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RECENT PROGRESS IN THE DEVELOPMENT OF POLYHERBAL FORMULATIONS FOR TREATING ASTHMA AND ASSOCIATED RESPIRATORY DISORDERS

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ABSTRACT

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In India, Ayurveda is one of the oldest and most widely used medical systems. It is the goal of Ayurveda to keep people healthy and happy for as long as possible. Ayurveda emphasizes the use of natural components to treat the underlying cause of illness while also promoting a healthy way of life to avoid recurrence. More than 80% of the world's population still uses conventional medications for their health care, according to the WHO. Known as one of the world's biodiversity hotspots, the subcontinent of India has over 45,000 plant species. An estimated 7,500 medicinal plants have been identified in India, with the local populations relying on those to treat a wide range of ailments. Single or many herbs (polyherbal) are utilized for therapy in Ayurveda. In order to obtain the desired therapeutic effects, the active phytochemical elements of individual plants do not enough. Therapeutic effects and toxicity are reduced when herbs are combined at a certain ratio. Polyherbal and its clinical importance are the topics of this study. The present article focuses on the development of polyherbal formulations for treating asthma and associated respiratory disorders. This study on polyherbal formulations will positively open avenues towards alternative treatment options for respiratory diseases.

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1. INTRODUCTION

1.1. Plant as a bioresource

Our reliance on plants extends back to our earliest days as a species. Humans' most fundamental requirements are shelter, clothes, food, taste and aroma, and, of course, medicine. Medicines derived from plants are widely used. Ayurvedic, Unani, and Chinese medicine all have their roots in the sophisticated structures created by ancient medicine via the use of plants. Plants were revered as heavenly and miraculous healers in ancient cultures including

those of India, Egypt, China, Rome, and Greece. The Edwin Smith Papyrus, an ancient Egyptian medical document on wound healing, was written by Edwin Smith. Herbs have long been used to treat a wide range of health problems, both internally and externally. Herbalists in the past saw these plants as a gift from nature that might be used to treat disease [1].

1.2. Traditional herbal medicine

Traditional herbal medicine refers to the use of plants or plant materials to cure illness, whether in their raw or processed form. As a

result of ethnomedicinal value, the medicinal plants are being tested for therapeutic efficacy. Traditional and herbal remedies are studied using an ethnopharmacological method, which incorporates both social and natural disciplines. Anthropogenic ethnopharmacological investigations are based on ethnographic studies of local usage of natural medicines. Many disorders have been successfully treated using herbal remedies throughout the years. Because of the enormous range of functionally relevant secondary metabolites in microbial and plant species, natural products and related structures are crucial sources for novel medications [2].

1.3. Asthma

Asthma is a medical condition in which a person's airways become inflamed, narrowed, and swollen, as well as produce copious mucus, making breathing difficult. Asthma may be moderate or severe, making it difficult to carry out daily chores. In certain cases, it may lead to a life-threatening assault. Breathing difficulties, chest pain, coughing, and wheezing are all symptoms of asthma. Symptoms may flare up now and then. Rescue inhalers (salbutamol) are widely used to ease symptoms while controller inhalers are used to prevent symptoms (steroids). In severe cases, longer-acting inhalers (formoterol, salmeterol, tiotropium, etc.) and inhalant steroids may be necessary [3].

2. PATHOPHYSIOLOGY OF ASTHMA

2.1. Physiological basis of Asthma

Some processes have a strong link to being inherited in the asthma phenotype, however, the mechanism is more complicated since asthma does not follow a Mendelian pattern. Asthma is most likely passed down over numerous generations, with some variance in locus heterogeneity and polygenic inheritance leading to diverse asthma manifestations. Atopy or IgE antibodies are antibodies that attack certain antigens or contaminants, aggravating the condition. According to studies, asthma is associated with high levels of total IgE in the blood. Asthma sensitization has been linked to increased IgE response to environmental variables such as home dust mites, animal

allergens, mildew, and farm animals, worsening symptoms and leading to increased airway reactivity. The reason for this is that people are being exposed to these allergens at higher levels, but there is less evidence of their causation. Although there is no relationship between air pollution and asthma, there is a correlation between smoking and an increased risk of asthma. Surprisingly, obesity was shown to have a positive linear connection with increasing BMI and asthma [4].

2.2. Anatomical basis of Asthma

To acquire a deeper knowledge of the multifactorial condition, further study is required. The lungs are the organ system that suffers the greatest damage from asthma. The lungs are split into lobes and segments, with ten segments in the right lung and eight or nine in the left, depending on how the lobe is divided. The conducting zone and the respiratory zone are anatomically separated in the respiratory system. The respiratory zone (where gas exchange happens) stretches from the alveolar duct to the alveoli, whereas the conducting zone extends from the nose to the bronchioles. The bronchial tree is predominantly affected by asthma, and its main job is to move air throughout the lungs until it reaches the alveolar sacs. The bronchi begin at the trachea's end and split into left and right bronchi. The right bronchus is longer and more vertical, whereas the left is shorter and more horizontal. After then, the bronchi are separated into secondary and tertiary bronchi. The bronchi include smooth muscle and elastic fibers to preserve their wall integrity, which fluctuate based on the contraction and relaxation of smooth muscle by inflammatory mediators, bronchoconstrictors, and bronchodilators. As one moves from the bronchi to the alveoli, smooth muscle fibers become increasingly engaged. Lung compliance refers to the lungs' propensity to expand during normal respiratory physiology, while elastance refers to the lungs' ability to return to their resting state. The physiologic processes of asthmatic patients alter as a consequence of

inflammation, lowering the radius of the airway [5].

2.3. Immunological basis of Asthma

There are two phases to an asthma exacerbation: the early phase and the late phase. The early phase is initiated by IgE antibodies, which are sensitized and released by plasma cells. Environmental stimuli, such as the risk factors outlined above, cause these antibodies to respond. IgE antibodies thus have a strong affinity for mast cells and basophils. Mast cells produce cytokines and ultimately degranulate when exposed to a pollutant or risk factor. Mast cells produce histamine, prostaglandins, and leukotrienes, among other substances. The smooth muscle contracts as a result of these cells, creating airway constriction. Th2 lymphocytes are involved in the synthesis of

interleukins (IL-4, IL-5, and IL-13) and GM-CSF, which facilitate cell communication and inflammation maintenance. Eosinophils and basophils both benefit from the presence of IL-3 and IL-5 (**Figure 1**). Remodeling, fibrosis, and hyperplasia have all been associated with IL-13. The late phase develops during the following several hours, when eosinophils, basophils, neutrophils, and helper and memory T-cells all congregate in the lungs, producing bronchoconstriction and inflammation. Mast cells also aid in the delivery of late-phase reactants to inflamed areas. It is crucial to detect both of these processes to focus treatment and alleviate both bronchoconstriction and inflammation, depending on the severity of the condition [6].

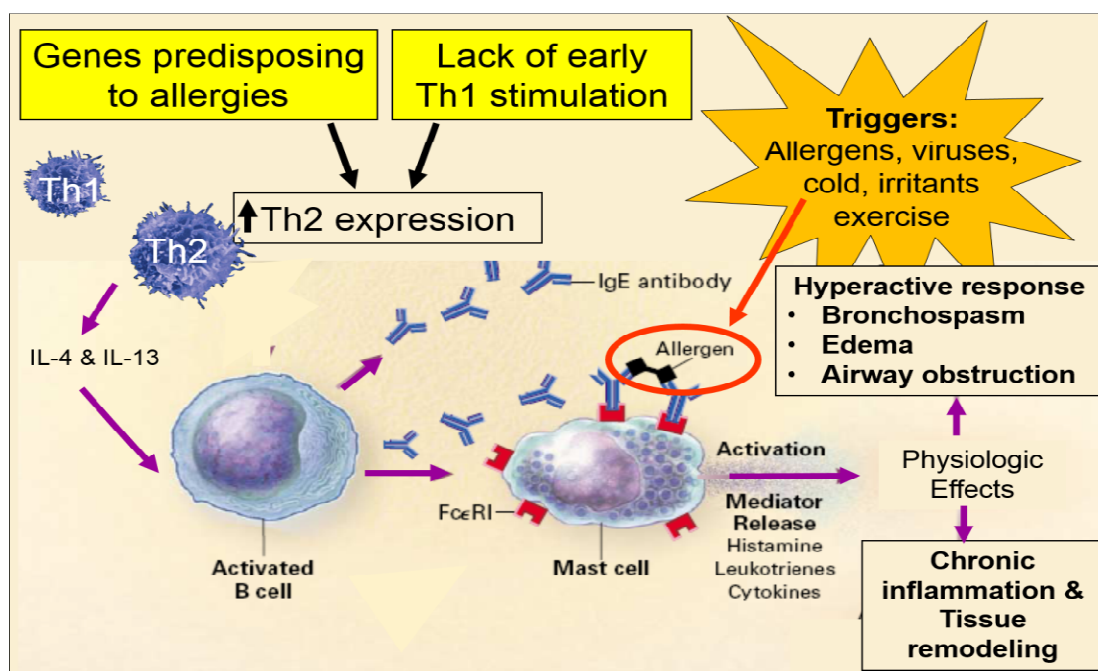


Figure 1. Basic pathways of the Asthma Pathophysiology.

3. DEMOGRAPHY

Asthma has been increasingly prevalent since the early 1990s. Between 1982 and 1992, asthma rates climbed from 34.7 to 49.4 per thousand people. In the United States of America, around 8% of the population suffers from asthma (USA). There have also been some contradictory patterns throughout the globe,

with certain nations reporting either an increase in cases of stagnation. Until the age of 20, asthma is more frequent in males, after which it is equally prevalent in both sexes. Atopy or the fact that males have a narrower airway than girls might produce differences in childhood [7]. Asthma has a genetic component to it as well.

However, the genes that cause asthma to be inherited are still unknown.

4. DRAWBACK OF CURRENT ANTI-ASTHMATIC TREATMENT

4.1. Problems with inhaled medications

Despite the availability of various oral and inhaled treatments for the long-term care of individuals with persistent asthma, the condition nevertheless has a high morbidity and death rate. Due to their documented clinical effectiveness, capacity to decrease bronchial inflammation, and tolerability, inhaled glucocorticoids have been a cornerstone of maintenance treatment in recent years. Other inhaled drugs (such as sodium cromoglycate, nedocromil, and long-acting beta-2 agonists) are also used to treat asthma patients long-term [8]. Many patients (especially youngsters and the elderly) find inhalers difficult to use, and poor inhaling techniques may impact the quantity of medicine that reaches the lungs and the patient's reaction to treatment.

4.2. Associated side effects

Oral asthma medication has typically consisted mostly of sustained-release theophylline and glucocorticoids, despite the simplicity of delivery. Because theophylline has a narrow therapeutic index, blood medication concentrations must be checked frequently, and long-term oral glucocorticoid treatment has been linked to major side effects such osteoporosis and bone fractures. Orally administered leukotriene receptor antagonists (e.g., zafirlukast) and 5-lipoxygenase inhibitors (e.g., zileuton) have recently been developed, providing novel mechanisms of action as well as potential solutions to the compliance issues associated with regular inhaled asthma therapy administration [9]. These medications are effective as asthma maintenance treatment and, more crucially, do not have the adverse effects associated with long-term systemic glucocorticoid therapy (**Figure 2**).

SIDE EFFECTS OF ANTI-ASTHMATIC DRUGS		
Inhaled steroids	β_2 -Agonist	Theophylline
Oral candidiasis	Tachycardia	Nausea
Hoarseness	Arrhythmia	Abdominal pain
Cough	Tremor	Tachycardia
Surrenal supression	Hypopotassemia	Arrhythmia
Osteoporosis	Hyperglisemia	Anxiety
Cataract	Anxiety	Convulsion
Glaucom		
Hypertension		
Diabetes		
Obesity		

Figure 2. Common side effects of Anti-Asthmatic drugs.

4.3. Drawbacks in long term asthma management

Receptor antagonists and 5-lipoxygenase inhibitors are employed in the long-term care of asthma sufferers. Montelukast has a safety profile equivalent to placebo, according to a

recent assessment of its safety and acceptability in children with episodic (viral) and chronic multi-trigger wheeze. Montelukast is a safe medicine in many clinical studies. However, fresh research has cast doubt on the benefit-to-risk ratio of leukotriene receptor antagonists in

both pediatric and adult patients. Both psychiatric and non-psychiatric adverse effects are being reported in increasing numbers. We learn more about their adverse effects as they become more widely utilized. When risk factors for LTRAs are recognized and alternate treatment approaches are employed on patients who are at risk of side effects, side effects associated with LTRAs will be decreased [10].

5. POLYHERBAL THERAPY

5.1. Use of herbal principles

In Indian Traditional Medicine, or Ayurveda, the drug formulation is completely based on two primary principles: the use of a single medication and the use of many medicines, the latter of which is known as polyherbal method (PHM) or polyherbal formulation (PHF). Polypharmacy or polyherbalism is a fundamental traditional therapeutic herbal method that involves mixing many medicinal plants to increase therapeutic efficacy. There are a few Ayurvedic herbs combinations to be cited here:

1. The heating and mucous-reducing properties of ginger are enhanced when it is combined with black pepper and long pepper.
2. Bitter and cold plants are paired with warming herbs (a neem-ginger mixture) to counteract any excessive effects.
3. Cumin, black pepper, and asafoetida are historically used to relieve bloating caused by poor digestion.
4. The combination of guduchi and turmeric boosts immunity [11].

5.2. Underlying mechanisms of action(s)

There are two processes through which synergism works, depending on the nature of the relationship (i.e., pharmacodynamics and pharmacokinetics). The capacity of one herb to promote the absorption, distribution, metabolism, and elimination of other herbs is the focus of pharmacokinetic synergism. Pharmacodynamic synergism, on the other hand, investigates the synergistic impact that occurs when active elements with equivalent therapeutic efficacy are directed at the same

receptor or physiological system. Apart from that, it is thought that illnesses are caused by a variety of variables and complications in the majority of instances, resulting in both apparent and unseen symptoms. In this case, a mixture of herbals may work on many targets at once to offer complete relief [12].

5.3. Advantages of polyherbal formulations

As previously said, PHF is just lately gaining popularity throughout the globe since it offers benefits not found in allopathic medications. To begin with, PHFs are well-known for their excellent efficacy in a wide range of disorders. As previously stated, herbal medicines have therapeutic benefits owing to the presence of several phytoconstituents, and these effects are amplified when appropriate herbals are mixed in PHFs. Many studies on PHF have been conducted to date to assess their efficacy, and these studies have been published in international publications. Srivastava *et al.*, for example, found in their research that anti-diabetic PHFs such as Dihar[®], Diabet[®], Diasol[®], Dianex[®], DRF/AY/5001[®], Diashis[®], Diabrid[®], Diakyur[®], Diasulin[®], and others had similar effects to traditional allopathic drugs. According to statistical research conducted in the United Kingdom, the major reason for the usage of medicinal herbalism is the treatment's efficacy and beneficial effects. PHF is a good therapy of choice for all of the following reasons: effectiveness, safety, low cost, ubiquity, and improved acceptability, resulting in increased patient compliance and superior therapeutic impact [13].

5.4. International status of polyherbal therapy

Polyherbal therapy is currently being researched by scientists, who are either developing new formulations or using old traditional formulations that have been used for decades, such as Ayurveda, which dates back to 5000 BC, Korean traditional medicine such as Mahwangyounpae-tang (MT), which contains 22 types of herbal extracts for the treatment of respiratory disorder, and the African Herbal Formula (AHF), which consists of a

combination of plant materia. For generations, members of the Haya family and close friends have used AHF to treat a variety of health issues, and it is especially popular among those from the region's lower socioeconomic classes. The region's diverse ethnic groups in the Lake Victoria Basin, as well as Pakistani and Indian traditional medicine, have fostered a vibrant exchange of knowledge and skills among the Kagera people of northwestern Tanzania. It was founded in Greece by ancient Greek philosophers, and documented by Muslims during the golden age of Islamic civilization. Muslim scholars brought it to the Indo-Pak region, where it has been practiced for centuries [14].

6. RECENT REPORTS ON POLYHERBAL FORMULATIONS

Gheware *et al.*, 2021 demonstrated the physiological, histological, and molecular levels, and also reveal the therapeutic benefits and mechanistic basis of *Adhatoda vasica* aqueous extract on mice models of acute allergic and severe asthma subtypes. In severe asthmatic mice, oral treatment of *A. vasica* extract reduces enhanced airway resistance and inflammation, as well as molecular markers of steroid (dexamethasone) resistance such as IL-17A, KC (murine IL-8 homolog), and HIF-1 (hypoxia-inducible factor-1). HIF-1 levels are inhibited by *A. vasica* through restoring the expression of its negative regulator, PHD2 (prolyl hydroxylase domain-2). In the acute and severe asthma paradigm, the alleviation of hypoxic response mediated by *A. vasica* is further validated. Bioenergetic profiles and morphological characterization of mitochondria show that *A. vasica* cures cellular hypoxia-induced mitochondrial failure in human bronchial epithelial cells. HIF-1, IL-6, Janus kinase 1/3, TNF- α , and TGF- α were identified as the key actors in hypoxic inflammation. In silico docking of *A. vasica* components reveals a stronger negative binding affinity for C-glycosides and O-glycosides. For the first time, a molecular basis of action and impact of *A. vasica* entire extract, which is extensively

utilized in Ayurvedic treatment for a variety of respiratory disorders, is provided in this work. The research also emphasizes its potential to treat severe steroid-resistant asthma by highlighting its influence on hypoxia-induced mitochondrial dysfunction. The present literature supports the use of *A. vasica* in current research [15].

Yokum *et al.*, 2020 in a mouse asthma model, looked at the impact of 6-shogaol, a bioactive ingredient of ginger, on reducing lung inflammation. Chronic treatment of whole ginger extract or 6-shogaol, a bioactive component of ginger, reduces *in vivo* house dust mite antigen-mediated lung inflammation in mice, according to the researchers. It was also shown that this reduction in inflammation is linked to a reduction in *in vivo* airway responsiveness. Authors showed that 6-shogaol increases cAMP levels in CD4 cells, which is consistent with phosphodiesterase inhibition, and inhibits nuclear factor- $\kappa\beta$ signaling and the generation of pro-inflammatory cytokines in activated CD4 cells *in vitro*. Effector T-cell function is known to be inhibited by sustained increases in cAMP concentration. Regulatory T-cells (Tregs) use cAMP as a mediator of their immunosuppressive actions, and also showed here that 6-shogaol increases Treg polarisation in naive CD4 cells *in vitro*. These observations, when combined with prior findings, imply that ginger and 6-shogaol can treat asthma via two mechanisms: immediate ASM relaxing and long-term inflammation inhibition. The present literature supports the use of ginger in contemporary research [16].

Shan *et al.*, 2020 investigated the phytochemistry, pharmacokinetics, and toxicity of herbal preparations. According to the authors, the polyherbal compositions have synergistic pharmacological efficacy against a particular disease with minimum adverse effects [17].

Mortazavi *et al.*, 2019 had researched on a polyherbal traditional combination known as "Monzej-e-balgham," which was based on Iranian traditional medicine texts and subjected to quality control assessments. *Vitis venifera* L.,

Ficus carica L., *Foeniculum vulgare* Mill., *Glycyrrhiza glabra* L., *Adiantum capillusveneris* L., *Rosa damascena* Herm., and *Onopordum acanthium* L. are among the formulation's primary constituents. The content was crushed, combined, and decoction extracted with distilled water. The combination was used to create syrup compositions. The syrup's physicochemical, microbiological, and rheological characteristics were investigated, and the total phenolics content of the formulation was determined. During a 6-month accelerated stability test, the syrup was examined. This study's findings demonstrate how polyherbal combinations may be analyzed and manufactured to commercial standards [18].

Sadr *et al.*, 2019, has looked into the effectiveness and safety of an Iranian polyherbal formulation (compound honey syrup) in the treatment of mild to moderate asthma in children. The aforementioned research was a randomized clinical trial that lasted eight weeks and included 80 individuals with mild to moderate asthma who were divided into two groups (n=40 each). The control and experimental groups received standard asthma therapy with fluticasone spray; if symptoms worsened, salbutamol spray was given for a brief time. Compound honey syrup was also given to the experimental group (the combination of honey and an extract of the following five medicinal plants: ginger, cinnamon, saffron, cardamom, and galangal). Before and after therapy, the items and total scores of the Asthma Control Questionnaire (ACQ) were examined. The Iranian polyherbal formulation may be a safe and effective supplemental medicine for the treatment of juvenile asthma, according to the findings of this research [19].

Parasuraman *et al.*, 2018 had given a thorough understanding of the notion of polyherbal formulation in Ayurveda. The research also covered the fundamentals and justification for employing polyherbal formulations [20].

Korukola *et al.*, 2015 produced a polyherbal formulation in the form of syrup with ginger and black pepper. The present study sheds light on how pre-formulation investigations for a polyherbal formulation should be carried out. The research also showed that bioavailability in polyherbal syrup has improved [21].

Nawaz *et al.*, 2014 studied the toxic potentials of the polyherbal syrup through a toxicological screening. The existing literature will assist us in comprehending how the toxicological assessment will be carried out throughout the creation of a polyherbal product [22].

Sellappan *et al.*, 2014 created a polyherbal formulation for anti-asthmatic action and examined its effect. The present study's major goal was to create and standardize herbal asthma formulations utilizing well-studied herbs. *Tylophora indica*, *Tephrosia purpurea*, and *Vitex negundo* were chosen for this study because of their anti-asthmatic, anti-histaminic, and anti-inflammatory properties [23].

Sheikh *et al.*, 2014 studied the physicochemical assessment of polyherbal syrup, including pH, density, polysaccharide identification, tanning agents, ascorbic acid, and shelf life. The polyherbal syrup was also subjected to qualitative analysis. The existing literature will assist us in comprehending the many physiochemical qualities that must be assessed, as well as the quantitative tests that will be used when building a polyherbal formulation [24].

Thangarathinam *et al.*, 2013 produced polyherbal syrup and assessed it using characteristic parameters such as pH, total solids, specific gravity, and viscosity. The accelerated stability investigations were also carried out by the author. The existing literature will aid us in the development of a polyherbal syrup as well as its assessment and stability tests [25].

Mali *et al.*, 2011 showed that in the treatment of asthma, plant herbs have shown promising results in bronchodilation, mast cell

stabilization, anti-anaphylactic, anti-inflammatory, anti-spasmodic, anti-allergic, immunomodulatory, and inhibition of mediators such as leukotrienes, lipoxygenase, cyclooxygenase, platelet-activating, phosphodiesterase, and cytokine [26].

Pattanayak *et al.*, 2010 examined the mechanism of action of *Ocimum* species in many disorders, including asthma, and documented it comprehensively. The active ingredients of *O. sanctum* L., eugenol (1-hydroxy-2-methoxy-4-allylbenzene), are principally responsible for the medicinal potentials [27].

Fazel *et al.*, 2008 studied the spectroscopic properties of total alkaloids in a polyherbal mixture [28].

Singh *et al.*, 2007 conducted a thorough study of the plants with anti-asthmatic properties. The plant that was chosen for the research was chosen based on the present review [29].

Moore *et al.*, 2001 investigated the mechanism behind asthma pathogenesis, as well as the involvement of interleukin-10 and the interleukin-10 receptor in asthma pathophysiology [30].

Bielory *et al.*, 1999 discussed the role of herbal-based therapies in asthma and allergic rhinitis therapy. The information was analyzed and grouped into groups based on culture and the effects of medicinal herbs on asthma and allergies. Several studies have been found to support the use of herbal medications in the treatment of asthma and allergies. Antiasthma components were found as various compounds from certain medicinal plants, and several methods of action were investigated. The findings reveal that these herbs have beneficial effects on bronchodilation, pulmonary function tests, antagonism of asthma mediators such as histamine and platelet-activating factor, corticosteroid levels, and mucus clearance. Patients with allergic rhinitis, who had histamine-induced responses, such as rhinorrhea, sneezing, and itching, had improved symptoms. Some herbal treatments may have a

function in the treatment of asthma and allergic rhinitis, according to the study [31].

CONCLUSION

Many countries employ polyherbal formulations, although there is currently no conclusive proof that they are safe or effective. Even though clinical studies have not been performed on many herbal remedies, *in vivo* testing is still being done on a number of them. There haven't even been any safety assessments like toxicological tests. Clinical trials, potential bioactive ingredients, and mechanisms of action must all be given enough time to analyze polyherbal formulations scientifically.

CONFLICT OF INTEREST

No conflict of interest is declared.

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REFERENCES

1. McCracken JL, Veeranki SP, Ameredes BT, Calhoun WJ. Diagnosis and management of asthma in adults: a review. *JAMA*. 2017;318(3):279-90.
2. Barik CS, Kanungo SK, Tripathy NK, Panda JR, Padhi M. A review on the therapeutic potential of polyherbal formulations. *Int J Pharm Sci Drug Res*. 2015;7(3):211-28.
3. Santosh J, Jyotiram S. Standardization of poly-herbal formulations: A comprehensive review. *Res J Pharmacog Phytochem*. 2016;8(2):85-9.
4. Mannino D, Homa D, Akinbami L, Moorman J, Gwynn C, Redd SC. Surveillance for asthma—the United States, 1980-1999. *MMWR Surveill Summ*. 2002;51(1):1-3.
5. Centers for Disease Control and Prevention (CDC). Vital signs: asthma prevalence, disease characteristics, and self-management education: The United

- States, 2001--2009. MMWR Morb Mortal Wkly Rep. 2011;60(17):547-52.
6. Maio S, Baldacci S, Carrozzi L, Pistelli F, Angino A, Simoni M, *et al.* Respiratory symptoms/diseases prevalence is still increasing: a 25-yr population study. *Respir Med.* 2016; 110:58-65.
 7. Weiss ST, Gold DR. Gender differences in asthma. *Pediatr Pulmonol.* 1995;19(3):153-5.
 8. Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG. Association of asthma with serum IgE levels and skin-test reactivity to allergens. *N Engl J Med.* 1989;320(5):271-7.
 9. Gilliland FD, Islam T, Berhane K, Gauderman WJ, McConnell R, Avol E, Peters JM. Regular smoking and asthma incidence in adolescents. *Am J Respir Crit Care Med.* 2006;174(10):1094-1100.
 10. Papiris S, Kotanidou A, Malagari K, Roussos C. Clinical review: severe asthma. *Crit Care.* 2001;6(1):1-5.
 11. Sumanth M, Anusha M, Swetha S. Elucidation of mechanism of anti-arthritic action of arthosansar-A polyherbal formulation. *Indian J Trad Knowl.* 2012; 11:704-13
 12. Aslam MS, Ahmad MS, Mamat AS, Ahmad MZ, Salam F. An update review on polyherbal formulation: A global perspective. *Syst Rev Pharm.* 2016;7(1):35-41.
 13. Karole S, Shrivastava S, Thomas S, Soni B, Khan S, Dubey J, Dubey SP, Khan N, Jain DK. Polyherbal formulation concept for synergic action: a review. *J Drug Deliv Ther.* 2019;9(1-s):453-66.
 14. Aswal S, Chauhan V. Current status of polyherbal formulation derived from ethnobotanicals. *Arch Biomed Sci Eng.* 2020;6(1):48-9.
 15. Gheware A, Panda L, Khanna K, Bhatraju NK, Jain V, Sagar S, Kumar M, Singh VP, Kannan S, Subramanian V, Mukerji M, Agrawal A, Prasher B. Adhatoda vasica rescues the hypoxia-dependent severe asthma symptoms and mitochondrial dysfunction. *Am J Physiol Lung Cell Mol Physiol.* 2021;320(5): L757-L769.
 16. Yocum GT, Hwang JJ, Mikami M, Danielsson J, Kuforiji AS, Emala CW. Ginger and its bioactive component 6-shogaol mitigate lung inflammation in a murine asthma model. *Am J Physiol Lung Cell Mol Physiol.* 2020;318(2): L296-L303.
 17. Shan QY, Sang XN, Hui H, Shou QY, Fu HY, Hao M, Liu KH, Zhang QY, Cao G, Qin LP. Processing and Polyherbal Formulation of *Tetradium ruticarpum* (A. Juss.) Hartley: Phytochemistry, Pharmacokinetics, and Toxicity. *Front Pharmacol.* 2020; 11:133.
 18. Rezghi M, Mortazavi SA, Fahimi Sh CR, Sheikholeslami MA, Hamzeloo-Moghadam M. Polyherbal tablet based on Iranian traditional medicine. *J Med Plants.* 2021;20(77):15-25.
 19. Karimi M, Zarei A, Soleymani S, Jamalimoghadamsiahkali S, Asadi A, Shati M, *et al.* Efficacy of Persian medicine herbal formulations (capsules and decoction) compared to standard care in patients with COVID-19, a multicenter open-labeled, randomized, controlled clinical trial. *Phytother Res.* 2021;35(11):6295-6309.
 20. Parasuraman S, Thing GS, Dhanaraj SA. Polyherbal formulation: Concept of Ayurveda. *Pharmacogn Rev.* 2014;8(16):73-80.
 21. Korukola N, Mediseti VK, Sravanam S, Sanga KR. Preformulation and formulation studies of the poly herbal syrup of hydroalcoholic extracts of *Zingiber officinale* and *Piper nigrum*. *Int J Pharm Sci Rev Res.* 2014; 24:251-6.
 22. Khan RA, Aslam M, Ahmed S. Evaluation of Toxicological Profile of a

- Polyherbal Formulation. Pharmacol Pharm. 2016;7(1):56-63.
23. Sellappan M, Ponnambalam H. Polyherbal Formulation Development for Anti-asthmatic activity. Int J Res Pharmacol Pharmacother. 2021;3(2):90-6.
24. Khanum K, Zahoor A, Ali R, Usmanghani K, Rehman H, Alam MO, *et al*. Clinical studies of linkus syrup for efficacy and safety for the treatment of cough, respiratory infection in children. RADS J Pharm Pharm Sci. 2017;5(2):36-43.
25. Imtiyaz A, Shamsi S, Shadab M. Physicochemical evaluation of Sharbat Aloo Baloo. Int J Res Ayurveda Pharm. 2021;12(1):68-74.
26. Mali RG, Dhake AS. A review on herbal antiasthmatics. Orient Pharm Exp Med. 2011;11(2):77-90.
27. Pattanayak P, Behera P, Das D, Panda SK. Ocimum sanctum Linn. A reservoir plant for therapeutic applications: An overview. Pharmacogn Rev. 2010;4(7):95-105.
28. Fazel S, Hamidreza M, Rouhollah G, Verdian-rizi M. Spectrophotometric determination of total alkaloids in some Iranian medicinal plants. Thai J Pharm Sci. 2008; 32:17-20.
29. Taur DJ, Patil RY. Some medicinal plants with antiasthmatic potential: a current status. Asian Pac J Trop Biomed. 2011;1(5):413-8.
30. Iyer SS, Cheng G. Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease. Crit Rev Immunol. 2012; 32(1):23-63.
31. Bielory L, Lupoli K. Herbal interventions in asthma and allergy. J Asthma. 1999;36(1):1-65.
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