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Agent-Based Modeling of Herbal Compound Treatment for Allergic Inflammation in Asthma

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Abstract

Asthma is a complex disease characterized by chronic airway inflammation and immune system dysfunction. In recent decades, researchers have conducted extensive studies on plants with anti-allergic and anti-asthmatic effects. In this study, an agent-based model is presented to simulate the interactions between immune cells and lung tissue during asthmatic inflammation. For the first time, herbal drug treatments for asthma have been incorporated into the model based on experimental data and previous modeling studies. The model parameters were determined using experimental data from laboratory studies on asthma treatment with herbal compounds. The model's outputs align well with experimental data and effectively replicate them. Using this model, we have investigated several phenomena related to asthma treatment: (1) Determining the optimal day to initiate treatment, (2) Evaluating the contribution of each inflammatory pathway to lung health, (3) Assessing the effect of anti-inflammatory pathways on lung tissue health, (4) Performing global sensitivity analysis and identifying key parameters in the model, (5) Examining how removing drug effects on pro-inflammatory and anti-inflammatory pathways influences the model's output. The findings of this study validate existing experimental research and provide valuable insights into understanding asthma pathogenesis and potential therapeutic approaches using herbal medicines.

Keywords

Inflammation, Asthma, Mathematical modeling, Differential equations, Agent-based model, Herbal Medicine

1. Introduction

Asthma affects roughly 300 million people globally, featuring airway inflammation, bronchospasm, and mucus production [1], and causes over 400,000 deaths annually [2]. While inhaled corticosteroids and bronchodilators suppress symptoms, they often fail to control underlying inflammation in severe cases [3]. Long-term corticosteroid use also has adverse effects, driving the need for safer, corticosteroid-sparing strategies.

Herbal compounds have been studied for their anti-asthmatic properties, offering multi-target effects, fewer side effects, and accessibility. Yet, understanding their immune interactions during inflammation remains challenging.

Mathematical modeling, particularly agent-based modeling (ABM), helps unravel asthma's biological complexity by simulating cellular and biochemical interactions in the respiratory system [4]. Unlike ordinary differential equations, ABMs capture discrete, spatially heterogeneous interactions and emergent behaviors from nonlinear cell-ECM dynamics. These models aid in exploring treatments, predicting disease progression, and evaluating efficacy.

Several ABMs have been developed for respiratory inflammation. Brown et al. [5] modeled immune responses to inhaled particles, incorporating macrophages, fibroblasts, collagen, and TNF-α. Pothen et al. [6] included T cells, mast cells, and cytokines, showing that disabling helper T cells or reducing pre-inflammatory cell lifespan could improve disease severity. Other models have examined epithelial-mesenchymal transition, fibrosis, and ECM roles.

However, most existing models fail to capture asthma's full complexity, and none incorporate herbal compound treatments. Our novel ABM integrates biotic (mast cells, Tregs) and abiotic (particulate matter, cytokines, ECM) elements, offering a comprehensive framework for studying asthma pathology and herbal interventions. This study fine-tunes parameters with empirical data to match observed trends, explores cellular interactions, and provides a quantitative basis to optimize herbal anti-inflammatory therapies.

2. Methodology

Particles such as plant pollen, pet dander, cigarette smoke, and air pollutants enter the lungs through respiration, triggering a two-stage inflammatory response: pro-inflammatory and anti-inflammatory. During the pro-inflammatory phase, damaged cells and pathogens are eliminated [7], with immune cells including neutrophils, eosinophils, macrophages, T lymphocytes, mast cells, and dendritic cells recruited to damaged areas.

Mast cells and antigen-presenting cells (M-APCs) initiate the immune response. Pro-inflammatory cells—eosinophils, neutrophils, Th2 cells, and M1 macrophages—amplify inflammation through cytokine release. Regulatory T cells (Tregs) regulate asthma inflammation by maintaining immune tolerance and suppressing excessive responses [8]. Goblet cells contribute to pathogenesis through mucus hypersecretion and airway obstruction, while fibroblasts differentiate into myofibroblasts and deposit extracellular matrix (ECM), driving airway remodeling.

Our model groups cells with similar functions into categories. Mast cells and APCs are combined as M-APC cells. Eosinophils, neutrophils, Th2 cells, and M1 macrophages form pro-inflammatory cells (PIC). Pro-inflammatory and anti-inflammatory cytokines are grouped separately. Tregs, goblet cells, fibroblasts, particles, mucus, and ECM are also incorporated (Figure 1).

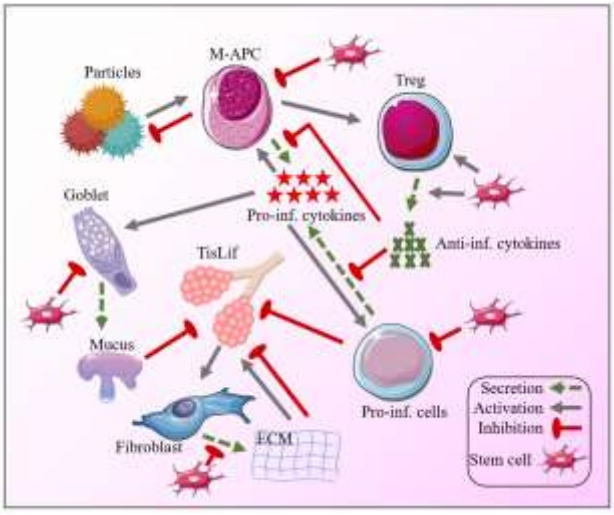

Figure 1. Interaction of different cells in the model

The framework builds on models [5] and [6], simulated in an 80×80 (6,400-patch) 2D environment with eight neighbors per patch. The space divides into three sub-regions: a perimeter blood vessel, adjacent alveolar tissue, and central air. Model variables include agents (migrating cells secreting substances) and concentrations (spatial distributions of secreted substances). Simulation steps involve defining parameters, updating variables in loops using mathematical equations, with 30 time steps equating to one physiological day [6].

Blood vessels serve as cell reservoirs, with permeability dependent on inflammatory cytokine levels. Specific cell numbers are positioned in vessels and tissue before particle entry. Alveolar tissue health (TisLif) is a composite metric (0-100) reflecting integrity, calculated from ECM density, mucus, and pro-inflammatory cytokines.

Experimental data from two studies used ovalbumin-sensitized Wistar rats (days 1, 7) with aerosol challenges from day 14–42 to model allergic asthma. From days 42–50, asthmatic rats received either quercetin or myrtenol treatment. Four groups were studied: Control, Asthma (untreated), Asthma+Q (quercetin), and Asthma+NM (myrtenol). Lung inflammation markers and tissue health were measured on day 50.

Model parameters were determined through direct adoption of literature-derived values where available, and systematic calibration against experimental data to minimize Mean Absolute Percentage Error (MAPE).

$$\text{MAPE} = \frac{100\%}{n}\sum_{i=1}^{n}\left|\frac{y_{exp}^{i} - y_{model}^{i}}{y_{exp}^{i}}\right| \quad (1)$$

The final parameter set successfully captured the essential dynamics of asthma inflammation and herbal therapy observed experimentally, with an overall MAPE of 13% across all datasets. This approach ensured both biological relevance and quantitative accuracy of model parameters.

3. Results and Discussion

Figure 2 illustrates the comparison between model outputs and experimental data. As shown in Figure 2, the MAPE values for different variables are at most 17%, which is considered an acceptable value (indicating low error). Furthermore, the overall MAPE for all data combined is calculated to be approximately 11%, demonstrating good agreement between the model results and the experimental data.

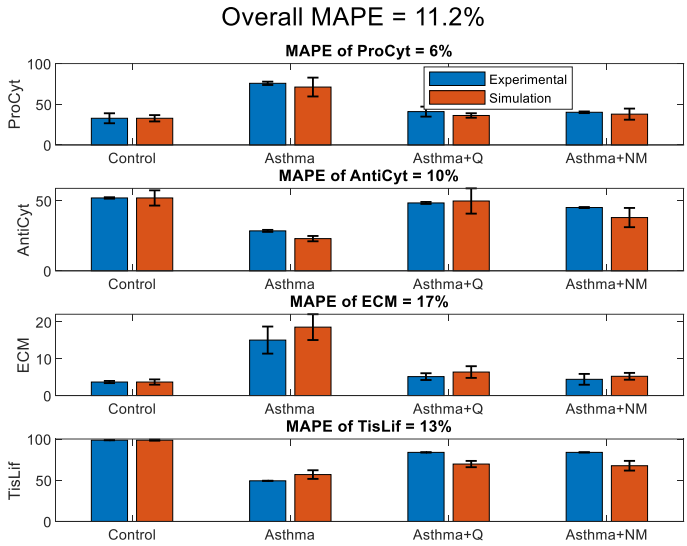

Figure 2. Comparison of experimental data and model outputs in the four study groups. Data represent mean ± standard deviation.

The Control group exhibits baseline levels of pro-inflammatory cytokines (ProCyt), Mucus, and ECM. The Asthma group shows elevated ProCyt, increased Mucus due to goblet cell hyperplasia, and ECM accumulation driven by fibroblast activation, consistent with asthmatic remodeling. The Asthma+Herbal group displays intermediate values, with herbal treatment attenuating pathological changes. Initially, Asthma and Asthma+Herbal groups exhibited higher mucus levels compared to Control, correlated with subsequent decline in TisLif. However, following herbal treatment, the Asthma+Herbal group showed therapeutic response marked by reduced mucus production and increased TisLif levels.

We compared final values of model variables across different treatment initiation timepoints, systematically varying administration from day 20 (prior to particle challenge) to day 30 (after particle introduction). Results suggest optimal treatment initiation is around days 24 and 25, during which treatment results in lowest levels of inflammatory factors, mucus, and ECM, and highest levels of anti-inflammatory cytokines. Herbal treatment should commence shortly after first particle introduction for maximum effectiveness.

Analysis of pathways contributing to decreased tissue health revealed that activated PICs play a more substantial role than other pathways. This aligns with the fact that in early stages of asthma, immune cell activation and pro-inflammatory cytokine production are more prominent than ECM contribution. In later stages, fibroblasts and ECM production likely become more important in airway remodeling.

Global sensitivity analysis assessed how uncertainty in model output can be attributed to uncertainty in parameters. The primary outcome of interest was average TisLif on last day of simulation. Analysis revealed parameters related to cytokine clearance rate and particle-induced pro-inflammatory potency have significant impact on tissue health. Rapid elimination of inflammatory cytokines mitigates adverse effects on tissue health. Additionally, mucus secretion rate emerged as a critical parameter. Mucus accumulation can obstruct airways, leading to airflow limitation. In asthmatic patients, mucus plugs are linked to increased dyspnea, poor asthma control, and higher exacerbation frequency.

We simulated the Asthma+Herbal group in six scenarios, each time removing one drug mechanism while maintaining others. Results demonstrate that drug effects on PICs and Tregs were particularly influential on AntiCyt, ECM, and ultimately TisLif. No parameter was without influence, indicating all mechanisms contribute to therapeutic efficacy.

4. Conclusions

This study developed an agent-based mathematical model to describe dynamics of asthmatic inflammation, incorporating critical variables including cytokines, inflammatory and anti-inflammatory cells, ECM, goblet cells, fibroblasts, and inhaled particles. For the first time, the model incorporates herbal compound treatment, highlighting therapeutic potential. By estimating model parameters using experimental data, we demonstrated the model accurately captures complex interactions within the asthmatic environment.

Key findings from model simulations include:

1. Optimal timing: Herbal compound efficacy is significantly influenced by inflammatory state at time of administration. Treatment should commence shortly after allergen exposure (days 24-25) for maximum effectiveness. This nuanced understanding underscores importance of timing in therapeutic interventions.
2. Critical pathways: Activated inflammatory cells play more substantial role in determining lung tissue health than other pathways, emphasizing need for therapies targeting these cells. Sensitivity analysis identified cytokine clearance rates and particle-induced pro-inflammatory potency as pivotal for lung recovery.

3. Mechanistic insights: Drug effects on PICs and Tregs are particularly influential, but all mechanisms contribute to therapeutic efficacy.
4. Clinical implications: Model predictions align with existing research on cytokine-targeted asthma therapies and underscore need for precision in treatment strategies. Identifying critical parameters allows for targeted therapeutic approaches.

The model's clinical translation potential is substantial given growing interest in herbal and alternative therapies for lung diseases. Preclinical trials demonstrate herbal compound efficacy in reducing airway inflammation in murine asthma models. Hypothetically, the model could guide clinical strategies by optimizing treatment timing to minimize ECM or enhance TisLif. While computational constraints prevented extensive optimization using established algorithms, results demonstrate the model's potential as a tool for designing herbal-based therapies.

The model is based on experimental data from mice, which may not fully capture complexity of human asthma. While we included several key factors, other potential variables such as genetic factors and environmental influences could further refine the model. Future work should validate model predictions in clinical settings and explore integration of additional factors to create more comprehensive representation of asthma pathology. Additionally, investigating combination therapies (herbal compounds with conventional treatments) and personalized medicine approaches would be valuable extensions.

In conclusion, this mathematical model serves as a valuable tool for understanding asthmatic inflammation dynamics and guiding enhancement of herbal-based therapies. By identifying optimal treatment timing and highlighting critical parameters influencing lung health, this model has potential to inform clinical practices and contribute to personalized medicine approaches in asthma management.

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