in experimental model of bronchial asthma. They showed that in rats (vehicle treated) immunized and challenged with ovalbumin, there was massive mast cell degranulation and mortality, whereas rats pretreated with UNIM-352 at a dose of 200 or 400 mg/kg showed significant reduction in mast cell degranulation with no mortality. UNIM-352 dose dependently inhibited the histamine induced bronchoconstriction of isolated guinea pig tracheal chain in both normal and sensitized animals. Further, Guhathakurta *et al.* (2013) demonstrated the anti-inflammatory and immunomodulatory effects of UNIM-352 in keyhole limpet hemocyanin (KLH) immunized rats. In delayed type hypersensitivity experiments, this polyherbal preparation did not show any significant change in footpad thickness in KLH sensitized and challenged rats. Further, Rai *et al.* (2015) followed up the work and showed that pretreatment with UNIM-352 (200 or 400 mg/kg) significantly decreased the number of eosinophil and neutrophil cells in both blood and BALF in ovalbumin immunized and challenged rats. The polyherbal preparation also reduced TNF-α, IL-4, GMCSF and NF-κB levels, whereas levels of histone deacetylase (HDAC) were increased, in both the biological fluids. All effects of polyherbal drug were comparable with the standard drug, prednisolone. Rai *et al.* (2016) also explored the effects of UNIM-352 in allergen induced experimental model of bronchial airway-remodeling. Rats were sensitized intraperitoneally with ovalbumin adsorbed on aluminium hydroxide on day 1 followed by exposure to aerosolized ovalbumin inhalation for 30 minutes/day from day 15 to 21. After 24 hours of last ovalbumin challenge, blood and BALF were collected for the assay of TGF-β and IL-13. Immediately after the collection of blood and BALF, lung tissues were removed for the measurement of hydroxyproline content and histopathological studies, and the effects of UNIM-352 (200 or 400 mg/kg) were assessed on these parameters. The results showed that treatment with polyherbal agent for 21 days markedly attenuated the TGF-β and IL-13 levels in both blood and BALF, in a dose dependent manner. UNIM-352 also reduced the levels of hydroxyproline in lung homogenates and these reductions were comparable with the standard drug, prednisolone. Histopathological studies of lung tissue showed that UNIM-352 had an attenuating effect on inflammatory cells infiltration, goblet cell hyperplasia and sub epithelial fibrosis. The results suggested that UNIM-352 may act on multiple targets to reduce the severity of bronchial asthma. Thus, anti-inflammatory, immunomodulatory, anti-remodeling and bronchorelaxant effects of UNIM-352 may be contributing to its therapeutic benefits in asthmatic patients in the Unani system of medicine.

Studies with Yoga in Respiratory Disorders

Yoga has strongly emerged as an alternative form of traditional therapy for improving the psychosocial well being of humans and its benefits are being acknowledged globally. The main aim of yoga practice is to achieve coordination of mind, body and spirit. Yoga practitioners mainly use meditation, breathing exercise, posture and stretch to attain a state of maximum energy and efficacy. The maximum respiratory benefits are achieved by regular practice of pranayama and some other selective yoga asana which work directly on respiratory system. Regular yogic intervention may strengthen lung muscles, widen airways and may provide relief from obstructive airway diseases (Lavretsky, 2009). Gulati *et al.* (2017) assessed the effects of yogic intervention on pulmonary functions, inflammatory marker and quality of life in asthmatic patients. The study was a randomized, open label, parallel design, controlled clinical study and was approved by the Institutional Ethics Committee. The study was conducted as per GCP guidelines. 40 patients with mild to moderate asthma were enrolled for the study. The patients were randomly divided into two groups, 20 patients in Group I patients received conventional drug treatment (inhaled corticosteroids + long acting β_2-agonist) and Group II patients received conventional drug treatment + Yoga intervention for 50 minutes daily for three months. The yogic intervention consisted of selective physical practices, pranayama, meditation and shavasan performed in a fixed schedule under the guidance of a qualified Yoga teacher. All patients were examined for pulmonary function test (spirometry), fractional exhaled nitric oxide, IL-6 and Quality of

Life (QoL) at baseline and after 3 months of treatment.The QoL was evaluated by Asthma Quality of Life Questionnaire (AQLQ) in asthma patients prepared by Professor Elizabeth Juniper, Mc Master University, Canada. It consists of 32 questions which are divided in four sub-domains i.e., Symptoms which has 12 questions, Activity limitation has 11 questions, emotional function has 5 questions and response to environmental stimuli has 4 questions. The results showed that pulmonary functions (FEV1 and FEV1%), fractional exhaled nitric oxide and Quality of life were significantly improved, which was accompanied with decrease in the levels of markers of inflammation, IL-6 in Group II patients. The results suggest that yoga improved the pulmonary functions by reducing the airway inflammation. They concluded that introducing yoga as an adjunct therapy in bronchial asthma can minimize the need for medication which may reduce systemic toxicity of drugs and improve the quality of life.

Studies on Immunotherapy in Respiratory Disorders

Allergic airway diseases like allergic rhinitis and asthma are increasing in prevalence worldwide. Allergen-specific immunotherapy is a potentially curative treatment approach in allergic diseases and has been used for almost 100 years. The induction of peripheral T cell tolerance and promotion of the formation of regulatory T-cells are key mechanisms in allergen-SIT. Allergen-specific immunotherapy produces persistent clinical benefit after termination of treatment. The efficacy of allergen-specific immunotherapy has been shown in terms of reducing medication consumption, symptoms, and improving QoL in allergic asthma and rhinitis. Among several types of allergen specific immunotherapy, treatment of allergic airway diseases by intranasal immunotherapy had not been studied in detail. So, the contribution of Treg cells and their mechanistic pathways using intranasal immunotherapy in-vivo were investigated. In an earlier study, it had been shown that intranasal allergen immunotherapy attenuates allergic airway inflammation with reduction in IL-4, IL-5, IL-13 and total IgE levels (Datta *et al.*, 2016). Moitra *et al.* (2017) studied the modulation of regulatory T-cells(Treg) by intranasal allergen immunotherapy in an experimental model of airway allergy in rats. Allergen specific immunotherapy using *Alstonia scholaris* pollen extract has been shown to induce Treg cells in allergic patients. They showed that immunization and challenge with *A. scholaris* pollen extract caused reduction of CD4 + CD25 + Foxp3+ Treg cells whereas, intranasal immunotherapy with *A. scholaris* resulted in augmentation of CD4+CD25+Foxp3+Treg cells and thus attenuated allergic airway inflammation. In addition, intranasal immunotherapy increased CD4 + CD25 + IL10 + Tr1 cells, CD4 + CD25 + TGF-β + T-cells, CD4+CD25 + CTLA4 + T-cells, Foxp3 + GITR + Treg cells, Foxp3 + CD39 + Treg cells, Foxp3 + CD73 + Tregcells, whereas decreases the OX40 expression in CD4+ CD25+ T-cells. They have suggested that intranasal immunotherapy in animal model can help to chart out newer molecular targets for the treatment of allergic asthma or rhinitis.

Nanoparticles in Respiratory Disorders

Treatment of respiratory and infectious diseases has been a very challenging task, especially with the increasing incidence of these ailments globally. Nanotechnology-based drug delivery systems provide a possible solution to some of the drawbacks of the modern treatment regimen. Nanotechnology-based drug delivery systems have transformed the field of pharmacotherapy by modifying the pharmacokinetics of the conventional drugs to increase the drug retention time, decrease the side effects and extend the half-life of the drugs (Swai *et al.,* 2009). Gelli *et al.* (2015) studied the pulmonary toxicity of MgO nanoparticles in male Wistar rats. Rat lungs were exposed to MgO nanoparticles, carbonyl iron (negative control) and Quartz-crystalline silica particles (positive control) intratracheally with a single dose of 1 mg/kg or 5 mg/kg. The levels of alkaline phosphatase and lactate dehydrogenase were measured in BALF after 24 h, 7 days and 1 month for assessing the pulmonary toxicity of MgO nanoparticles. It was observed that similar to quartz, exposure of rats with MgO nanoparticles resulted in elevated levels of alkaline phosphatase and lactate dehydrogenase in BALF as compared to sham control group. This increase was more after 24 h post exposure period, and then gradually decreased after 7 days and 1 month post exposure period. Instillation of both doses of carbonyl iron to rats produced insignificant changes in alkaline phosphatase and lactate dehydrogenase levels in BALF as compared to sham control group at all post-

instillation period. The histopathological examinations of rat lungs exposed to MgO nanoparticles showed dilated and congested vessels, infiltration of interstitial lymphocytes, lymphoid aggregation, granulomatous reactions, peribronchiolar lymphocytic infiltration and alveolar macrophages at 24 h post-exposure period and were worsened at 7 days and were reduced at 1 month period, supporting the destruction of lung tissues, which was comparable with quartz nanoparticles. The results of the study suggested that intratracheal exposure of MgO nanoparticles increased the pulmonary enzymatic levels and this was also supported by histopathological results, indicating the pulmonary toxicity of MgO nanoparticles.

Nutraceuticals in Respiratory Disorders

The relevance of nutrition to human health and the importance of nutritional supplements and natural substances in preventive health care are being widely recognized. Herbal supplements, functional foods and beverages, are being promoted worldwide to meet the specific nutritional needs. Nutraceuticals are natural bioactive chemical compounds that have medicinal properties and that help in treatment and prevention of disease states. They are primarily used in dietary supplements and functional foods.Nutraceuticals are of particular interest now a day because they have the potential tomarkedly decrease the high costs and compromised safetyissues of current pharmaceuticals that are being used worldwide to treat pathophysiological states and provide viable therapeutic options and thus been recommended for the prevention and treatment of respiratory disorders (Dillard and German, 2000; Gulati *et al.,* 2016; Nicoli *et al.,* 1999).

Sharma *et al.* (2017a) studied the role of vitamin D supplementation in asthma and seasonal allergic rhinitis in eastern India. The study included 66 allergic rhinitis and asthma patients and 46 control subjects. Serum vitamin D levels were found to be significantly decreased in allergic rhinitis and asthma patients as compared to that in control group. They observed that vitamin D supplementation (cholecalciferol-1000 IU) increased the serum vitamin D levels in allergic rhinitis and asthma patients. The results of the study suggested that supplementation of vitamin D may be beneficial in the prevention of the pathogenesis of allergic rhinitis and asthma.

Newer Targets for Respiratory Disorders

Kinase signaling pathways delineate an attractive therapeutic target to treat anti-inflammatory diseases such as bronchial asthma. Specific kinase inhibitors such as Phosphoinositide 3 kinase (PI3K) and Janus kinase 3 (JAK3) diminish the critical kinase signaling cascade activity and improve the QoL in patients suffering from allergic airway inflammation. However, PI3K and JAK3 are involved in mast cell recruitment, activation, proliferation, migration and prolong the survival of inflammatory cells. Wagh *et al.* (2017) investigated the role of PIK3 and JAK3 Kinase inhibitors in acute and chronic murine models of asthma. Mice were sensitized and challenged with ovalbumin and the effects of JAK3 inhibitor, PI3K inhibitor and Dexamethasone on airway inflammation and airway remodeling were evaluated. They found that treatment with kinase inhibitors significantly reduced the number of basophils, neutrophils, macrophages and lymphocytes in BALF in acute and chronic model of asthma. In both the animal models, the levels of pro-inflammatory cytokines (TNF-α and IL-6) in BALF and lung homogenate were also decreased. PI3K inhibitor reduced the level of hydroxyproline in lung homogenate in chronic animal model. Lung histopathological analysis showed extensive infiltration of inflammatory cells, hyperplasia of goblet cells and increased airway collagen deposition, which were markedly reduced after treatment with kinase inhibitors. This study suggested that PI3K and JAK3 kinase inhibitors can be promising alternative therapeutic strategy in bronchial asthma, which might significantly counteract the airway inflammation in allergic asthmatic patients.

Angiotensin converting enzyme-I (ACE) is positively correlated with obstructive airway diseases and is highly expressed in the lungs. Angiotensin converting enzyme-2(ACE2), the counteracting enzyme of ACE, was proven to be effective in cardiovascular and pulmonary diseases. Dhawale *et al.* (2016) studied the effect of ACE2 in rat model of asthma. Rats were immunized and challenged with ovalbumin and then treated for two weeks with diminazene aceturate (ACE2 activator). They demonstrated that diminazene aceturate prevented airway hyperresponsiveness to carbachol and decreased infiltration of inflammatory cells. It also reduced the pulmonary expression of ACE1, IL-1β,

IL-4, NF-κB, BCL2, phosphorylated protein kinaseB(p-AKT) and phosphorylated p38 mitogen activated protein kinase (p-p38). Histopathological studies showed that diminazene aceturate treatment prevented intra alveolar interstitial thickening, inflammatory cell infiltration, fibrosis, oxidative stress and right ventricular hypertrophy as compared to that in control animals. The results of the study suggested that ACE2 activation by diminazene aceturate conferred protection against asthma as evident from biochemical, functional, histological and molecular parameters and ACE2 can be a novel target in the pharmacotherapy of asthma.

5-aminosalicylic acid (5-ASA) and sodium salicylate are known to suppress activation of NF-κB by inhibiting IκB. 5-ASA is a derivative of salicylic acid and is being used in the inflammatory bowel disease therapy due to its immunomodulatory role. 5-ASA inhibits IκB in intestinal epithelial cells of mouse where it was hypothesized to suppress the production of pro-inflammatory cytokine (TNF-α) and other Th_2 cytokines (Yan and Polk, 1999). It is also a powerful scavenger of peroxy radical (Pearson *et al.,* 1996). Raju *et al.* (2014) evaluated the effect of 5-ASA on airway inflammation and oxidative stress in ovalbumin (OVA) induced allergic asthma in Balb/C mice. Treatment with oral 5-ASA (65, 130 and 195 mg/kg) for 6 days significantly reversed the OVA induced total and differential leucocyte count, IL-6, TNF-α, IL-13, nitrite and nitrate levels in BALF. It also reduced MDA, myeloperoxidase and total lung protein levels in the lung homogenate in a dose dependent manner. The lung tissue sections of mice treated with OVA showed marked histopathological changes, such as enlarged submucosal mucus glands, goblet cell hyperplasia, goblet cell metaplasia, increased airway smooth muscle mass, enhanced matrix deposition in the airway wall, wall thickening and abnormalities in elastin. The extent of the above changes was found to be significantly reduced in 5-ASA treated mice at all three tested doses, which was comparable with the dexamethasone treated group. However, 5-ASA (195 mg/kg) showed mild degree of sub-epithelial fibrosis which might be due to the acidic nature of the drug. Raju and coworkers suggested that 5-ASA is a potent immunomodulator and attenuated allergen induced airway inflammation and oxidative stress in experimental model of asthma.

Further, the role of ions channels like K^+ channels, receptors like GABA, NMDA have been suggested in the regulation of airway diameter, and may be targeted pharmacologically to relieve airway hyper-constriction. Bashir and Sibgatullah (2017) studied the broncho-relaxant effect of Flupirtine, a non-opioid analgesic in experimentally induced asthma in guinea pigs. Administration of Flupirtine (46.5 mg/kg) for 5 days significantly increased the Pre-convulsive time as compared to the control group.

Adverse Drug Reactions (ADR) Surveillance in Respiratory Disorders

Pharmacotherapy of bronchial asthma and COPD invariably involves polypharmacy whereby multiple drugs and routes of administration are seen. Thus, complex drug-drug/disease interactions are always a possibility, a problem that is compounded by factors like long term therapy, especially with drugs with low therapeutic indices. ADR are thus common and the detection, assessment and strategies of prevention or treatment is of utmost significance in the interest of safe and effective drug therapy. Pharmacovigilance is defined as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems" (WHO 2002).

ADRs can be a complex phenomenon and several factors like the drug, the individual, and the disease state could contribute to its genesis. Specific and methodical ADR monitoring is the need of the hour and is in the interest of national health priorities. Long-term drug use particularly those with low therapeutic index, polypharmacy related drug-drug/disease interactions and multiple routes of administration contributes to ADRs during therapy in respiratory disorders. Focused ADR reporting/monitoring could be of great help and provide specific information for prevention/alleviation of such ADR related problems, thereby cutting health costs. Environmental and occupational factors may further compound this problem. The knowledge of clinical pharmacodynamics and pharmacokinetics in these specific situations are also of great importance. A study was conducted in 120 patients of obstructive airway disease (bronchial asthma and COPD) in outpatients and inpatients at the Vallabhbhai Patel Chest Institute, University of Delhi. Ethical clearance was obtained

and GCP guidelines were followed. All patients received multidrug therapy schedules by inhalation, oral or parenteral routes. Most patients received bronchodilators and/or corticosteroids, besides other forms of therapy. The pattern of ADR generation and profile were recorded and causality assessment was done using the Naranjo's scale. Dechallenge and rechallenge were done wherever appropriate. Overall analysis of the data showed that 93% of enrolled patients were males and rest were females, and COPD patients were predominantly males. Each patient received multidrug therapy schedules (inhalation and oral) and whereas most patients received inhaled corticosteroids and bronchodilators, few received mucolytics, antibiotics, analgesics, etc. General ADR incidence profile of patients revealed the following: inhaled corticosteroids (56%), inhaled anticholinergics (22.7%), oral methylxanthines (46.5%), oral corticosteroids and antibiotics (21%) and short acting β_2 agonists (5%). Detailed analysis of ADR characteristics showed that (a) inhaled corticosteroids induced one or more ADRs (sore throat, dysguesia, glossitis, hoarseness, etc.) in 90% of asthma and 50% of COPD patients; (b) Inhaled anticholinergics (dry mouth, thirst and urinary difficulty) in 62% asthma patients and 23% COPD patients; (c) inhaled β agonists (hand tremors) seen in 43% asthma and 5% COPD patients; (d) oral steroids (weight gain, acne, cramps, mood changes) in 87% asthma and 21% COPD patients; and (e) oral theophylline (anxiety, dyspepsia, muscle spasms, paresthesia) in 70% asthma and 46% COPD patients (Tyagi *et al.*, 2008). Further, out of the total 120 OAD patients 63 received oral theophylline (33% in asthma and 71% in COPD). ADR incidence with theophylline was 70% in asthma and 46% in COPD. Most patients complained of dyspepsia and anxiety (60%), whereas few others complained of muscle spasms and paresthesia. Causality analysis showed that muscle spasms fell in the highly probable category, whereas the other ADRs were in the probable category. Most ADRs were mild to moderate in nature and tolerable. Few, particularly those related to oral steroids and theophylline, were intolerable and required dose reduction (Gulati and Ray 2015). Such focused studies are being continued at Vallabhbhai Patel Chest Institute, University of Delhi, Delhi as a part (Adverse Monitoring Centre) of the Pharmacovigilance Programme of India (PvPI), with National Coordination Centre, IPC. This pharmacovigilance activity is helpful in reducing ADRs in OAD and rationalizing drug therapy. Further, studies have been initiated to evaluate the reasons for such ADRs and translate the knowledge acquired to suggest strategies to prevent or counteract them.

Conclusion

Respiratory pharmacology and toxicology are one of the most challenging fields of health sciences and is vital for the development of new drugs with more efficacy and greater margin of safety. Though treatment of communicable (infectious) diseases has improved remarkably, the same cannot be said for non-communicable diseases (including allergic conditions). Pharmacotherapy for conditions like bronchial asthma, COPD, ILD and lung cancer is still not well defined due to the complex etiopathologies involved. Awareness for basic and clinical research in this field has been enhanced considerably and newer strategies/modalities are being constantly explored. For example, the complementary role of traditional medicinal systems in pharmacotherapy of respiratory diseases is being widely advocated. The Government of India's initiatives in this direction have given a boost to the research in traditional medicine with an aim to bring them to the mainstream of the health care system of India. Several medicinal plant preparations (both monoherbals and polyherbals) from the Ayurveda and Unani systems of medicine are being evaluated for their efficacy and safety by using modern medical techniques and biomarkers. In addition, the effects of yogic intervention on pulmonary functions, cellular and molecular markers and quality of life in patients of obstructive airway disease are being assessed. Further, a lot of work is also going on novel aspects like immunotherapy and nanomedicine in the management of respiratory disorders. Research in the field of pharmacogenomics could provide interesting data and the way forward. This review also highlights the relevance of neutraceuticals in prevention and treatment of respiratory diseases and its pharmacoeconomic impact. Many clinical trials are being conducted to compare the efficacy and safety of already marketed individual drugs and combination therapy. Pharmacotherapy of respiratory diseases invariably involves polypharmacy whereby multiple drugs and routes of administration are used, thus, increasing the chances of drug-drug and drug-disease interactions and resultant adverse drug reactions

(ADRs). Research is going on to monitor the ADRs during pharmacotherapy of respiratory diseases, assessing the causal relationship and finding ways to prevent the ADRs to rationalize the therapy. However, more translational research is needed to bring scientific advances and knowledge into clinical practice, and there is a great need to find effective ways for a multidisciplinary, collaborative approach to promote meaningful interactions between traditional and modern medicine. Basic pharmacology and toxicology research in the field of respiratory diseases can unravel the molecular mechanisms that are involved in major lung disorders and can provide new directions for the development of innovative therapeutic strategies. There should also be a focus on earlier and more specific diagnosis of respiratory diseases as well as better targeted and personalized treatments which may be cost-saving, by decreasing the number of adverse effects of currently existing therapies, refining them and improving disease outcomes and quality of life.

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