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Nanoparticle-Based Drug Delivery In Asthma Therapy

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Abstract

According to the World Health Organization, the combined economical effect of AIDS and tuberculosis exceeds that of asthma (WHO). Due to the high rates of disability and mortality, it has developed into a significant public health problem. Asthma is a complicated disorder influenced by both inherited and environmental factors. Nanotechnology advancements have reintroduced hope for the early detection, treatment, and prevention of asthma, owing to the disease's intricate pathogenesis. Nanotechnology offers the ability to deliver pharmaceuticals or genes exactly where they are required, while also minimising adverse effects and improving drug absorption. In recent years, a major research emphasis has been on the development of innovative nanodrugs and the modification of current treatments. Clinical experiments have shown that nanocarriers are both safe and effective. However, various hurdles must be cleared before nanotherapy may be employed in clinical practise. We'll look at some of the most current research discoveries in the subject of nanotechnology and asthma therapy in this article.

Keywords: Nanotechnology; asthma; nano-modifications of drug; new nano-drugs; nanotherapy

Introduction

There are a variety of chronic and non-communicable diseases that affect children and adults, but asthma is one of the most common. Asthma affects more than 300 million people worldwide, including 30 million in China. The frequency of asthma has been progressively increasing worldwide during the past many years. Asthma is a complicated disorder influenced by both inherited and environmental factors. It may be classified into a variety of unique subgroups based on clinical criteria (e.g., onset age and severity of sickness), triggers (exercise and viral infection), and inflammatory types (e.g., eosinophilic, neutrophilic, paucigranulocytic, and mixed granulocytic)(1, 2). Due to the complexity of the biology of asthma, no single medication has been identified; nonetheless, long-term systematic therapies may effectively decrease symptoms, minimise episodes, and improve the prognosis for asthmatics. The majority of asthmatics benefit from inhaled corticosteroids. Steroids, when used with bronchodilators such as LABA or SABA, are considered the first-line therapy for asthma. Even when the

maximum corticosteroid dose is used, some asthmatic patients continue to have poor control. These

patients account for more than 60% of the medical costs related with asthma. In addition to inhaled glucocorticoids, patients with severe refractory asthma have been treated with human monoclonal antibodies and cytokine/chemokine antagonists(3, 4). These treatments, however, are only partly helpful due to the great diversity of asthma symptoms (Figure 1).

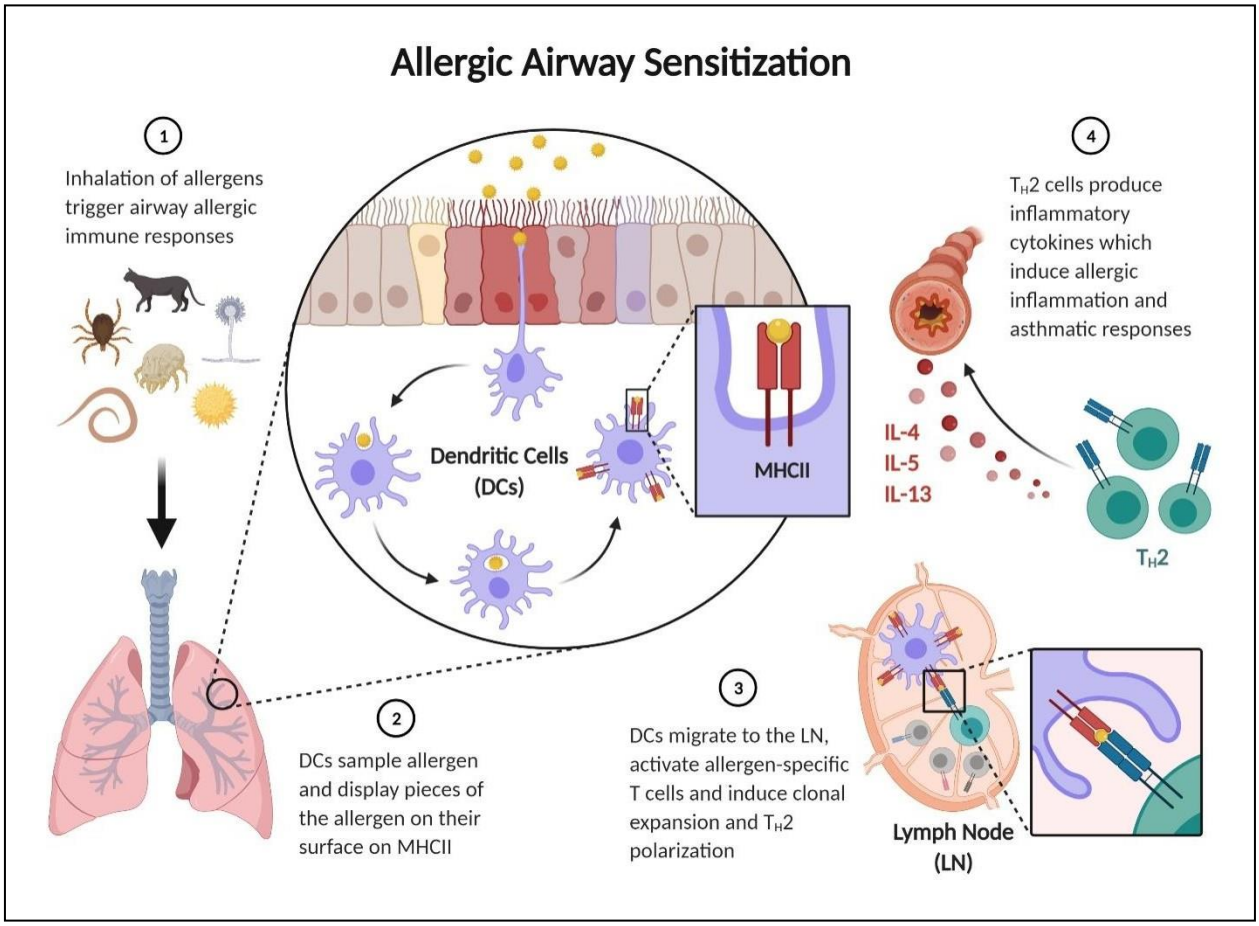

Figure 1: Allergic airway sensitization

Nanotechnology

Nanotechnology research is multidisciplinary in nature and focuses on the manipulation and control of atoms and molecules with diameters ranging from 0.1 to 100 nm, as well as the development of novel materials and designs. Nanotechnology's importance in early disease diagnosis, treatment, and prevention, as well as in bioengineering research, has accelerated advancements in biomedical research. To far, researchers in the biomedical sector have worked with tens of thousands of various nanomaterials. Over the past decade, over 25,000 papers have been published addressing the use of nanoparticles as a method of medicine delivery. Doxil, a nanotechnology platform that was authorised in 1995, has found commercial success(5, 6). Since then, the FDA has approved a number of nanoparticle-based medications, and others are now undergoing clinical testing. Nanomedicine is mostly concerned with cancer and infectious diseases. For instance, injectable anticancer agents such as doxorubicin liposomes and paclitaxel linked to albumin have been developed. Additional anticancer

drugs are now undergoing phase II and III clinical trials. However, the creation of asthma treatment nanoparticles has gotten little attention. We'll examine some of the most recent breakthroughs in this field in order to get a better understanding of nanoparticles' potential in the treatment of asthma(7, 8) (Figure 2).

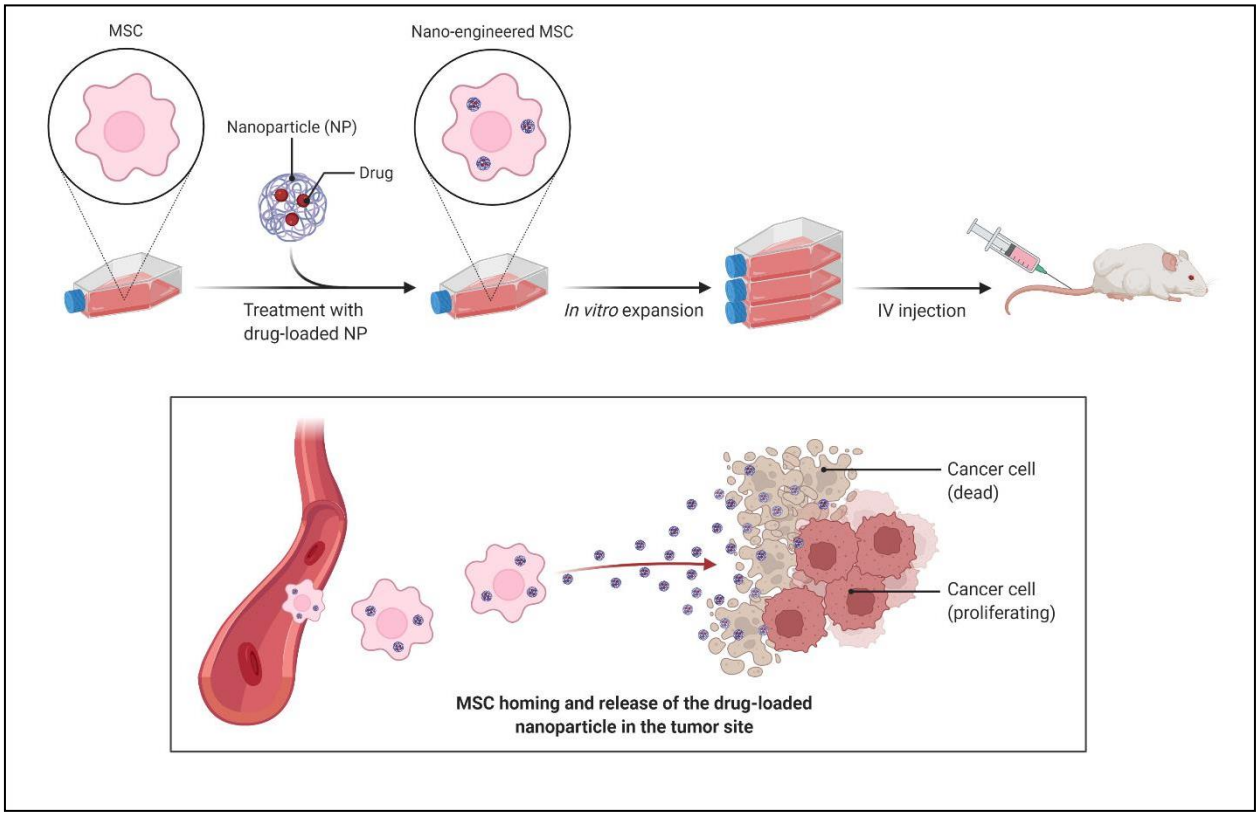

Figure 2: Nano engineered MSCs as active targeting drug delivery

Potentials of nanotechnology in asthma treatment

At the moment, nanodrugs are classified into two categories: (I) traditional molecular pharmaceuticals that have been strengthened by nanotechnology; and (II) unique nanodrugs. One emphasises the utilisation of nanomaterials, while the other represents a step forward from normal therapies. We'll discuss how each of these two forms of nano-drugs may be used to treat asthma in this section(9-11).

Application of nano-modified anti-asthma drugs

For instance, nanoparticle carriers with precise surface patterns and drug-targeting reagents, as well as drug-targeting reagents, are some of the techniques being used to increase the solubility of intractable pharmaceuticals, as well as to mitigate the harmful side effects of conventional medications. Long-term medication is required for asthma prevention and treatment. Historically, asthma medications have been administered intravenously, orally, or by inhalation. Asthma inhalers are the most often given medications, and their effectiveness and bioavailability are inversely proportional. In compared to systemic drug administration, this form of targeted medicine delivery by inhalation eliminates the first-

pass impact and increases bioavailability. Glucocorticoids that regulate asthma are the most effective medicines available. After inhalation, glucocorticoids exert strong anti-inflammatory effects on the skin(12-14). The medication acts directly on the respiratory tract, which results in a lower dosage and less systemic adverse effects. Over a decade ago, a multi-center clinical trial in China discovered that half of the Global Initiative for Asthma's recommended ICS dosage had the same impact on Chinese asthmatics as the recommended inhaled corticosteroid ceiling dose (ICS). While long-term high-dose hormone inhalation therapy will surely result in unpleasant side effects such as adrenal suppression, oral fungal infection, and osteoporosis, hormone inhalation therapy dramatically reduces adverse effects. The PEGylated Poly(amidoamine) (PAMAM) dendrimer, a kind of dendrimer, has been widely explored and used to mitigate the adverse effects of long-term high-dose hormone inhalation and to further boost hormone bioavailability. According to Nasr et al., PAMAM may be used to transport beclomethasone dipropionate (BDP) and other insoluble medications(15-17). Along with improving the solubility and lung accumulation capacity of the medication, this may also result in a reduction in the dosage and frequency of administration, as well as the drug's dangerous and bad effects. Among the nanocarriers that outperform micelles in terms of loading capacity and durability is the well-defined, non-toxic telomere dendrimer (for more than 6 months). Through this nanocarrier, hydrophobic medicines (such as dexamethasone) may be transported directly into the lungs, reducing allergic pulmonary inflammation, inflammatory cytokines, and eosinophils. As a consequence, it is more effective in reducing airway hyperresponsiveness than dexamethasone. At the time of publishing, the most frequently used drugs for symptom relief were anticholinergics, 2-receptor agonists, and short-acting theophylline. Bronchospasm may be relieved within a few minutes after taking these drugs, and the effects may last for many hours(18, 19). They may be used to treat acute symptoms and to prevent exercise-induced asthma in patients with moderate to severe asthma. Excessive long-term use of a single drug should be avoided, as should the use of these medicines unless when absolutely essential. Muscular tremor, hypokalemia, and arrhythmia are all possible adverse effects. There was an increased risk of death from asthma among long-term users of a single LABA. Matsuo et al. discovered that nanocarrier-encapsulated steroids were more effective than free steroids in treating airway inflammation. Another benefit of utilising a nanocarrier is the capacity to interact more efficiently with salbutamol's pleural membranes. To give long-lasting relief from bronchospasm, the effective medicine concentration may be maintained for a prolonged period of time in the target location(20, 21). According to Chen et alresults .'s from the prior two trials, liposomes were demonstrated to prolong the retention of salbutamol sulphate in the lungs and maintain an effective drug concentration for over 10 hours. As a result, they achieved much more efficacy than the complimentary medical treatment. Comparing nanoparticles loaded with salbutamol sulphate to their micronized counterparts revealed that the nanoparticles were less affected in the human oropharynx and deposited more peripherally, indicating that the nanoparticles were smaller, had greater topical bioavailability, and could last for a longer period of time. Long-term, regular asthma treatment may be effective in managing asthma symptoms, avoiding asthma attacks, and preserving normal lung function, despite the fact that no specific medicine for asthma has been produced due to the disease's complex biology. Additionally, bronchodilators have been phased out in favour of medications that target inflammation and decrease airway responsiveness. Additionally, researchers are investigating gene therapy and molecularly targeted treatment(22-24).

Application of brand-new nano-drugs

They are very effective and safe therapeutic and diagnostic agents based on unique nanoparticle designs or nanocharacteristic characteristics. Due to the close association between asthma episodes and abnormal gene expression, novel nanotherapies for asthma are being researched. One intriguing new approach to asthma therapy is the combination of nano-gene carriers and genes. DNA and RNA, for example, may be encased in nanoparticles, while specialised target molecules such as monoclonal antibodies can be linked to the nanoparticle surface to assist gene transfer. Nanoparticles may enter cells through cellular absorption by adhering to specific receptors on the cell surface, enabling safe and effective targeted medicine and gene therapy. As a consequence, nanocarrier selection and fabrication are hot topics in asthma gene therapy(25, 26). Asthma patients are increasingly turning to cutting-edge nano-gene therapy as a therapeutic option. The delivery of DNA or RNA molecules into the appropriate cells has long been a challenge in gene therapy. Due to the rapid degradation of free DNA and RNA molecules by the body's defence mechanism against foreign genetic material, they are unable to exert the therapeutic effects required. There has been research on lipid nanoparticles for DNA and RNA encapsulation. When the sizes and chemical compositions of these nanoparticles are adjusted, they may be safely transported into lung tissue. Despite the benefits of the nanocarrier-based gene delivery technology, another significant obstacle is the difficulty of generating sustained, high-level gene expression in vivo. Numerous nonviral liposome and macromolecule polymer-based vectors for nucleic acid delivery to the lungs have been developed. Polyethyleneimine is a major polymeric gene carrier (PEI)(27-29). Additionally, nucleic acid may be transported to lung tissue using nanoparticles such as chitosan, dendrimers, and biodegradable poly(lactic-co-glycolic) acid (PLGA). Using nanoliposomes, nasopharyngeal cancer cells may be effectively transfected with the p53 gene, therefore inhibiting tumour cell growth and inducing apoptosis. However, the toxicity of nanoparticles has prompted investigation of microbubble nanocarriers. The pulmonary surfactants are composed of surfactants and amphiphilic compounds that are nontoxic, biocompatible, and biodegradable. Liposomes delivered by inhalation and liposome-drug-liposomes may also be utilised to treat lung and systemic illnesses, as well as gene therapy. A novel solid-lipid nanoparticle with a size range of 50-1000 nm has been produced. With great biocompatibility, it protects compounds from degradation and improves medicine release control. Kumar et al. discovered that Chitosan-IFN-pDNA nanoparticles (CIN) significantly decreased airway hyperresponsiveness and lung histology in BALB/c mice with allergic asthma induced by ovalbumin(30-32). In another study, researchers discovered that CIN effectively controlled pro-inflammatory factors in the lung OVA-specific CD8+ T lymphocyte population and lowered the activation level of dendritic cells. Its ability to effectively treat allergic asthma may be related to its capacity to modulate the Th1/Th2 immune response. When regulatory T cells detect an increase in IFN- expression, they boost Th1 cytokine levels and decrease Th2 cytokine levels, respectively. Additionally, efforts have been made to enhance the anti-inflammatory characteristics of medicines by delivering them through chitosan and cyclodextrin nanoparticles in the respiratory system. When PEG nanoparticles are delivered to mice, DNA sequencing demonstrates that they can reach the lungs. Additionally, another research reveals that lung nanoparticles are capable of efficiently transferring RNA into lung cells and suppressing gene expression. Due of the high cationic charge density of polyethyleneimine (PEI), it may effectively concentrate negatively charged DNA into nanoscale complexes, protecting it from nuclease

degradation. PEI Because of its high toxicity, PEI is an unacceptable carrier for gene therapy for asthma. The complement system may be activated and apoptotic genes expressed by adding PEG to the PEG/PEI complex. As a consequence, safe and efficient biodegradable carriers are urgently needed. By inhaling thick and biodegradable DNA nanoparticles developed by Mastorakos et alvery., the mucus barrier may be circumvented with great safety. There was no evident toxicity after intravenous administration(33-35). For instance, dust mites have been involved in the creation of a possible vaccine containing cytokine-phosphate-guanine (CpG) nanoparticles that might be used to treat allergy diseases. As a potent adjuvant, it may modulate the immunological response of Th1 cells and reduce asthma caused by Th2 cells. Asthma is a chronic inflammatory disease of the airways that affects a wide variety of cells and cellular components on a broad scale. Numerous molecular targets exist for asthma, including transcription factors that regulate gene expression, costimulatory molecules that promote gene silencing or overexpression of certain targets, which may be given in nanoparticles together with medicines, and tyrosine kinases and their receptors(36-38).

Summary and prospect

The purpose of this article is to discuss the possible benefits of nanocarrier-based drugs and gene therapy for asthma patients. Nanotechnology has risen to prominence as a potentially useful strategy for the treatment and diagnosis of lung ailments. Nanocarriers' safety and effectiveness have been shown in preclinical study using nanocarriers. Numerous obstacles, however, must be overcome before nanotherapy may be used in clinical practise. A thorough understanding of the mechanism of action of nanocarriers and their improved chemical structures is required for the design and execution of more acceptable clinical studies.

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References

1. Agarwal H, Shanmugam V. A review on anti-inflammatory activity of green synthesized zinc oxide nanoparticle: Mechanism-based approach. Bioorganic chemistry. 2020;94:103423.
2. Alsaleh NB, Brown JM. Engineered Nanomaterials and Type I Allergic Hypersensitivity Reactions. Frontiers in immunology. 2020;11:222.
3. Amaral-Machado L, Oliveira WN, Moreira-Oliveira SS, Pereira DT, Alencar É N, Tsapis N, et al. Use of Natural Products in Asthma Treatment. Evidence-based complementary and alternative medicine : eCAM. 2020;2020:1021258.
4. Anderson CF, Grimmett ME, Domalewski CJ, Cui H. Inhalable nanotherapeutics to improve treatment efficacy for common lung diseases. Wiley interdisciplinary reviews Nanomedicine and nanobiotechnology. 2020;12(1):e1586.

5. Ansari SH, Islam F, Sameem M. Influence of nanotechnology on herbal drugs: A Review. Journal of advanced pharmaceutical technology & research. 2012;3(3):142-6.
6. Ashrafizadeh M, Zarrabi A, Hushmandi K, Zarrin V, Moghadam ER, Hashemi F, et al. Toward Regulatory Effects of Curcumin on Transforming Growth Factor-Beta Across Different Diseases: A Review. Frontiers in pharmacology. 2020;11:585413.
7. Azid NA, Ahmad S, Boer JC, Al-Hatamleh MAI, Mohammad N, Mohd Ashari NS, et al. A profile of TNFR2(+) regulatory T cells and CD103(+) dendritic cells in the peripheral blood of patients with asthma. Human immunology. 2020;81(10-11):634-43.
8. Bonner JC. Nanoparticles as a potential cause of pleural and interstitial lung disease. Proceedings of the American Thoracic Society. 2010;7(2):138-41.
9. Boraschi D, Penton-Rol G. Perspectives in immunopharmacology: the future of immunosuppression. Immunology letters. 2014;161(2):211-5.
10. Cattani-Cavalieri I, Valença SDS, Schmidt M. Nanodomains in cardiopulmonary disorders and the impact of air pollution. Biochemical Society transactions. 2020;48(3):799-811.
11. Chan WC, Udugama B, Kadhiresan P, Kim J, Mubareka S, Weiss PS, et al. Patients, Here Comes More Nanotechnology. ACS nano. 2016;10(9):8139-42.
12. Chapman MD, Wuenschmann S, King E, Pomés A. Technological Innovations for High-Throughput Approaches to In Vitro Allergy Diagnosis. Current allergy and asthma reports. 2015;15(7):36.
13. Chellappan DK, Hansbro PM, Dua K, Hsu A, Gupta G, Ng ZY, et al. Vesicular Systems Containing Curcumin and Their Applications in Respiratory Disorders - A Mini Review. Pharm Nanotechnol. 2017;5(4):250-4.
14. Chen Z, Vong CT, Gao C, Chen S, Wu X, Wang S, et al. Bilirubin Nanomedicines for the Treatment of Reactive Oxygen Species (ROS)-Mediated Diseases. Molecular pharmaceutics. 2020;17(7):2260-74.
15. Da Silva AL, Santos RS, Xisto DG, Alonso Sdel V, Morales MM, Rocco PR. Nanoparticle-based therapy for respiratory diseases. Anais da Academia Brasileira de Ciencias. 2013;85(1):137-46.
16. da Silva AL, Silva LA, Cruz FF, Rocco PRM, Morales MM. Application of novel nanotechnologies in asthma. Annals of translational medicine. 2020;8(5):159.
17. Daum N, Tscheka C, Neumeyer A, Schneider M. Novel approaches for drug delivery systems in nanomedicine: effects of particle design and shape. Wiley interdisciplinary reviews Nanomedicine and nanobiotechnology. 2012;4(1):52-65.
18. Dellinger A, Zhou Z, Connor J, Madhankumar AB, Pamujula S, Sayes CM, et al. Application of fullerenes in nanomedicine: an update. Nanomedicine (London, England). 2013;8(7):1191-208.
19. Dinh T, Nguyen T, Phan HP, Nguyen NT, Dao DV, Bell J. Stretchable respiration sensors: Advanced designs and multifunctional platforms for wearable physiological monitoring. Biosensors & bioelectronics. 2020;166:112460.
20. Dobrovolskaia MA, Shurin MR, Kagan VE, Shvedova AA. Ins and Outs in Environmental and Occupational Safety Studies of Asthma and Engineered Nanomaterials. ACS nano. 2017;11(8):7565-71.
21. Doroudian M, A ON, Mac Loughlin R, Prina-Mello A, Volkov Y, Donnelly SC. Nanotechnology in pulmonary medicine. Current opinion in pharmacology. 2021;56:85-92.
22. Doroudian M, MacLoughlin R, Poynton F, Prina-Mello A, Donnelly SC. Nanotechnology based therapeutics for lung disease. Thorax. 2019;74(10):965-76.

23. Drmosh QA, Olanrewaju Alade I, Qamar M, Akbar S. Zinc Oxide-Based Acetone Gas Sensors for Breath Analysis: A Review. Chemistry, an Asian journal. 2021;16(12):1519-38.
24. Dua K, Bebawy M, Awasthi R, Tekade RK, Tekade M, Gupta G, et al. Application of Chitosan and its Derivatives in Nanocarrier Based Pulmonary Drug Delivery Systems. Pharm Nanotechnol. 2017;5(4):243-9.
25. Dua K, Chellappan DK, Singhvi G, de Jesus Andreoli Pinto T, Gupta G, Hansbro PM. Targeting microRNAs using nanotechnology in pulmonary diseases. Panminerva Med. 2018;60(4):230-1.
26. Dubus JC, Bosdure E, Bakuridze L, Andrieu V. [Nebulized drugs: the evolution?]. Archives de pediatrie : organe officiel de la Societe francaise de pediatrie. 2007;14(5):504-6.
27. Duguay BA, Lu L, Arizmendi N, Unsworth LD, Kulka M. The Possible Uses and Challenges of Nanomaterials in Mast Cell Research. Journal of immunology (Baltimore, Md : 1950). 2020;204(8):2021-32.
28. Fan PS, Sun MJ, Qin D, Yuan CS, Chen XG, Liu Y. Nanosystems as curative platforms for allergic disorder management. Journal of materials chemistry B. 2021;9(7):1729-44.
29. Gantait S, Mahanta M, Bera S, Verma SK. Advances in biotechnology of Emblica officinalis Gaertn. syn. Phyllanthus emblica L.: a nutraceuticals-rich fruit tree with multifaceted ethnomedicinal uses. 3 Biotech. 2021;11(2):62.
30. Gaspar N, Zambito G, Löwik C, Mezzanotte L. Active Nano-targeting of Macrophages. Curr Pharm Des. 2019;25(17):1951-61.
31. Gessler T. [Inhalative pharmacotherapy in the future--nanocarriers for pulmonary drug delivery]. Pneumologie (Stuttgart, Germany). 2009;63 Suppl 2:S113-6.
32. Gulati N, Dua K, Dureja H. Role of chitosan based nanomedicines in the treatment of chronic respiratory diseases. Int J Biol Macromol. 2021;185:20-30.
33. Hashoul D, Haick H. Sensors for detecting pulmonary diseases from exhaled breath. European respiratory review : an official journal of the European Respiratory Society. 2019;28(152).
34. Hough KP, Chanda D, Duncan SR, Thannickal VJ, Deshane JS. Exosomes in immunoregulation of chronic lung diseases. Allergy. 2017;72(4):534-44.
35. Ihrie MD, Bonner JC. The Toxicology of Engineered Nanomaterials in Asthma. Current environmental health reports. 2018;5(1):100-9.
36. Kaur SS. Pulmonary drug delivery system: newer patents. Pharmaceutical patent analyst. 2017;6(5):225-44.
37. Keil TWM, Baldassi D, Merkel OM. T-cell targeted pulmonary siRNA delivery for the treatment of asthma. Wiley interdisciplinary reviews Nanomedicine and nanobiotechnology. 2020;12(5):e1634.
38. Korani S, Korani M, Sathyapalan T, Sahebkar A. Therapeutic effects of Crocin in autoimmune diseases: A review. BioFactors (Oxford, England). 2019;45(6):835-43.