Review Article

An overview on nanoparticle based approach for treatment and management of asthmatic disorder

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Abstract

According to the World Health Organization, Asthma is the fastest-growing disease in the world alongside HIV/AIDS, and its socioeconomic burden exceeds the sum of HIV/AIDS and tuberculosis. Its high disability and mortality rates have become serious social and public health concerns. Asthma is a heterogeneous disease in which genetic polymorphisms interact with the environmental factors. While no specific treatment has been available for asthma due to its complex pathogenesis, the advances in nanotechnology have brought new hope for the early diagnosis, treatment, and prevention of asthma. Nanotechnology can achieve targeted delivery of drugs or genes, reduce toxic effects, and improve drug bioavailability. The nano-modifications of drugs and the development of new nano-drugs have become new research directions. Studies have demonstrated the safety and effectiveness of nanocarriers. However, many challenges still need to be overcome before nanotherapy can be applied in clinical practice. In this article we review the new research highlights in this area, with an attempt to explore the great potential and feasibility of nanotechnology in treating asthma.

Keywords: Nanotechnology, asthma, nano-modifications, new nano-drugs, nanotherapy

Introduction

Nano is a prefix used to describe one billionth, or 10^{-9} of something. The concept of nanotechnology was introduced was introduced by physics Noble laureate Richard P Feynman in his famous lecture entitled “there is plenty of room at the bottom” at the December 1959 meeting of American physical society. Nanotechnologies are now widely considered to have the potential to bring benefits in areas as diverse as drug development, water decontamination and the production of stronger and lighter materials. Nanotechnologies involve the creation and manipulation of materials at the nanometer scale, either by scaling up from single groups of atoms or by refining or reducing bulk materials. Nanotechnology deals with materials in the size of 0.1 to 100 nm, however it is also inherent that these materials should display different properties such as

electrical conductance, chemical reactivity, magnetism, optical effects and physical strength, from bulk material as a result of their small size. The nano scale is the place where the properties of most common things are determined just above the scale of an atom. Nano scale objects have at least one dimension (height, length, depth) that measures between 1 and 999 nanometers (1-999 nm). Pharmaceutical nanotechnology is divided into two basic types of nano tools viz. Nano-particles/materials and nano devices. These materials can be subdivided into nano-crystalline and nano structured material. Nano structures consists of nano particle, dendrimers, micelles, drug, Conjugate, metallic nano-particle etc (Figure 1).

Application of Nanotechnology

The different fields that find potential application of nanotechnology are as health and medicine, electronics, energy and environment, agriculture, etc.

Nanotechnology in health and medicine

With the help of nano medicine early detection and prevention, improved diagnosis, proper treatment and

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Figure 1. Nanocarriers utilized as drug delivery device (Garg et al., 2017)

follow up of disease is possible. Certain nano scale particle are used as tags labels, the testing has become more efficient and flexible gene sequencing has become more efficient with invention of nano device like gold nano particles, these gold nano particles when tagged with short segments of DNA can be used for detection of genetic sequence of sample.

Drug delivery

Nano particles are used for site specific drug delivery.

- Nano medicines used for drug delivery are made up of nano-scale material or particles which can improve bioavailability.
- The pharmacological and therapeutic properties of drugs can be improved by proper designing of drug delivery system, by use of lipid and polymers. Based nano particles.(4)
- Nano medicines are designed to avoids body's defence mechanism and can improve drug delivery.

A drug with poor solubility will be placed by a drug delivery system having improved solubility due to presence of both hydrophilic and hydrophobic environment. With drug delivery system larger clearance of drug from body can be reduced by altering the pharmacokinetics of the drug. Potential nano drugs will work by very specific and well understood mechanisms, one of the major impacts of nanotechnology and nanoscience. Will be in leading development of completely new drugs with more useful behavior and fewer side effects. Thus nanotechnology is promising tool for the advancement of drug delivery, as diagnostic sensor and bio imaging. The bio distribution of these nano materials is still imperfect due to the complex host's

reactions to nano and macro sized materials and the difficulty and the difficulty in targeting specific organs in the body, efforts are made to optimize and better understand the potential and limitation of nano-system.

Nanoparticles and its utility in drug delivery

The benefit of nanoparticle to modern medicine is numerous. Indeed these are some instances where nanoparticles enable. Analysis and therapies simply cannot be performed otherwise out of plethora of size dependent physical properties available, optical and magnetic (Chen et al., 2014) effects are the most used for biological application.

• Site-specific imaging in-vivo

1. Imaging of lymph nodes, lung blood vessels, and tumours.
2. Greater intensity and resistance to photo bleaching compared with conventional methods.
3. Site-specific targeting via surface functionalization.
4. Subcutaneous imaging without surgical incisions.

• Cancer detection

1. Enhanced contrast for imaging of liver lymph nodes and bone marrow.
2. Paramagnetic properties that can alter magnetic resonance relaxation times of selected regions or fluids in vivo.

• Cancer therapy

1. Targeted delivery of surface functionalization.
2. Strategies for prolonging residence times in vivo.
3. Strategies for solubilising water-insoluble drugs.
4. Multi- layer and multi-functional (eg- chemotherapeutic and anti-angiogenic).

• Neurodegenerative disease therapy

1. Transport across blood brain barrier.
2. Superior to direct drug administration.
3. Therapies for diseases unresponsive to small molecule drugs.

• HIV/AIDS therapy

1. Solubilising water-insoluble drugs by emulsification.
2. Ability to transfect cells by DNA incorporation in nanoparticle.

• Ocular disease therapy

1. Alternative to frequent application of high-drug conc. drops.
2. Ability to prolong drug residence times within ocular

mucus layer or retina.

- *Respiratory disease therapy*

1. Mitigation of inflammatory responses in respiratory tract.

- *Anti-inflammatory*

Asthma

Asthma is one of the most common chronic and non-communicable diseases in children and adults. At present, more than 300 million people are living with asthma worldwide, among whom about 30 million asthmatic patients are in China. In recent years, the global asthma prevalence is rising annually. Asthma is a heterogeneous disease in which genetic polymorphisms interact with environmental factors. It can be divided into different phenotypes according to clinical characteristics (e.g., the age of onset and disease severity), triggers (exercise and viral infection), and inflammation types (e.g., eosinophilic, neutrophilic, paucigranulocytic, and mixed granulocytic) (Tarlo et al., 2006). While no specific treatment has been available for asthma due to its complex pathogenesis, long-term standardized therapies can effectively alleviate symptoms, reduce attacks, and improve the prognosis (Figure 2). Most asthmatic patients respond well to corticosteroid inhalation. The combinations of steroids with bronchodilators such as long- or short-acting beta-receptor agonists (LABA or SABA) or leukotriene receptor antagonists (LTRAs) are considered to be the first-line control strategy for asthma. However, asthma control is still poor in some asthmatic patients, even after the use of the maximum dose of corticosteroids. Importantly, the expenditure in these patients accounts for more than 60% of asthma-related medical costs. In addition to inhaled glucocorticoids, human monoclonal antibodies and cytokine/chemokine antagonists have been used to treat moderate to severe refractory asthma. However, these strategies can only achieve limited success due to the heterogeneity of asthma (Vos et al., 2010).

Application of nano-modified anti-asthma drugs

The nano-modification technology of traditional drugs mainly includes the research and development of nano-particle carriers

with precise surface patterns, the carrying of existing drugs through drug-targeting reagents, and so on, to achieve targeted drug delivery, reduce toxic and side effects, and improve the solubility of insoluble drugs.

The prevention and treatment of asthma require long-term medication. The traditional anti-asthma drugs are mainly administered intravenously, orally, or by inhalation. The inhaled agents are the mainstream medications to maintain good asthma control, and their sizes are closely related to their bioavailability and efficacy. Compared with systemic drug administration, the targeted drug delivery by inhalation enables the drugs to directly reach the lungs, thus avoiding the first-pass effect and improving bioavailability (Figure 3). Glucocorticoid is the most effective drug to control airway inflammation caused by asthma. After a glucocorticoid is inhaled, it has a potent topical anti-inflammatory effect. The drug directly acts on the respiratory tract, which requires less dosage and has fewer systemic adverse reactions. A multi-center clinical trial of fluticasone in the treatment of asthma in China many years ago showed that half of the Global Initiative for Asthma-recommended dose of inhaled corticosteroids (ICS) in the management of Chinese asthmatics achieved similar efficacy as the recommended ceiling dose (Chen et al., 2005). Although hormone inhalation therapy dramatically reduces the side effects (compared with systemic hormones), long-term high-dose hormone inhalation will inevitably bring some adverse reactions such as inhibition of adrenal axis, oral fungal infection, and osteoporosis. To reduce the side effects of long-term high-dose hormone inhalation and further improve the bioavailability of hormones, PEGylated Poly(amidoamine) (PAMAM) dendrimer, a typical dendrimer, has been widely studied and applied. According to Nasr et al., PAMAM could be used as a carrier of beclomethasone dipropionate (BDP) and other insoluble drugs (Nasr et al., 2013). It could improve drug solubility and increase its lung accumulation capacity, thereby improving the bioavailability of the drug, reducing

Figure 2. Process of induction of asthma (Wang et al., 2019)

Figure 3. The targeted drug delivery by inhalation enables the drugs to directly reach the lungs, thus avoiding the first-pass effect and improving bioavailability (Wang et al., 2019)

dosage and dosing frequency, and reducing toxic and side effects. Also, the well-defined non-toxic telomere dendrimer has also been reported to be an efficient nanocarrier with greater loading capacity and better stability than micelles (for more than 6 months). This nanocarrier can also deliver hydrophobic drugs (e.g., dexamethasone) into the lungs directly, thus reducing allergic pulmonary inflammation and decreasing the eosinophils and inflammatory cytokines. Therefore, compared with the same dose of dexamethasone, it can improve airway hyperresponsiveness to a greater extent.

At present, the most commonly used drugs for alleviating symptoms included inhaled β_2 -receptor agonists, anticholinergic drugs, and short-acting theophylline. These drugs can rapidly relieve bronchospasm, usually within a few minutes, and the therapeutic effect can last for several hours. They are the first choice for alleviating acute symptoms in patients with mild to moderate asthma and also can be used for preventing exercise-induced asthma. These drugs should be used on demand, and long-term, excessive use of one single agent should be avoided. Their adverse reactions include skeletal muscle tremor, hypokalemia, and arrhythmia. Also, long-term use of a single LABA was associated with an increased risk of death from asthma. According to Matsuo et al., compared with free steroids, nanocarrier-encapsulated steroids achieved better and more lasting therapeutic effects in airway inflammation sites (Matsuo et al., 2009). Also, a nanocarrier can tightly be bound to salbutamol, yielding stronger interaction with pleura. The effective drug concentration could be maintained at the target site for a long period to achieve long-term relief of bronchospasm (Bhavna et al., 2009). Based on the above two studies, Chen et al.,

found that liposomes prolonged the retention of salbutamol sulfate in the lungs and maintained the effective drug concentration for more than 10 hours. Thus, they achieved significantly higher efficacy than the free drug solution (Chen et al., 2012). Compared with the micronized salbutamol sulfate, the nanoparticles loaded with the same drug were less affected in the human oropharynx and had higher peripheral deposition, which indicated that the nanoparticles had smaller size and greater topical bioavailability and could last for a longer period.

ENMs can be generally defined as purposefully designed materials possessing at least one dimension less than or equal to 100 nm and unique physicochemical characteristics not present in their non-nanoscale counterparts of the same composition (Auffan et al., 2009). In recent years the number of different kinds of ENMs has grown exponentially, and ENMs are being used in a wide range of applications including electronics, engineering and medicine (Elsaesser and Howard, 2012). ENMs come in a diverse array of materials and shapes including metal nanoparticles (NPs) (TiO_2 , ZnO , Au , NiO), carbon NPs, silica NPs, and fullerenes like carbon nanotubes (CNTs). Metal nanoparticles may be spherical or irregular in shape, and CNTs may be either single- or multi-walled. There are also nanofibers, which are similar to CNTs, but are solid, and may be composed of carbon or metals. Examples of the physical characteristics of different kinds of ENMs are depicted in Figure 4 (Xia et al., 2013). This diversity of ENMs means there are a variety of ways they could interact with biological systems to produce toxicity, and over the past 15 years there have been numerous studies into how ENMs may

Figure 4. Illustration of interactions of engineered nanomaterials (ENMs) and allergens with the immune system. ENMs directly stimulate innate immune cells such as macrophages or epithelial cells to produce chemokines that stimulate recruitment of other inflammatory cells such as eosinophils. ENMs also interact with allergens to exacerbate innate immune responses. Dendritic cells transport ENMs to lymph nodes to program T cells as part of the acquired immune system. Phenotypic changes in cells and tissues are shown in *blue boxes* (Ihrle et al., 2018)

cause lung diseases like fibrosis and asthma (Nel et al., 2006). The purpose of this review is to concisely summarize the current literature on the toxicology of ENMs in relation to asthma; studies on the uses of ENMs for asthma therapeutics will not be discussed. It will first focus on the way in which different types of ENMs exacerbate preexisting asthma, and follow by examining how ENMs may be able to initiate asthma directly, in the absence of allergens. These concepts are summarized and illustrated in and Figure 4, respectively. There is a severe lack of human evidence for ENM toxicity, meaning this review will focus primarily on evidence from animal and cell models; however, later the few relevant human based studies will be discussed.

ENM-Induced Asthma Exacerbations

Titanium dioxide (TiO₂) Nanoparticles

A number of different asthma models have been utilized to study the effects TiO₂ NPs on the immune response in asthma. Several studies utilize the common ovalbumin (OVA) mouse model, in which mice are sensitized and then challenged by OVA exposure to produce allergic airway disease (Mishra et al., 2016; Rossi et al.,

2010). One of the earliest TiO₂/OVA studies by Rossi et al. compared nanosized and fine TiO₂, and did not find significant differences in endpoints measured, and surprisingly exposure to either type of TiO₂ decreased asthma endpoints like eosinophil numbers, airway mucous production and AHR (Rossi et al., 2010). This could be due to the timing of TiO₂ NP exposure, because interestingly two other studies found that the order and timing of OVA and TiO₂ NP exposure affected the observed immune modulation (Mishra et al., 2016). Both of these studies found that TiO₂/OVA exposed mice had increased AHR and eosinophilia when TiO₂ NPs were given either between the OVA sensitization and challenge phases, or during sensitization, but not when TiO₂ was given during the challenge phase or later, suggesting an adjuvant-like effect (Mishra et al., 2016). Increases in the T_H2 cytokines IL-4, IL-13 and IL-5 were seen, and Mishra et al. found elevated *Socs3* expression, which is associated with airway inflammation, in TiO₂ exposed mice which was NF-κB-dependent (Mishra et al., 2016). TiO₂ NPs also increase levels of caspase-1 and activate the NLRP3 inflammasome to generate increased

production of pro-inflammatory IL-1 β , likely through reactive oxygen species (ROS) production. Genetic susceptibility has also been shown to affect the immune response in the OVA model; Gustafsson et al., 2014, found differences in TiO₂-induced inflammation in two susceptible rat strains, with both showing exacerbated IgE production and neutrophilia (Hussain et al., 2011). A study by Hussain et al. utilizing a toluene diisocyanate (TDI) mouse model of asthma similarly found that TiO₂ NPs significantly increased lung inflammation; however, AHR was not increased (Hussain et al., 2011).

Silica Nanoparticles

Several studies have used the OVA rodent model of asthma to examine the toxicity of silica NPs. In rats, SiO₂ NPs administered with OVA were found to increase AHR and disrupt the T_H2-T_H1 balance by increasing IL-4 and decreasing IFN- γ levels in lung protein (Han et al., 2011). Conversely, eosinophil numbers in bronchoalveolar lavage fluid (BALF) were decreased by SiO₂ exposure in this study (Han et al., 2011). The effect of silica NP size on asthma exacerbation was examined by another study, finding that the smaller 30 nm particles were the most bioactive, causing greatly enhanced IgE and IL-4 production when compared to the 70, 300 and 1000 nm particles they tested (Yoshida et al., 2013). Polyethylene glycol-coated (PEGylated) silica NPs have been shown to enhance OVA-induced eosinophilia and neutrophilia, as well as BALF levels of numerous cytokines (Brandenberger et al., 2013). Most interesting in this study was the examination of tracheobronchial lymph node cell activation by assessing CD69⁺ cells by flow cytometry; in particular, alveolar macrophages and dendritic cells were found to have increased activation in silica NP/OVA treated mice compared to OVA alone (Brandenberger et al., 2013). Other studies have examined the differences between spherical, mesoporous (meaning they contain pores between 2 and 50 nm in diameter, giving them a high surface area) and PEGylated silica NPs in OVA mice (Park et al., 2015; Han et al., 2016). Of these, spherical silica NPs were generally the most inflammatory, causing enhanced eosinophilia compared with OVA alone, although there was no change in OVA-induced AHR (Park et al., 2015). In another study by the same group, mesoporous silica NPs were seen to be more inflammatory than spherical, however both types of silica NPs significantly increased IL-5, IL-13, IFN- γ and IL-1 β over OVA alone (Han et al., 2016). Mesoporous silica NPs could be more inflammatory due to their increased surface area. It should be noted that this study used repeated co-exposure of NPs with OVA and found greater exacerbation than the previous study, which gave NPs only during the challenge phase, indicating again the importance of exposure timing. Silica NPs have been studied *in vitro* by using spleen-derived antigen presenting cells to present OVA peptides to T cells, followed by exposure to modified silica NPs

(Chen et al., 2014). This study found that silica NP exposure enhanced IL-2 and IFN- γ production by CD8⁺ T cells, indicating the ability of silica NPs to stimulate antigen-specific T cell responses (Chen et al., 2014).

Silver Nanoparticles

Ag NPs, which are well known for their antimicrobial properties, have been found to modulate inflammatory signaling in asthma models (Park et al., 2012). Ag NPs attenuate OVA induced allergic inflammation in mice, decreasing total BALF cell counts, IL-4 and IL-13 levels, and *Muc5ac* expression (Park et al., 2012). This same study also found that Ag NPs decreased VEGF levels and had similar effects *in vivo* compared to the VEGF inhibitor SU5614, indicating this Ag NP inhibition of VEGF may be at least partly responsible for the attenuated inflammation (Park et al., 2012). Ag NP's ability to attenuate allergic inflammation is supported by another study, which found Ag NPs decreased IL-13, IL-4, IL-5 and NF- κ B levels, as well as AHR (Park et al., 2010). Conversely another study found that Ag NPs increased IgE and IL-13 levels in allergic mice, as well as ROS (Cheng et al., 2013). However, Ag NPs did not cause any increases in neutrophil or eosinophil BALF numbers, and lung histological changes were not striking (Cheng et al., 2013).

Gold Nanoparticles

Au NPs have been examined in several different ways in relation to asthma. In the study by Hussain et al. discussed above, Au NPs were also used in their TDI-induced asthma model and were found to be even more inflammatory than TiO₂ NPs, showing increased AHR and total BALF cell counts. In the OVA asthma model, Au NPs have been found to actually decrease OVA-induced allergy as seen by decreased inflammatory cell lung accumulation, decreased mucus production and lower cytokine levels (Barreto et al., 2015). Similarly, both PEGylated and citrated Au NPs have been shown to attenuate OVA-induced inflammation: both types of Au NPs decreased AHR, total BALF cell counts and eosinophil numbers (Omlor et al., 2017). This study also examined extrapulmonary uptake of Au NPs, finding that asthmatic mice had more NPs deposited in the spleen. The effects of the protein corona (that is, the proteins that adsorb to the surface of NPs) on Au NP toxicity have been examined by conjugating Au NPs with coronas of common allergens, and Au NPs conjugated with the allergen Der p 1, which is a component of house dust mite, enhanced its protease activity and increased basophil activation in *in vitro* assays, suggesting that co-exposures of allergens with NPs could enhance inflammation in asthma through corona formation. It has also been found that Au NPs are taken up

by eosinophils on the airway surface in OVA-exposed mice (Geiser et al., 2014). More research will be needed to fully understand the impact of Au NPs on pre-existing asthma as the current studies show somewhat conflicting evidence, with the outcomes depending on the type of asthma model used.

Iron, Zinc, Copper and Nickel Nanoparticles

Different sizes of iron oxide NPs have been tested in OVA asthma models and been found to inhibit allergic inflammation, with nanosized particles significantly decreasing eosinophil cell counts and OVA-specific IgE levels, and larger submicron iron oxide particles having no effect (Ban et al., 2013). Hematite NPs have been observed to decrease total immune cell numbers in the lungs and lymph nodes of OVA sensitized mice, an effect which the authors speculate could be due to the acidic nature of the inflammatory environment causing Fe ion release from the nanoparticles, increasing ROS production (Ban et al., 2013). Zinc NPs are well known for their toxicity, and ZnO NPs have been tested in the OVA asthma models and were found to increase BALF cell counts and serum IgE levels over OVA alone, an effect that was determined to be Zn ion-independent (Huang et al., 2015). Copper oxide NPs have also been shown to exacerbate asthma: in an OVA model they exacerbate numerous endpoints including AHR, inflammatory cell counts, cytokines, IgE and ROS (Park et al., 2016). This study also found CuO NPs to increase phosphorylation of the MAPKs Erk, JNK and p38. Finally, Ni NPs have been found to exacerbate lung inflammation in a transgenic mouse model of asthma susceptibility. This was determined by using mice lacking the T-bet transcription factor, which is involved with T_H1 development, and mice lacking it consequently develop T_H2 -type allergic inflammation similar to asthma; this study found Ni NPs enhanced mucous production in T-bet knockout mice and increased BALF levels of the chemokine CCL2. Interestingly, through the use of an anti-CCL2 antibody it was determined that the Ni NP-induced mucous production was at least partly due to these increased CCL2 levels (Glista-Baker et al., 2014).

Carbon Nanoparticles

Carbon black NPs, which are produced through combustion processes, are often used as a control when testing more active types of NPs, however carbon black NPs themselves have been shown to have the potential to exacerbate asthma (Koike et al., 2008). OVA-sensitized mice exposed to 14 nm carbon black NPs had increased numbers of dendritic cells, macrophages and B cells, as determined by cell surface markers; the larger 56 nm NPs used in this study did not elicit any change from OVA alone, indicating the importance of particle size. These results are supported by another study, which found carbon black NPs given during OVA sensitization increased inflammatory cell numbers in the lungs as well as $CD8^+$ T cells, $CD4^+$ T cells and B cells in the

lymph nodes. These effects were likely not due to direct particle action on antigen presenting cells, as *in vitro* assays on dendritic cells only yielded dendritic cell activation with cell free-BALF from carbon black NP-exposed mice plus carbon black NPs (Kroker et al., 2015). Carbon black NPs also increases T cell activation *in vitro*; splenic leukocytes sensitized by OVA peptides with carbon black NPs had enhanced expression of T_H2 associated genes, IL-13, IL-4 and IL-10 (Lefebvre et al., 2014). Graphene particles have also been studied in OVA models, yielding contrasting results to carbon black NPs (Shurin et al., 2014). Graphene oxide was found to decrease markers of T_H2 inflammation like IL-4, IL-13, IL-5 and eosinophils, while increasing airway remodeling and AHR; this increased remodeling may be due to production of chitinases by classically activated macrophages, as macrophages isolated from BALF had elevated acidic mammalian chitinase levels when treated with graphene oxide (Shurin et al., 2014). *In vitro* assays with sensitized mast cells and basophils indicate that C_{60} fullerenes inhibit allergic responses, an effect that is in part due to the inhibition of cellular ROS levels (Ryan et al., 2007).

Polymeric Nanoparticles

Limited work has been done on asthma and polymer NPs; polystyrene NPs have been examined by two studies, first one is, Glycine coated polystyrene NPs were tested in OVA-induced allergy in mice and were found to inhibit serum IgE, mucus production, and T_H2 cytokines in the lung-draining lymph node. The mechanisms of this inhibition were examined and polystyrene NPs decreased the numbers of migratory dendritic cells in the lymph nodes, as well as inhibited dendritic cell activation in the lung (Hardy et al., 2012) and second is, Extrapulmonary transport of polystyrene nanoparticles has been examined by using ^{64}Cu -labeled NPs, and the OVA mouse model was used to determine how asthma affects transport (Enright et al., 2013). Asthmatic mice had significantly less lung retention of NPs than control mice, and NPs were found in the liver, bladder and gastrointestinal tract; these results indicate that asthma may cause a predisposition for greater extrapulmonary toxicity of NPs.

Medicinal plants used in asthma

Medicinal plant used for the treatment of asthma should have anti-inflammatory, immunomodulatory, antihistaminic, smooth-muscle relaxants and allergic activity. According to Ayurveda anti-asthmatic drug should have properties such as anti-kapha and anti-vata. Antioxidant supplements are effective in reducing bronchoconstriction severity by inhibiting pro-

inflammatory events as a result of neutralizing the effects of excess reactive oxygen species and reactive nitrogen species. Current asthma therapy lack satisfactory success due to adverse effect, hence patients are seeking complementary and alternative medicine to treat their asthma. Quercetin is one of the most widely occurring flavonoids ingested in food by humans. Quercetin inhibits mast cell degranulation and subsequent release of histamine.

Adverse effects of current treatments used in asthma

Isoprenaline: Causes tachycardia.

Salbutamol: Muscle tremors (dose related), palpitation, restlessness, nervousness, throat irritation and ankle edema.

Theophylline: Convulsions, shock, arrhythmias, increased muscle tone, tachapnoea, (dose dependent) flushing, hypotension, restlessness, tremors, vomiting, palpitation, diuresis, dyspepsia, insomnia etc.

Anticholinergics: Dry mouth, difficulty in swallowing and talking, scarlet rash, photophobia, blurring of near (Atropine and its congeners) vision, palpitation, ataxia, delirium, hallucinations, hypotension, weak and rapid pulse, cardiovascular collapse with respiratory depression, convulsions and coma (in severe poisoning).

Ketotifen: Sedation, dizziness, dry mouth, nausea and weight gain.

Corticosteroids: Cushing's habitus, fragile skin, purple striae, hyperglycemia, muscular weakness, susceptibility to infection, delayed healing of wounds and surgical incisions, peptic ulceration, osteoporosis, glaucoma, growth retardation, psychiatric disturbances, suppression of hypothalamo-pituitary-adrenal (HPA) axis etc.

As a consequence, the search for effective low-risk, non-drug strategies that provide a valuable adjunctive or alternative treatment in asthma management is clinically attractive and relevant. There is much interest in complementary and alternative medicine, and its use in the management and treatment of asthma is growing at a significant rate. Present review describes some plants that have been pharmacologically evaluated for those parameters involved in asthma.

Some traditional plants with antiasthmatic potential

Aerva lanta Linn (Amaranthaceae): *Aerva lanta* (*A. lanta*) is an erect or prostrate herbaceous common wayside weed which is recognized by its white axillary bunches of small woolly flowers. It is abundant on the plains in the warmer parts of India. Ethanol extract of aerial parts of *A. lanata* at 100 µg/mL in the isolated goat tracheal chain preparation model and 30 and 60 mg/kg doses orally in clonidine-induced catalepsy and mast cell degranulation in mice possesses antiasthmatic activity.

Ageratum conyzoides L.: Ageratum conyzoides (*A. conyzoides*) is an erect, herbaceous annual plant from the family Asteraceae (Compositae), native to tropical America, but with a distribution range in tropical and subtropical areas around the world. Hydroalcoholic extract of leaves of *A. conyzoides* at doses of 250, 500 and 1 000 mg/kg shows antihistaminic activity by inhibiting clonidine induced catalepsy in mice.

Argemone Mexicana: Argemone mexicana (*A. mexicana*) is common everywhere by road-sides and fields in India. It possesses antiallergic and antistress activity of aqueous extracts of *A. mexicana* stem at dose 50 mg/kg, *i.p.* using milk-induced leucocytosis and milk-induced eosinophilia.

Asystasia gangetica T. Adams (Acanthaceae): *Asystasia gangetica* (*A. gangetica*) is used in many parts of Nigeria for the management of asthma. Akah, *et al.* evaluated hexane, ethylacetate, and methanol extracts of the leaves of *A. gangetica* for antiasthmatic activity using guinea pig trachea; rat stomach strip; guinea pig ileal preparation and egg albumin-induced acute inflammation. The results indicated that the extracts did not exhibit contractile or relaxant activity in isolated tissue preparations; however, they inhibited the contraction evoked by spasmogens.

Bacopa monnieri L. (Scrophulariaceae): *Bacopa monnieri*: Samiulla, *et al.* evaluated petroleum ether, chloroform, methanol and water extracts of *B. monnieri* leaves at doses 10 µg/mL for mast cell stabilizing activity in rats. The result of investigation observed that all the extract significantly inhibits mast cell degranulation.

Cassia sophora (caesalpinaceae): *Cassia sophora* (*C. sophora*) is used in traditionally for treatment of asthma and bronchitis. Chloroform, ethyl acetate and ethanol fractions isolated from ethanol extract of leaves of *C. sophora* possesses significant antiasthmatic activity in carrageenan induced paw edema, histamine induced bronchoconstriction, clonidine and haloperidol induced catalepsy, milk induced leukocytosis, and eosinophilia and passive paw anaphylaxis animal models at doses 250, 500 and 750 mg/kg and this activity may be due to presence of flavonoids.

Casuarina equisetifolia Linn (Casuarinaceae): *Casuarina equisetifolia* (*C. equisetifolia*) is evergreen tree; generally attain height up to 50 m, cultivated on Coastal regions from Gujarat to Orissa, some parts of West Bengal and in Andamans. The methanol extract of extracts of wood and bark possesses antihistaminic activity by inhibiting the histamine induced contraction of trachea (10-80 mcg/mL), clonidine induced catalepsy and mast cell degranulation at

doses 100 mg/kg.

***Clerodendrum Serratum* Linn (Verbenaceae):** *Clerodendrum Serratum* (*C. serratum*), known as bharangi in ayurveda, is traditionally useful in treating pain, inflammation, rheumatism, respiratory diseases, and malarial fever. Ethanol extract of roots of *C. serratum* showed antiasthmatic activity using isolated goat tracheal chain preparation, clonidine induced catalepsy; Milk induced leucocytosis and eosinophilia in mice at doses 50, 100 and 200 mg/kg.

***Cnidium monnieri* (Umbelliferae):** *Cnidium monnieri* (*C. monnieri*) in traditional medicine of China has been used for treatment of pain in female genitalia, impotence and suppurative dermatitis as an antipruritogenic agent. Matsuda *et al.* reported antiallergic activity of ethanol extract and Osthol a chromane isolated from ethanol extract of fruits of *C. monnieri* in passive cutaneous anaphylaxis in rats.

***Crinum glaucum* (Amaryllidaceae):** *Crinum glaucum* (*C. glaucum*) is popular in Yoruba of South West Nigeria. Traditional medicine practitioners reported it as an effective remedy in the relief of cough, asthma and convulsions. The aqueous extract of *C. glaucum* possesses antiallergic activity at dosed 100-400 mg/kg by reduction in area of dye leakage in passive cutaneous anaphylactic reaction, protecting degranulation of mast cell and histamine induced bronchoconstriction in the guinea pig.

***Curculigo orchoides* Gaertn (Amaryllidaceae):** *Curculigo orchoides* (*C. orchoides*) is a tiny herbal plant widely distributed in India, China, Malaya, and Japan. Alcoholic extract of *C. orchoides* rhizomes at doses (100-400 mg/kg) shows mast cell stabilizing and antihistaminic activity on Compound 48/80-induced mast cell degranulation and systemic anaphylaxis. It also inhibited histamine-induced contraction in goat trachea, guinea pig ileum and bronchoconstriction in guinea pigs; egg albumin induced passive paw anaphylaxis in rats; milk induced leucocytosis and eosinophilia; clonidine induced catalepsy in mice.

***Eclipta alba* Linn (Asteraceae):** The 50% ethanol extract shows antianaphylactic and antihistaminic activity at doses 250 and 500 mg/kg on compound 48/80-induced degranulation of mast cell, egg albumin induced passive Cutaneous and paw anaphylaxis; bronchoalveolar lavage (BAL) study on guinea pig trachea; and determination of histamine.

***Euphorbia hirta* (Euphorbiaceae):** Popularly known as asthma weed, *Euphorbia hirta* is an herbaceous wild plant which grows in the hotter parts of India. Ethanol extract of whole aerial part of the plant at doses (100-1000 mg/kg) shows antihistaminic and antiallergic activity by inhibiting inhibited the passive cutaneous anaphylaxis and paw anaphylaxis

reaction; protection of mast cell from degranulation.

***Ficus bengalensis* Linn (Moraceae):** *Ficus bengalensis* (*F. bengalensis*) is a very large tree reaching about 30 m high and sending down many aerial roots from the branches. Ethyl acetate, ethanol and aqueous extracts as well as fractions isolated from aqueous extract of *F. bengalensis* bark possesses antihistaminic activity by inhibiting clonidine induced catalepsy in mice at dose 50 mg/kg. This activity may be due to presence of flavonoids.

***Gakani*:** *Gakani* is a polyherbal drug contains *Cenchrus biflorus* Roxb. *Gramineae* *Ola* *subscorpioidea* Oliv. (*Ola* *aceae*), *Piper guineense* schum Thonn (*Piperaceae*), *Psorospermum guineense* Hochr. (*Hypericaceae*), *Securidaca longipedunculata* Tresen (*Polygalaceae*), *Syzygium aromaticum* (L.) Merr. (*Myrtaceae*). The anti-asthmatic potential of *Gakani*, a popular herbal drug was investigated using guinea pig tracheal chain; guinea pig ileum preparation; on the rat stomach strip and egg albumin induced hind paw edema. Result indicates that the extract blocked the effects of histamine and isoprenaline on the guinea pig tracheal chain. It shows inhibition contraction of isolated guinea pig ileum and rat stomach strip, caused by histamine and 5-hydroxytryptamine (5-HT). The extract had good anti-inflammatory effect in rats.

***Hemidesmus indicus* R. Br. (Asclepiadaceae):** *Hemidesmus indicus* (*H. indicus*) is a twining shrub commonly found in India. Bhujbal *et al.* reported antiasthmatic activity of ethanol extract of *H. indicus* roots at doses 25, 50, 100 mg/kg using isolated goat tracheal chain preparation, passive paw anaphylaxis in rat and clonidine-induced catalepsy in mice.

***Amburana cearensis* (Fabaceae):** *Amburana cearensis* (*A. cearensis*) is a medicinal plant common to the Brazilian Northeastern "caatinga" (savannah), and popularly used in respiratory tract diseases including asthma. The flavonoid isokaempferide isolated from Trunk barks of *A. cearensis* shows significant relaxation of KCl induced contraction on guinea pig trachea.

Plants from Zinziberaceae: Tewtrakul *et al.* reported antiallergic activity of ethanol and water extract of some plants of Zinziberaceae family.

***Lepidium sativum* Linn (Cruciferae):** Commonly known as Asaliyo, it is an erect, glabrous annual herb cultivated as a salad plant throughout India. The ethanol extract and ethyl acetate, n-butanol and methanol fractions isolated from ethanol extract inhibit bronchospasm induced by histamine and acetylcholine.

***Mentha spicata* L:** The four new flavonoids and three new glycosides isolated from ethyl acetate soluble fractions of *M. spicata* leaves shows antihistaminic activity by inhibiting antigen stimulated rat basophile.

***Momordica dioica*:** *Momordica dioica* is climbing creeper plant. Its fruits and leaves are traditionally used as medicinal agent of asthma, leprosy, bronchitis, fever, tridosha. Methanol and aqueous extract of pulp possesses antihistaminic activity by inhibiting clonidine induced catalepsy in mice at dose 50 mg/kg; this activity may be due to polar constituents.

***Mucuna pruriens*:** The L-DOPA isolated from methanol extract of seed possesses antihistaminic activity by inhibiting clonidine induced catalepsy and mast cell degranulation in mice at dose 50, 100 and 200 mg/kg.

***Myrica esculenta* Buch. Ham. (Myricaceae):** *Myrica esculenta* is commonly known as Kaiphal. It is used for treatment of asthma and bronchitis in ayurvedic system of medicine. Patel *et al.* reported antiallergic and anti-inflammatory activity of ethanol extract of aerial parts using acetic acid induced vascular permeability and allergic pleurisy in mice methods at doses 75 and 150 mg/kg. Stem bark of this plant possesses bronchodilator and antianaphylactic activity by inhibiting acetylcholine induced bronchospasm in guinea pigs, egg albumin induced anaphylaxis in guinea pigs at dose 75 mg/kg and by relaxing histamine and acetylcholine induced guinea pig trachea and ileum.

***Nyctanthes arbortristis*:** It is used traditionally in the treatment of asthma. The petroleum ether extract shows antihistaminic activity by inhibiting clonidine-induced catalepsy in mice at dose 50 mg/kg.

***Olea europea* (Oleaceae):** It is a small evergreen tree, from 12 to 20 feet high, with hoary, rigid branches, and a grayish bark. Aqueous extract of ripe olives possesses antiasthmatic activity by inhibiting clonidine induced peritoneal mast cell degranulation in rats and catalepsy in mice at doses 4 and 8 mg/kg and also by protecting histamine induced contraction of goat trachea and guinea pig ileum at concentration of 100 µg/mL.

***Phymatodes scolopendria* (Burm.) Ching (Polypodiaceae):** *Phymatodes scolopendria* is a crawling fern growing in the sandy areas of the East coast of Madagascar. Ramanitrahasimbola *et al.* reported bronchodilator activity of 1, 2-benzopyrone (coumarin) isolated from ethanol extract of aerial parts by inhibiting histamine or carbachol pre-contracted guinea pig trachea.

***Piper betel* Linn:** *Piper betel* is traditionally used to cure cough, cold, pruritis, asthma and rheumatism. Ethanol and aqueous extract of leaves at doses 100 and 200mg/kg possesses

antiasthmatic activity on histamine induced bronchoconstriction in guinea pig and histamine induced dose dependent contraction of guinea pig tracheal chain and isolated guinea pig ileum preparation.

***Striga orobanchioides* Benth (Scrophulariaceae):** *Striga orobanchioides* is a parasitic plant, lives on the roots of various plants. Ethanol and aqueous extracts of whole plant shows antihistaminic and mast cell stabilizing activity by inhibiting histamine-induced contractions of the guinea-pig ileum at the concentration 2.5-25 µg/mL in a dose-related manner and inhibiting degranulation of mast cells at dose 100 and 200 mg/kg.

***Sphaeranthus indicus* Kurz (Asteraceae):** *Sphaeranthus indicus* is a medicinally important plant used as folk medicine. The ethanol extract at the doses of 150, 300 mg/kg and its ethyl acetate extract at the dose of 100, 150 mg/kg and 300 mg/kg showed slightly better protection against sheep serum and Compound 48/80-induced mast cell degranulation than the standard drug ketotifen.

***Cynodon dactylon* (Poaceae):** *Cynodon dactylon* is one of the most commonly occurring perennial grass throughout India, commonly known as Dhub. The petroleum ether, chloroform and methanol extracts of whole plant and fractions isolated from chloroform extract possess antianaphylactic activity but fractions isolated possesses more potent activity at doses 10, 25, 50 and 100 mg/kg using compound 48/80-induced mast cell degranulation, determination of level of nitric acid in serum, compound 48/80-induced anaphylaxis.

Conflict of interest: None

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