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Dosha phenotype specific Ayurveda intervention ameliorates asthma symptoms through cytokine modulations: Results of whole system clinical trial

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ABSTRACT

Ethnopharmacological relevance: Over the past few decades, there have been significant scientific advances leading to improved understanding of asthma as a disease and treatment providing immediate relief. However, prevention of recurrent attacks, exacerbations and disease cure remains a challenge. Ayurveda refers to bronchial asthma as *Tamaka Swasa* and it is well explained in *Charaka Samhita*. Management of asthma in Ayurveda includes removal of vitiated Kapha through Shodhana, Shamana procedures, herbal and herbomineral formulations in addition to advising a healthy lifestyle and diet. Several clinical trials on Ayurvedic formulations for treatment of asthma are reported, however, whole system management of asthma has rarely been studied in the manner in which it is actually being practiced. Ayurveda therapeutics provides Dosha specific approaches, which needs biological investigation.

Aim of the study: The objective of our study was to investigate lung functions and cytokine changes in Asthmatic individuals in response to Ayurvedic intervention.

Methods: The study design was approved by the Institutional Ethics Committee of Tilak Ayurveda Mahavidyalaya (TAMV) & Sheth Tarachand Ramnath Charitable Ayurveda Hospital and followed guidelines of the Declaration of Helsinki and Tokyo for humans. It was conducted as a whole system individualized pragmatic clinical trial and written consent of patients was collected before enrollment.

One hundred and fifteen patients with mild-to-moderate asthma were divided into 2 sub-groups depending on their disease subsets and administered phenotype specific ayurvedic interventions. Seventy six asthma patients completed the treatment. Serum IgE levels, blood eosinophil counts, spirometry and blood cytokine levels were measured before the start of treatment and six months at the end of treatment. Age and sex matched healthy participants ($n=69$) were recruited in the study for comparison of cytokines levels.

Results: Significant improvements in FEV1(% predicted) ($p<0.0001$) and FVC (% predicted) ($p=0.0001$) was observed in asthmatic patients who underwent Ayurvedic treatment. Circulating levels of IgE ($p<0.03$) and eosinophil numbers ($p=0.001$) reduced significantly in the asthmatics after Ayurvedic treatment. This was associated with significant reduction in levels of circulating cytokines. Levels of Th2, Th1 and inflammatory cytokines in the peripheral blood were higher than healthy control participants at baseline (p values <0.0001) and reduced significantly after ayurvedic intervention.

Conclusion: This proof of concept study highlights the potential benefits and possible mechanism of Ayurvedic interventions in patients with mild-to-moderate asthma. The interventions significantly reduced IgE and eosinophil count, also improved lung function and reduced levels of circulating Th2 cytokines.

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1. Introduction

Asthma is a chronic inflammatory disease of the airways associated with bronchial hyperresponsiveness and airway remodeling and presents with symptoms including variable chest tightness, cough, shortness of breath and wheeze. Although the genesis of the mucosal airway inflammation in asthma is not known, it is believed that in most cases it is driven by IgE (immunoglobulin E), mast cells, eosinophils and a T-cell mediated immune response that is Th2-predominant. Increased expression of cytokines, chemokines, adhesion molecules and inflammatory mediators drive alteration in the balance between Th1-Th2 responses, cause inflammatory cell recruitment, activate and release of mediators from mast cells, eosinophils and epithelial cells, which ultimately leads to bronchospasm, bronchial hyper-responsiveness and airway remodeling (Barnes, 2008).

Although substantial progress in diagnosis, biology, and genetics of asthma has been made in past decade, treatment remains a challenge. Current treatment of asthma focuses mainly on symptomatic relief but not exacerbation or progression of disease and the most desirable-the primary prevention of asthma is a vision that has not yet become a reality (Mutius et al., 2012). A Combination of inhaled corticosteroids and long-acting beta-agonists, improve symptoms, quality of life and reduce mortality. However, these medications need to be taken on a long-term basis, and do not seem to have any significant impact on Th2 driven airway inflammation (Salvi et al., 2001).

Ayurveda is an ancient form of Indian Medicine that has been practiced for more than 3000 years. It was based on foundation of rational enquiry into the nature of the truth and was first described in “Charak Samhita” (Sharma, 2001), this ancient classic (1000 BCE) gave detailed descriptions of over 1500 herbs and 10,000 formulations that could be used in the treatment of various ailments. Central to the philosophy of Ayurveda is the fact that the human body is made of three biological regulators (tridoshas namely Kapha, Vata and Pitta) that are in a state of dynamic equilibrium. An imbalance in tridosha leads to the development of disease, which can be reverted once the imbalance is corrected with different interventions (Hankey, 2005). Disease states are believed to originate from an imbalance in the dosha, driven by the specific prakriti, and restoring this balance using interventions that are individually selected leads to a healthy state. According to Ayurveda Tamaka Swasa or asthma arises from aggravation of Vata and Kapha and could be controlled by eliminating Kapha. Various medications are described in Ayurveda that include single drugs and polyherbal formulations (Goyal, 1997).

Emerging evidence published more recently in reputed journals have demonstrated the scientific basis of Ayurvedic treatment for different disease states (Agarwal et al., 2010; Sehgal et al., 2012; Chopra et al., 2013) and indicates that the ancient system of Ayurveda can offer a knowledge base that can be used to develop novel therapeutic strategies (Patwardhan and MashelkarR, 2009). For example, *Withania somnifera*, is a nootropic ayurvedic herb that has been shown to promote cognition, including memory (Kulkarni and Dhir, 2008) by promoting neuritic regeneration (Kuboyama et al., 2005) and reversing plaque formation (Sehgal et al., 2012). Herbal medicines have been shown to modulate the secretion of multiple cytokines and this has been argued as the scientific basis for therapeutic benefits (Spelman et al., 2006).

Ayurveda is explored to develop novel therapeutics creating scientific evidence through *in vivo* studies or randomized controlled trials. However, translation and scientific validation of holistic approach of Ayurveda remains an area of emerging research (Periyasamy et al., 2015; Rotti et al., 2015). According to principles of Ayurveda, asthma is managed by body purification procedures called panchakarma, herbal formulations and specific diet as per individual phenotype (Sharma, 2001; Kaviraj, 2003; Shrikantha Murth, 2003). As a proof of concept; we evaluated effects of whole system ayurvedic intervention on lung function, quality of life, circulating cytokines in patients with mild-to-moderate asthma.

2. Materials and methods

2.1. Study design and study characteristics

Asthmatic patients visiting outpatient department of Tilak Ayurveda Mahavidyalaya and Sheth Tarachand Ramnath Charitable Ayurveda Hospital (TAMV), Pune during April 2011–Oct 2013 were recruited. The recruitment was as per following inclusion criteria: Male and female asthmatics between the age of 20–65 years. The study design was approved by the Institutional Ethics Committee of Tilak Ayurveda Mahavidyalaya (TAMV) & Sheth Tarachand Ramnath Charitable Ayurveda Hospital, (IEC Approval No. RSTH/RES/IEC/429/2011). Written consent was obtained from the patients before recruitment. The study was conducted as a prospective non-randomized clinical trial and followed guidelines of the Declaration of Helsinki and Tokyo for humans. The trial protocol is available on Clinical Trial Registry of India (CTRI), (protocol no CTRI/2014/12/005322). Patients with accompanying diagnosis of heart disease, other infectious disease, arterial hypertension and patients with COPD (chronic obstructive pulmonary disease), bronchiectasis were excluded. Patients who had long-term history of smoking, abnormal baseline hematology, blood chemistry or urine analysis, lactating mothers and pregnant ladies were excluded.

Mild to moderate asthma was defined as forced expiratory volume in one second (FEV1) $< 80\%$ predicted and FEV1/FVC $< 70\%$ (National Institutes of Health, 2007). Sample size was determined considering prevalence rate (P) of bronchial asthma in Adults as 2–4% and confidence level as 95%. Considering the number of drop outs, 75 sample number was finalized. Age and gender matched healthy participants ($n=69$) were also recruited from the general population as a control group for cytokine analysis. Diagnosis of Bronchial asthma was done by a chest physician with the help of diagnostic criteria as per ICD-9-CM classifications (American Medical Association, 2005; ICD, 2005). Spirometry was performed according to 2005 ATS/ERS norms to measure FEV1 and forced vital capacity (FVC) and asthma control questionnaire (ACQ) was obtained at baseline and at the end of the treatment. Diagnosis of asthma was confirmed by improvement of FEV1 by $> 12\%$ and 200 mL after using a short acting inhaled salbutamol. Ayurvedic physicians classified the patients as Vata or Kapha dominant based on the ayurvedic criteria. Vata (V) dominant asthma is defined as asthma with dry cough without sputum. Kapha (K) dominant asthmatics have productive cough with sputum (Sharma, 2001).

Peripheral blood venous samples were collected from the study and control population, followed by separation of plasma and measurement of IgE and cytokine levels using Bioplex kits.

On recruitment demographic & clinical data was recorded in specially designed case record form. The study was assessor blind evaluation of outcome variables. The samples were coded and the physician, who assigned the treatment, and person who did spirometry, pathological and cytokine analysis were different.

2.2. Ayurvedic intervention

The intervention was administered as per predefined whole system protocol that allowed individualized management as per disease stage. K or V specific treatment protocol was developed based on literature reviews of classical Ayurveda texts Charaka