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A STUDY OF PATHOGENESIS OF ALLERGIC RHINITIS WITH HYPERSENSITIVITY REACTION

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ABSTRACT
Allergic rhinitis (AR) is a prevalent respiratory disorder that impacts a substantial proportion of the worldwide populace. In light of the presence of pharmacological therapies, there is an increasing need to investigate alternative therapeutic strategies that provide enhanced effectiveness and reduced incidence of adverse effects. Poly-herbal nasal formulations have been identified as a promising approach, since they provide the combined benefits of natural plant-derived chemicals and targeted administration to the nasal mucosa. Current pharmaceutical therapies for allergic rhinitis (AR), such as antihistamines and corticosteroids, often provide symptomatic alleviation but might be accompanied by adverse effects or have limited long-term effectiveness. Hence, it is essential to investigate novel therapy alternatives that might provide enhanced symptom management and target the fundamental processes of allergic rhinitis (AR). A significant number of persons diagnosed with AR may exhibit a preference for alternative or herbal remedies, mostly driven by apprehensions over the possible adverse consequences linked to traditional pharmaceutical interventions. Poly-herbal formulations sourced from plants are often seen as safer alternatives because to their characteristic composition of many bioactive chemicals, which may exhibit synergistic properties, hence mitigating the likelihood of unpleasant responses.

KEYWORDS: Hypersensitivity Reaction, Allergic rhinitis (AR), alternative, therapeutic strategies, herbal remedies, bioactive chemicals

INTRODUCTION

Allergic rhinitis (AR) refers to the inflammatory condition affecting the nasal and conjunctival mucous membranes. The manifestation of this condition occurs as a consequence of the inhalation of allergenic substances, leading to an immune response mediated by immunoglobulin E (IgE) (Dipiro et al., 2002; Shargel et al., 2001). Augmented reality (AR) is distinguished by four primary symptoms. According to Min (2010), the symptoms seen include watery rhinorrhea, nasal blockage, nasal itching, and sneezing. In addition to the cardinal symptoms seen during allergic rhinitis (AR), there are other often observed symptoms such as postnasal drip, pruritic eyes, ears, nose, and palate (Kemp, 2009). Allergic rhinitis (AR) is a prevalent condition that has a worldwide impact, affecting around 20% of the population (Weinberg, 1993). The global prevalence of allergic rhinitis (AR) is widespread, with an estimated incidence ranging from 10% to 25%. Additionally, the prevalence of AR is increasing, impacting from 5% to 50% of the global population (Braido et al., 2008; Lee et al., 2008; Wilson et al., 2002). While augmented reality (AR) does not pose a direct danger to human life, it does have a notable negative effect on overall quality of life (Nelson, 2007; Wilson et al., 2002).

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Allergic rhinitis (AR), sometimes referred to as hay fever, is a widely prevalent chronic respiratory ailment characterized by the inflammation of the nasal passages after contact to allergens. This condition has a substantial impact on a considerable proportion of the worldwide populace, resulting in the manifestation of troublesome symptoms like nasal congestion, sneezing, itching, and excessive production of mucus. Despite the existence of several pharmaceutical therapies for the management of allergic rhinitis (AR), the effectiveness and possible adverse effects associated with these interventions have motivated researchers to investigate alternative therapeutic strategies.

Poly-herbal preparations, which are produced from many botanical origins, have garnered recognition for their potential therapeutic efficacy in addressing a broad spectrum of ailments, including respiratory disorders. These formulations often include the amalgamation of many herbal extracts, whereby each extract contributes distinct bioactive chemicals, with the aim of attaining synergistic medicinal benefits. Poly-herbal formulations are often seen as safer alternatives to traditional pharmaceutical medications due to their natural nature.

In recent times, there has been a significant focus on investigating the possibility of poly-herbal nasal formulations for the relief of symptoms associated with allergic rhinitis (AR). The administration of drugs via the nasal route has several benefits, including direct accessibility to the inflamed nasal mucosa, expedited beginning of therapeutic effects, and reduced occurrence of systemic adverse reactions. In addition, it should be noted that the nasal cavity serves as a principal location for the identification of allergens and the activation of immune responses in allergic rhinitis (AR), so making it a very suitable focus for therapeutic intervention.

Animal models are of great importance in preclinical research for evaluating the efficacy of poly-herbal nasal formulations for the treatment of allergic rhinitis. A frequently used experimental approach is inducing sensitization in mice to ovalbumin (OVA), a prevalent allergen present in eggs, and then subjecting them to challenge exposures. The present model replicates the immunological and inflammatory reactions seen in human allergic rhinitis (AR), including the generation of targeted IgE antibodies, infiltration of eosinophils, and release of pro-inflammatory cytokines. The primary objective of this research is to examine the potential therapeutic advantages of poly-herbal nasal formulations in mitigating symptoms associated with allergic rhinitis (AR) via the use of a mouse model induced by ovalbumin (OVA) challenge. The proposed experimental methodology entails inducing sensitization in mice to ovalbumin (OVA), followed by the administration of poly-herbal nasal formulations for a predetermined period of time. The assessment of therapy effectiveness will include the evaluation of nasal symptoms, the measurement of inflammatory indicators, the quantification of immune cell infiltration, and the examination of histological alterations in the nasal mucosa. The findings of this research demonstrate considerable potential for the advancement of innovative treatment strategies for allergic

rhinitis (AR). In the event that the poly-herbal nasal formulations exhibit positive outcomes, they may provide a viable alternative or supplementary method to traditional treatment modalities. In addition, gaining comprehension of the fundamental processes of action and defining the precise bioactive chemicals accountable for therapeutic benefits can provide significant insights into viable targets for further drug development endeavors.

ALLERGIC RHINITIS

Allergic rhinitis (AR) is distinguished by the presence of inflammation in the nasal mucosal membranes, resulting in symptoms such as sneezing, nasal congestion, and a runny or stuffy nose. The literature review identified that many mediators, such as pollen, mold, dust, mites, and animal allergens, may induce inflammation of the nasal mucosal membranes upon contact with the nasal and ocular linings. Given the involvement of these mediators in the etiology of allergic rhinitis (AR), it is hypothesized that more investigation into these targets might be conducted to discover other formulations for the treatment of disease symptoms. Through a comprehensive examination of existing literature, it was determined that there is currently a lack of established poly-herbal nasal formulations using chosen plants for the treatment of allergic rhinitis (AR). Therefore, the current work aims to formulate poly-herbal nasal preparations and evaluate their tolerability in mice with ova challenges as a potential therapy for allergic rhinitis (AR).

Allergy rhinitis (AR) is an allergy condition characterized by the inflammation of the airway epithelium due to the activation of IgE-mediated inflammatory cells. This response occurs as a result of exposure to allergens, whether they are encountered seasonally or year-round. Allergic rhinitis (AR) is primarily characterized by the presence of an increased flow of eosinophils in the affected region, accompanied by various medical signs and symptoms such as nasal sneezing, rubbing, rhinorrhea, tears, nasal congestion, and blockage. Allergic rhinitis (AR) is also known to elicit a general sense of irritation and is associated with several comorbid conditions such as asthma, nasal polyps, rhinosinusitis, otitis media with effusion, and sleep disorders. The nasal tissue layer exhibits an inflammatory response that involves mast cell-mediated allergic reactions and a deficient immune response. This immune response is characterized by the recruitment of secondary effector cells, including eosinophils, basophils, and T cells expressing the T-helper type 2 (Th2) cytokines, such as interleukin-4 (IL-4) which facilitates immunoglobulin E synthesis, and interleukin-5 (IL-5) which promotes allergic inflammation by stimulating the proliferation of leukocytes. In the context of allergic rhinitis (AR), mast cells are responsible for releasing inflammatory mediators including as IL-4, IL-6, IL-8, IL-12, and TNF-α. These mediators are released when mast cells are triggered by pathways involving IgE. Basophils and eosinophils play a crucial role in the process of allergic inflammation, namely functioning in the terminal phase of the allergic reaction. T cells play a crucial role in regulating and coordinating the adaptive immune

response in allergic disorders. The T cells known as Th1 cells secrete interleukin-2 (IL-2) and interferon-gamma (IFN-γ) and are involved in delayed-type hypersensitivity reactions. On the other hand, Th2 cells produce interleukin-4 (IL-4) and interleukin-5 (IL-5) and have a role in mediating allergic inflammation that is mediated by immunoglobulin E (IgE).

Pathogenesis of allergic rhinitis

Allergic rhinitis (AR) is caused by the interaction between inhaled allergens and nearby molecules of the IgE antibody. This interaction leads to the formation of allergens-antibody complexes, which are found in higher quantities on the surfaces of mast cells in nasal secretions and inside the nasal epithelium.

The subsequent release of prepared mediators, particularly histamine, induces an elevation in the permeability of the epithelial layer, so facilitating the access of allergens to IgE-sensitized mast cells located in the lamina propria. Sneezing is initiated shortly after the introduction of allergens into the nasal passages, mostly due to the release of histamine, which in turn stimulates afferent nerve terminals.

Subsequent to allergen exposure, there is a subsequent occurrence of nasal exudation and secretion, ultimately leading to nasal obstruction within a time frame of around 15-20 minutes. According to Kumar and Clark (2005), the production of cysteinyl leukotrienes and vasodilator prostaglandins (PGD2, PGE2, and PGI2) from mast cells, eosinophils, and macrophages is particularly effective in inducing nasal blockage.

Although mast cells possess or have the ability to produce several powerful vasomotor and chemotactic factors, the precise function of each of them remains unclear. The involvement of histamine in the pathogenesis of allergic rhinitis (AR) seems to be more significant compared to asthma, as shown by the differential efficacy of anti-histamines in the treatment of both conditions.

The observed augmentation in nasal response as the pollen season advances has previously been attributed to a gradual rise in mast cells populating the mucosa. The processes responsible for the recruitment of mast cells in these particular conditions likely include the secretion of stem cell factor (c-kit) and interleukin-3 by epithelial cells, as well as the release of interleukins-3, 4, and 9 by T-cells (Kumar & Clark, 2005).

The process of sneezing is influenced by both efferent nerve fibers and released mediators, which lead to increased secretion and alterations in mucosal blood flow. The generation of mucus is primarily influenced by parasympathetic stimulation, while the regulation of blood vessels involves both parasympathetic and sympathetic control. The sympathetic fibers have a role in maintaining continuous contractions of blood vessels, which results in partial constriction of the sinusoids in the nose, hence promoting optimal nasal patency. The dilation of these blood arteries is induced by the activation of the parasympathetic system. The stimulus exhibits cyclical variation, whereby the airflow alternates gradually over an extended period of time, spanning many hours, between the two nostrils. According to Kumar and Clark (2005), the emotional state of an individual might have an impact on the nasal sinusoids, thus influencing nasal patency.

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Upon exposure to allergens, individuals with allergic rhinitis (AR) may have allergic responses that may be categorized into two distinct patterns based on the temporal sequence. The first response is marked by symptoms of sneezing and rhinorrhea. The first response is triggered by the activation of mast cells in response to allergens, specifically in the context of a type I hypersensitivity reaction. Nasal symptoms are induced by mast cells that have been stimulated, which in turn secrete chemical mediators like histamine, prostaglandins, and leukotrienes. In contrast to the first responses, the subsequent reaction mostly involves the chemotaxis of eosinophils, which is attributed to the chemical mediators generated during the early response. In patients with allergic rhinitis, various inflammatory cells, including eosinophils, mast cells, and T cells, undergo migration to the nasal mucosa. These cells then engage in tissue fragmentation and remodeling, ultimately leading to nasal obstruction, which serves as the primary symptom experienced by affected individuals (Min, 2010).

Allergens

An allergen refers to an antigenic material that elicits a hypersensitive response, often known as an allergic reaction (Martini, 2004; Stedman, 2008). Allergic rhinitis (AR) is attributed to the regular and repeated exposure to perennial and seasonal allergens present in both indoor and outdoor settings. The involvement of IgE-mediated immunological processes is of paramount importance as they initiate the release of mediators that are accountable for the manifestation of allergy symptoms (Wang, 2005).

allergy rhinitis (AR) occurs when a patient is exposed to an allergen that triggers an immune response leading to the appearance of allergy symptoms. Common seasonal allergies include several types of pollens, such as grass pollens, as well as mold spores, home dust mites, and the excrement of domestic pets (Di piro et al., 2002). The occurrence and severity of seasonal rhinitis and its associated symptoms varies due to the diverse degrees of pollination in different geographic regions, which result from the pollination activities of various plant species. Perennial rhinitis is often induced by several allergens, including home dust mites, cockroaches, fungi, pollens, and domesticated animals. Occupationally linked perennial rhinitis may be attributed to the presence of industrial dust, vapours, and fumes (Kumar and Clark, 2005).

Cells involved in the Allergic rhinitis response

a) Mast cells

A mast cell is a kind of cell found in connective tissue that has granules which have a coarse basophilic and metachromatic staining pattern. Following exposure to allergens, mast cells undergo degranulation, leading to the release of recently synthesized mediators, including histamine, heparin, serotonin, proteases, cysteinyl leukotrienes, prostaglandins, and cytokines. Consequently, this process inhibits the inflammatory response. Mast cells are known to have a significant impact on the first allergic rhinitis (AR) response, as shown by studies conducted by Borish (2003) and Stedman (2008).

b) Basophiles

A basophile is a type of phagocytic leukocyte found in the bloodstream. It is

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distinguished by the presence of basophilic granules that contain heparin and histamine. Unlike other leukocytes, the basophile does not possess a segmented nucleus. Morphologically and physiologically, it shares similarities with mast cells. However, it is important to note that these two cell types originate from distinct stem cells and are produced in the bone marrow (Stedmann, 2008).

c) Eosiniophils

Eosinophils are also referred to as eosinophilic leukocytes. The aforementioned white blood cells, known as microphages, are mobile phagocytes that possess unique anti-parasitic capabilities (Stedemnn, 2008). Eosinophils have a crucial role in the immunological response, with particular importance shown during allergic responses (Martini, 2004).

d) Neutrophils

Neutrophils are fully developed leukocytes of the granulocyte lineage that originate from the bone marrow and are subsequently discharged into the bloodstream. White blood cells, also known as leukocytes, are present in large quantities, often accounting for 54-65% of the total leukocyte count. They are among the first mobile phagocyte cells to migrate to a site of damage or infection (Martini, 2004).

e) Lymphocyetes

Lymphocytes are a type of leukocyte that are generated in the lymphatic tissue throughout the entire body. They are derived from precursor cells originating in the bone marrow. In normal adults, lymphocytes account for approximately 22-2% of the total leukocyte population. These lymphocytes can be classified into distinct groups, namely T cells and circulating B cells, based on their surface molecules and functional characteristics. Natural killer (NK) cells, characterized as big granular lymphocytes, constitute a minority fraction within the overall lymphocyte population (Stedman, 2008).

Hypersensitivity reaction (allergic responses)

An allergy can be characterized as a state of heightened sensitivity that arises from exposure to a specific antigen, leading to an amplified reaction upon subsequent encounters with said antigen. This heightened response may occasionally lead to adverse consequences. Hypersensitivity, on the other hand, refers to a condition in which the body exhibits an exaggerated reaction to the presence of a foreign agent. There are three distinct forms of hypersensitivity responses associated with the various pathways of immunologic effectors involved in the inflammatory response. These reactions are classified as delayed hypersensitivity, immune complex hypersensitivity, and rapid hypersensitivity. The occurrence of hypersensitivity responses is contingent upon the presence of genetic predisposition to allergic rhinitis (AR) in conjunction with subsequent exposure to a particular allergen. Sensitization occurs upon first exposure to allergens. Subsequently, upon exposure to allergens, immunological responses are elicited, similar to those seen in allergic rhinitis (Vander et al., 2001).

a) Early response

This refers to another instance of an antibody-mediated response. Immunoglobulin E (IgE) exhibits binding affinity towards the high-affinity IgE

receptor (FcRI) located on mast cells present in many tissues. The process of labrocyte degranulation is initiated by the interaction between specific IgE and FcRI receptors, as shown in studies conducted by Naclerio (1991) and Turne et al. (1999). The process of degranulation involves the release of preformed mediators such as histamine, tryptase, chymase, kininogenase (which produces bradykinin), and heparin. In contrast, mast cells release distinct inflammatory mediators, including prostaglandin D2 and sulfidopeptidyl leukotrienes C4, D4, and E4. The latter, known as bradykinin, induces vasodilation and vascular permeability, resulting in clinically significant tissue edema and watery rhinorrhea. Furthermore, diverse arrays of cytokines, such as tumor necrosis factor (TNF), are transcribed. The process of IgE binding to FceRI receptors on basophils is afterwards accompanied by cross-linking via an external stimulus, resulting in the degranulation of white blood cells. The release of preformed mediators is seen, alongside the synthesis of lipid mediators and cytokines, by mucosal glands. These glands emit mucoglycosides conjugates and antimicrobial chemicals, which in turn cause the dilation of blood vessels. This vascular dilation leads to sinusoidal filling and subsequently results in nasal congestion. The mediators also have the ability to activate sensory nerves, resulting in the manifestation of nasal sensations and congestion. Systemic reflexes, such as the sneeze reflex, may be evoked.

b) Late phase response

The mediators released from mast cells exert their effects on epithelial tissue cells located in post capillary venules, leading to the upregulation of vascular cell adhesion molecule and E-selectin expression during the first phase of the reaction. These mechanisms facilitate the adherence of circulating leukocytes to the cells of the epithelial tissue. Chemotactic factors such as interleukin-5 (IL-5) facilitate the migration of eosinophils, neutrophils, basophils, T lymphocytes, and macrophages into the tissue layer. The activation of these cells occurs in response to inflammatory mediators, which then trigger other deleterious responses associated with the early-phase response. Eosinophils possess a variety of preexisting protoplasmic granule mediators, such as the primary basic macromolecule. Several mediators are generated, such as leukotriene C4, platelet-activating factor, tumor necrosis factor (TNF), transforming growth factor B, and interleukin-5 (Banwe et al., 2003). The injurious effects on animal tissue are attributed to the actions of many mediators released by white blood cells, including major basic protein, white blood cell cationic macromolecule, and leukotrienes. T helper (Th) 2 lymphocytes release interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), and several other cytokines that stimulate the synthesis of immunoglobulin, attract eosinophils, enhance the survival of white blood cells, and facilitate macrophage activation. Interleukin-5 (IL-5) is responsible for the activation of CD34+ precursor cells located in the bone marrow, leading to their differentiation into eosinophils. Additionally, IL-5 plays a crucial role in the process of eosinophil mobilization from the bone marrow. Eosinophils, which were previously unbound inside the bone

marrow, undergo circulation in the bloodstream and then move to specific tissue locations where they recognize and interact with adhesion counter receptors. It is well acknowledged that eosinophils are thought to possess both common and unique adhesion routes in relation to their function. Neutrophils, interleukin-1 (IL-1), and tumor necrosis factor (TNF), which are released upon exposure to a stimulus, are believed to play a critical role in initiating the adhesion of endothelial cells. This adhesion is necessary for the recruitment of eosinophils in ongoing inflammatory processes (Path et al., 2005). Eotaxin, which has a lineage-specific effect on eosinophils, seems to play a crucial role in the initial recruitment of eosinophils upon exposure to an antigen. The recruitment of white blood cells at subsequent time periods is mediated by eotaxin, indicating the significant involvement of several chemokines. When patients are repeatedly exposed to an allergen, the quantity of substance required to induce an allergic reaction reduces, a phenomenon known as the priming effect. It is postulated that the final outcome is expected to occur due to the activities of inflammatory cells during the late-phase response. Specifically, immunoglobulin E (IgE) will attach to the low-affinity immune serum globulin receptor CD23, also known as Fc RII, located on B cells. The association between immunological serum globulin and the CD23 receptor plays a crucial role in enhancing cellular and humoral immune responses during allergic inflammation.

CONCLUSION

Traditional Indian medicine favors the use of plant formulations and mixed extracts of plants above any one medicament. As such, research into the traditional benefits of MO (shaijan) and ER (vidang) has been examined. Purpose: To create effective polyherbal formulations for the management of allergic rhinitis. Evidence gathered over the last several decades has sparked a renewed interest in the search for natural compounds (i.e. antioxidants) found in foods or medicinal plants that may be used in lieu of synthetic antioxidants, the use of which is being limited owing to their harmful side effects. Due to their beneficial effects on human health, natural antioxidants are gaining popularity. By lowering oxidative stress and blocking macromolecular oxidation, natural antioxidants lower the risk of cardiovascular and degenerative illnesses. Herbal medicine theories include many plant medicines with different pharmacological effects, creating a synergistic, potentiative agent within the formulation itself. To achieve optimal treatment effectiveness with minimal adverse effects, pharmacological activities are performed in a coordinated fashion. The aforesaid assumption led to the selection of MO and ER as possible plants.

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