CHAPTER

Plant-based drug delivery systems in respiratory diseases

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Meenu Mehta[a,b,c], Parvarish Sharma[a], Simran Kaur[d], Daljeet Singh Dhanjal[d], Bhupender Singh[d], Manish Vyas[a], Gaurav Gupta[e], Dinesh Kumar Chellappan[f], Srinivas Nammi[g], Thakur Gurjeet Singh[h], Kamal Dua[b], and Saurabh Satija[a,b]

[a]*School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India*
[b]*Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Sydney, NSW, Australia*
[c]*Centre for Inflammation, Centenary Institute and University of Technology Sydney, Faculty of Science, Sydney, NSW, Australia*
[d]*School of Bioengineering and Biosciences, Lovely Professional University, Phagwara, Punjab, India*
[e]*School of Pharmacy, Suresh Gyan Vihar University, Jaipur, Rajasthan, India*
[f]*Department of Life Sciences, School of Pharmacy, International Medical University, Kuala Lumpur, Malaysia*
[g]*School of Science and Health, Western Sydney University, Penrith, NSW, Australia*
[h]*Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, India*

1 Introduction

Respiratory diseases like acute respiratory syndrome distress (ARSD), asthma, chronic obstructive pulmonary disease (COPD), and lung cancer have largely influenced the global mortality rate [1, 2]. Billions of people have surrender their lives due to these respiratory diseases. The prevalence of these respiratory diseases are now outgrowing globally, predominantly amid the infants, young children, and the elderly people [3]. Moreover the burden induce by these abnormalities have adversely affected the livelihood of the individuals. It has been predicted that in the coming future, a large number of population will get shredded because of these inflammatory diseases. Several preventive and disease management strategies have been employed in the developing and developed countries to improve the life of the suffering population [4]. Many times, these diseases remain untreated due to the unavailability of vaccination/medications, inability to diagnose, and due to the negligence of the patient and their family members toward the condition. The prime mediators of these inflammatory respiratory diseases are found to be smoking, indoor air pollution, occupational agents, allergens (pollen grains and dust particles), and in some cases diseases like schistosomiasis and sickle cell disease [5, 6].

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Hence, prevention of all these risk factors will have a significant impact on the morbidity and mortality imposed by these diseases. According to the World Health Organization (WHO), it has been estimated that approximately 4.6 million people died in 2005 due to chronic respiratory diseases. And this number has significantly increased to 13.5 million in 2015, equivalent to 10%–15% mortality rate worldwide [7]. Currently available treatments are found to be futile in treating these chronic diseases. In the 1970s nasal administration of corticosteroids was approved for treating these chronic diseases unveil the new option of treatment. In this line of interest, many discoveries took place in the past few decades. Numerous allopathic drugs such as bronchodilators, corticosteroids, mast cell stabilizers, antihistamine, and epinephrine were developed to be used as a therapeutic agent against these respiratory syndromes [8]. But these allopathic medicines led to the development of symptoms like dizziness, dyspepsia, rhinorrhea, tremors, sour throat, and xerostomia. Taking into account these adverse effects, there has been a paradigm shift toward the use of herbal medicine as they are safe and have a limited side effect. Currently, herbal medicine has gained the same attention as of ancient times, all around the world [9–13]. Now, diverse medicinal plants are used to treat and regulate these respiratory infections, and largely these plants belong to Asteraceae (15.7%), Fabaceae (6.1%), Lamiaceae (5.6%), and Amaryllidaceae (4.6%) families [14].

Recently, along with the discovery of various allopathic drugs, numerous new drug delivery approaches have also been developed including targeted and nanoparticle-based drug delivery system (NDDS) [15]. Out of which, NDDS has shown the promising result in treating various fatal diseases by delivering the high concentration of active pharmaceutical ingredient (API) to the target site [16]. Nowadays, researchers are extensively working on extracting new active phytoconstituent from the herbal plant's possessing API against these respiratory ailments [13, 17–19]. Also the incorporation of these active phytoconstituent into nanoparticles is another effective method for enhanced treatment [20]. This book chapter aims to describe the pathophysiology of the major respiratory diseases and highlight the current status of herbal medicines in neutralizing these diseases. Moreover the chapter will embark upon kinds and advantages of the nanocarrier systems used as the drug delivery vehicle.

2 Major respiratory diseases and their global epidemiology

See Fig. 1.

2.1 Acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is a progressive respiratory disorder that occurs mostly in critically ill or immune compromised patients [21, 22]. Various clinical symptoms involved in this disease include aspiration, drowning, inhalation

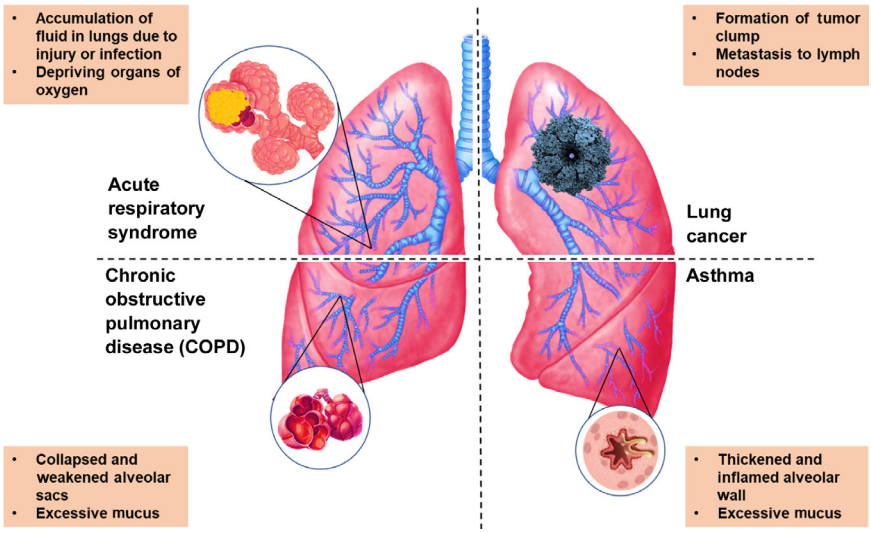

FIG. 1

Schematic representation of different respiratory diseases.

of harmful substances, severe pneumonia, sepsis (infection of the blood), and other reasons (burn, massive blood transfusion, overdose on sedatives or tricyclic antidepressants and pancreatitis). All these conditions eventually leads to various inflammatory reactions [23]. However, in few cases, these inflammatory reactions causes leakage in blood vessels that causes the accumulation of fluid in alveoli or air sacs [24]. The major complication of ARDS is induced by fluid-filled alveoli, which decrease the surface area for gaseous exchange and makes the person breathless. In some cases, this prevailing symptoms leads to organ failure [25]. Additionally, the accumulated fluid in alveoli makes the lungs inflexible and cause problem in breathing. To circumvent this condition, patients are subjected to ventilator to restore the normal functioning of lungs, whereas the patients suffering from this situation for prolonged time develop the scarring or fibrosis in the lungs, known as the fibrotic stage of ARDS [26]. ARDS is common above 65 years old people with chronic lung diseases, liver failure, and consumption of alcohol and smoking. People suffering from ARDS often prescribed with analgesics (to relieve pain), antibiotics (for the treatment of infection), and blood thinner to prevent the thrombus (internal clot) formation inside the legs or lungs. ARDS patients have to deal with all the side effects related to all these medications. According to the American lung association, about 30%–50% of a patient suffering from ARDS deceased every year. There are approximately 200,000 cases regarding ARDS reported in the United States each year. ARDS is a silent killer as many times around 30%–50% cases, it remains undiagnosed by the clinicians/physicians [27].

2.1.1 Asthma

Asthma is a chronic respiratory disorder, mainly caused due to inflammation of airways and results in obstruction of airflow. During its progression, airways of the patient become very sensitive to inhalation of any foreign substances mainly dirt particles, pollen grains, etc. [28, 29]. Because these foreign particles trigger the hypersensitive reaction in mucosa layer and result in overproduction of mucus that further restrict the airways. Thus this allergic sensitivity reaction is the foremost risk factor of asthma. Its symptoms often associated with the breathlessness, chest tightness, coughing, rhinitis, and wheezing [30].

Asthma affects around 300 million people of all ages including children and adults from all ethnic background worldwide. And out of these people about 250,000 die every year due to its chronic disorder [31]. According to reports submitted by the European Community Respiratory Health Survey (ECRHS) and the International Study of Asthma and Allergies in Childhood (ISSAC), trends in the prevalence of asthma have tremendously increased from last 40 years in all around the world [32]. Depending upon the lifestyles and urbanization, there will be an additional 100 million which will attain mortality due to asthma by 2025. The prevalence of asthma is not uniform throughout the world. Mortality due to asthma seems high in those countries that have quite low access to the essential asthma medication along with the unavailability of health care and therapist. The poor people often die of asthma, because they lack money to initiate or continue the medical treatment against this chronic disease [33]. In many countries, recent advancement in the research area of drugs and treatment techniques has reduced the fatality rate of this disease [34]. Various drugs like corticosteroids (oral, inhaled one), β2-agonists (short or long acting), leukotriene receptor antagonist, leukotriene synthesis inhibitors, and muscarinic antagonist (short or long acting) are being used with varied dosage to treat the people suffering from asthma [35].

2.2 Chronic obstructive pulmonary disease

COPD is a heterogeneous disease of lungs exhibiting numerous clinical presentations of chronic bronchitis and emphysema. In chronic bronchitis, bronchial tubes get inflamed, narrow, and lose their cilia and hence causes the overproduction of mucus in lungs [36], while in emphysema alveoli get damaged as the small sacs present in the alveoli wall become larger and decreases its oxygen absorption capacity. Due to which the air gets trapped inside the lungs and makes breathing difficult [37]. Hence, COPD is an incurable progressive disease involving all these clinical manifestations. The topmost cause of COPD is smoking, prolonged and continuous exposure to these chemical irritants [38]. COPD suffering patient shows symptoms like breathlessness, chest tightness, frequent coughing (with or without mucus), and wheezing. All these symptoms are such that COPD can progress for years without even noticed by the patient [39]. Many of these symptoms overlap with asthma symptoms, but they are very different from each other. Asthma is an inflammatory disease caused by an allergic reaction, while COPD is a progressive heterogeneous disorder caused by smoking [40].

COPD is one of the major public health issue and cause of global morbidity and mortality in subjects over the age of 40 years [41]. Also, people with the age group of 20–40 years are also affected by COPD, particularly smokers. According to a report, 12 Asian countries have been considered with high COPD prevalence and involves 56.6 million people with an overall 6.3% prevalence rate. In China, COPD is the second leading cause of death among various chronic respiratory diseases [5]. In the United States, about 24 million adults had COPD in the year of 2002. In 2000 in the United States, there were around 700,000 hospital admissions, and about 1.5 million emergency department visits of COPD suffering people [42]. In India a study reported that 12 million adult community were COPD patients, and many of them don't know about it. From the year 2010–30 the number of COPD patient will increase by 150%, and many of them will be from the aging population [43].

At the early stages of COPD, one may not be familiar with it but when it gets diagnosed then the patient has to approach to a therapist on a daily basis for the proper treatment. Untreated COPD will lead to a number of abnormalities like cardiovascular problems and lung cancer and also a reason for worsening the other respiratory infections [44]. For the treatment of COPD, doctors often prescribe anticholinergics, beta2 agonist, bronchodilators, steroids etc. But these COPD medications usually involves some side effects like fast heartbeat, nervousness, and tremors.

2.3 Lung cancer

Lung cancer also termed as lung carcinoma is a malignant type of tumor involving metastasis, that is, uncontrolled, undesired, and unregulated cell mitosis/growth, and has a tendency to spread to nearby tissue and other parts of the body. It includes symptoms like breathlessness, chest pain (angina), coughing with blood, and weight loss [45, 46]. About 85% of lung cancer cases are related to smokers, and the rest 15% includes nonsmoker. It is often caused by exposure to asbestos, radon gas, and air pollution; sometimes, genetic factors are also contributed to its cause [47].

The lung cancer is broadly classified into two types, that is, SCLC; occurs in small epithelial cells; and contributes approx. 10%–15% of lung carcinoma. First, it arises in one part of the lung nearby the lymph nodes, and then, it aggressively metastasize to many sites within the body. It is mainly caused due to smoking [48]. NSCLC occurs in large parts or cells (nonepithelial cells) of the lung and contributes 85% of lung tumors. NSCLC is differentiated in stages I, II, III, and IV depending on the tumor growth, site of action, and dispersal [49].

Depending upon the type of macrocells, NSCLC is of three types adenocarcinomas (AD), large-cell carcinomas (LC), and squamous cell carcinomas (SQ). Adenocarcinomas (AD) is the most common type and contributes 40%–45% of lung cancer (NSCLC) occurring in outer/peripheral areas of lungs. It also tends to spread across lymph nodes and alveolar walls [50]. During chest X-ray, it may look pneumonia; hence, it is challengeable to be diagnosed at early stages. Large-cell

carcinomas (LC) also called undifferentiated carcinoma and contributed 10%–15% tends to spread to lymph nodes and distant organs. Squamous cell carcinomas (SQ) called epidermoid carcinoma have 10%–15% abundance; it is benign mainly in the chest and in the bronchi. The most common symptoms of this carcinoma are coughing with blood, massive weight loss, breath shortness, and acute chest pain(angina) [51]. Over the past few decades, the prevalence of lung cancer has been exponentially increased at the global scale. According to the report submitted by American Cancer Society (ACS) in the year 2018, lung cancer contributed about 234,030 newly diagnosed cancer cases with 75% deaths among men and women with 80% deaths [52]. Depending upon the age, below the age of 44 years, the cases related to lung cancer are very rare. But beyond 44 years, the age group of 45–65 years, the cases and mortality rate due to lung cancer are enormously high.

3 Herbs used for pulmonary diseases

The rate of these pulmonary diseases has been increasing from decades and often related to the death of billions of people [53]. Mostly, all these pulmonary diseases often lead to acute or chronic inflammatory reactions. Though it is an important cellular response as a defense mechanism, specifically, chronic inflammation causes severe damage to the lungs. And this chronic inflammation involves the activation of eosinophils, lymphocytes, neutrophils, and macrophages that act as a source of numerous inflammatory mediator's like histamine, interleukins (IL-1β, IL-4,5,6), leukotrienes, nitric oxide, prostaglandins, and tumor necrosis factor (TNF-α) [54–56]. The release of these chemical mediators cause airways edema, hyperresponsiveness and obstruction, loss of lung's function, mucus hypersecretion, and remodeling of lungs [57].

The treatment of these chronic respiratory diseases include the use of anti-inflammatory therapies, along with that various allopathic drugs like β_2 agonist, bronchodilators, corticosteroids, and leukotrienes agonist [58], although the drugs mentioned earlier have very potent therapeutic effects against these chronic pulmonary diseases, whether they have been prescribed individually or in a combination [59], But they also have severe side effects that limits their long-term use in the line of defense. Thus it is essential to develop a new chemical compound having the same therapeutic effect, with minimal side effects, and can be used as a long-term treatment measure for chronic pulmonary diseases [60–63]. The traditional herbal medicinal plants and their bioactive natural phytoconstituent are being used as a therapeutic substitute for the treatment procedures [64–68]. The ongoing research have successfully isolated the various chemical compounds that exhibit the effective pharmacological actions toward these chronic syndromes [69]. Moreover, these natural compounds are having the least side effect than the current therapies and treatment methods and thus possess the potential to replace them [70]. Some of these natural product or the main chemical ingredient present in herbal plants are enlisted in Table 1.

Table 1 List of the herbal constituents with their mechanism of action.

Name of constituent	Source	Mechanism of action	References
Albiflorin	*Paeonia lactiflora*	Suppress the production of NO synthase and ROS	[71]
Apigen	Flavonoid	Regulates the IL-6/17A and TNF-α levels	[72]
Asperuloside	*Herba paederiae*	Regulates the TNF-α and IL-1β/6 levels	[73]
Asperulosidic acid	*Morinda citrifolia*	Act as antiinflammatory agent	[74]
Benzoylpaeoniflorin	*Paeonia lactiflora*	Suppress the production of NO synthase and ROS	[71]
Curcumin	*Curcuma longa*	Suppresses the inflammatory reactions	[75]
Deacetylasperulosidic acid	*Morinda citrifolia*	Act as antiinflammatory agent	[74]
D-Glucopyranoside	*Morinda citrifolia*	Act as antiinflammatory agent	[74]
Epicatechin	*Camellia sinensis*	Act as antioxidant and controls the TNF-α release	[76]
Epigallocatechin	*Camellia sinensis*	Act as antioxidant and controls the TNF-α release	[76]
Epicatechin gallate	*Camellia sinensis*	Act as antioxidant and controls the TNF-α release	[76]
Epigallocatechin gallate	*Camellia sinensis*	Act as antioxidant and controls the TNF-α release	[76]
Eugenol	Essential oil derived from many plants	Act as antioxidant and suppresses the COX-2 and NF-κB transcription	[77]
Galloylpaeoniflorin	*Paeonia lactiflora*	Suppress the production of NO synthase and ROS	[71]
Genistin	Soy isoflavanoids	Act as antiinflammatory agent	[78]
Huangqiyiesaponin C	*Astragalus membranaceus*	Suppresses the allergic responses	[79]
Kaempferol	Naturally occurring flavinoid	Reduces pulmonary edema and regulates the MAPK and NF-κB signaling pathways	[80]
Kaempferol-3-*O*-rhamnoside	*Morinda citrifolia*	Regulates the Th2 cytokine levels	[81]
Kaempferol-3-*O*-α-L-rhamnopyranosyl-(1 → 6)-β-D-glucopyranoside	*Morinda citrifolia*	Act as antiinflammatory agent	[74]
Kuwanon G	*Morus alba* L.	Regulate the IgE level	[82]
Lactiflorin	*Paeonia lactiflora*	Suppress the production of NO synthase and ROS	[71]
Luteolin	Flavonoid	Decreases the chances of pulmonary hemorrhage and interstitial edema	[83]

Continued

Table 1 List of the herbal constituents with their mechanism of action—cont'd

Name of constituent	Source	Mechanism of action	References
Naringin	*Citrus grandis*	Maintains the leukocytes and IL-4/5/13 level	[84]
Oxypaeoniflorin, oxybenzoyl-paeoniflorin, paeoniflorin, paeonin, paeonol, paeoniflorigenone, paeonolide	*Paeonia lactiflora*	Suppress the production of NO synthase and ROS	[71]
Picroside C	*Pseudolysimachion rotundum*	Regulates the synthesis of ROS and cytokines like TNF-α and IL-6	[85]
Picroside II	*Picrorhiza scrophulariiflora*	Act as immunomodulatory	[86]
Quercetin-3-*O*-L-rhamnopyranosyl-(1→6)-D-glucopyranoside	*Morinda citrifolia*	Act as antiinflammatory agent	[74]
Quercetin	Flavonoid	Controls the release of cytokines like TNF-α and IL1-α/6	[20]
Resveratrol	Stilbenes (red wine)	Inhibits the growth of cancer cell by senescence of DNA damage	[87, 88]
Rosmarinic acid	*Ocimum gratissimum*	Regulates the overproduction of mucus and IL-4 level	[89]
Sakuranetin	*Baccharis retusa*	Decrease the Th2 cytokines level	[90]
Toluene diisocyanate	*Boerhavia procumbens*	Decrease the number of eosinophils and lymphocytes	[91]
Trimethylquercetin, 3,4-*O*-dimethylquercetin, 3,7,4-*O*-trimethylquercetin	*Siegesbeckia glabrescens*	Controls the overproduction of mucus in airways, regulates the expression of COX-2 and iNOS and also controls the release of IL-4/5/13	[92]
Wogonin	*Scutellariae radix*	Regulates the IgE level	[93]

4 Need of nanodrug delivery systems

The onset of nanotechnology has revolutionized the medical field and has accomplished greater attention. Specifically the application of nanoparticles as nanocarrier for delivery of drug has emerged as growing field [94, 95]. There are various benefits of using the nanosized drug carriers like easy administration, enhanced circulation time of drug, improved drug concentration at targeted site, and regulated drug degradation/lose [96–98]. It is beneficial that nanoparticle usage has allowed the controlled release of drug at the targeted site and more importantly they are in range of 10–200 nm size [99]. This size of nanocarrier is alike to biological molecules like viruses and protein, which allows them to interact with cell surface and the cell [100]. According to properties of nanocarriers, the drugs are entrapped in these nanoparticles via different approaches and retain themselves as per interaction (e.g., electrostatic interaction and covalent bond) with its synthesized material [101–103]. Moreover, every nanoparticle has its affinity to entrapped the particular drug. Furthermore, material used for developing these nanocarriers and amendment of their surface determines the property and drug releasing ability of nanocarriers [104].

5 Different nanodrug delivery systems

The recent development has led to the development of the various novel drug delivery system for targeted drug as shown in Fig. 2. Moreover the most commonly used novel drug delivery system have been discussed in detail in the succeeding text.

5.1 Liposomes

Liposomes are microscopic vesicular structures consisting of concentric phospholipid bilayers enclosing aqueous medium. Such vesicles consist mainly of (synthetic or natural) phospholipids, sterols, and antioxidant [96]. The drug is distributed in the hydrophilic center or in the lipid surface according to its solubility. These carrier systems improves the bioavailability of drugs by delivering the drug to the target site and by improving the pharmacokinetics of drugs [28]. They are biodegradable and more compatible and hence less toxic in nature. Recently, liposomes have been used for pulmonary delivery to treat lung diseases such as pneumonia [105]. Liposomes are an efficient formulation for the treatment of cancer because they can enhance drug entry into cells [106].

Curcumin (main constituent of *Curcuma longa*) is a potential anticancer agent [107], but due to its lipophilic nature and high metabolism, it has very low bioavailability. Many studies reported that nanoliposomes of curcumin prepared by ethanol injection method using sodium hyaluronate and trimethyl CS form polymer-glycerosomes can effectively deliver curcumin to the lung so as to improve its therapeutic index [108, 109]. Zhang et al., in 2018, prepared curcumin liposomes and liposomal curcumin dry powder inhalers (LCDs) for inhalation treatment of primary

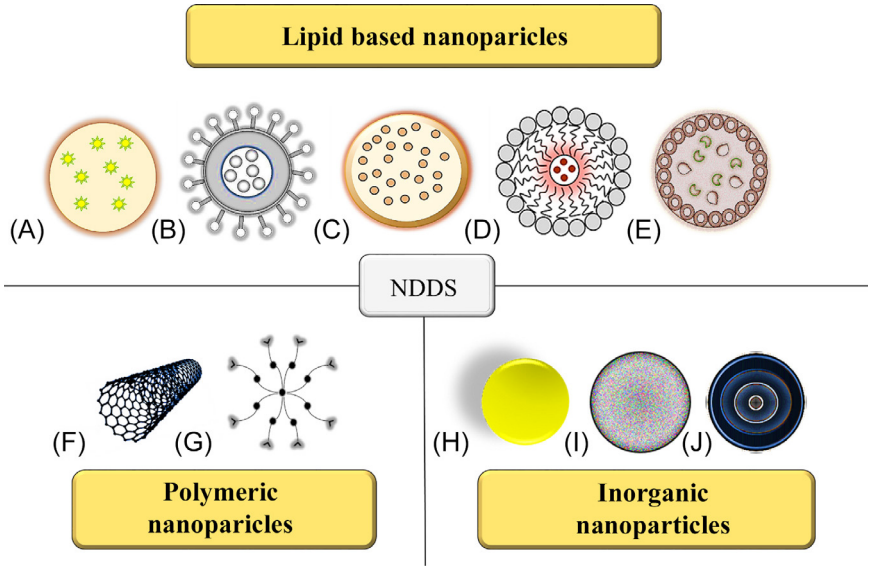

FIG. 2

Systematic representation of the potential NDDS, where (A) nanostructured lipid carrier, (B) liposomes, (C) nanostructured lipid emulsion, (D) lipid micelle, (E) solid lipid nanoparticles, (F) carbon nanotube, (G) dendrimers, (H) gold nanoparticles, (I) iron oxide nanoparticles, and (J) quantum dot.

lung cancer via pulmonary delivery. In this study, curcumin liposomes were delivered through pulmonary route; thereby, metabolism limitations can be bypassed. Moreover, liposomal formulation enhances the curcumin effect by increasing its water solubility hence significantly contribute toward enhanced anticancer effect [110]. Rahman et al. reported that cholesterol-based cationic liposomes were more potent against lung cancer A549 cells than free curcumin. Study also revealed that liposomes were not toxic to the normal cells up to the IC_{50} value of 600 μM [111, 112].

Andrographolide (AG), a diterpenoid isolated from *Andrographis paniculata*, has been used for the treatment of upper respiratory tract infections due to its antioxidant and antiinflammatory properties [113]. AG has low bioavailability due to its lipophilic nature or low water solubility. To overcome these limitations, inhalable liposomal AG dry powder inhalers were prepared for the treatment of bacterial pneumonia. Study showed that they produce 10 times stronger antipneumonic effect by significantly decreasing the level of proinflammatory cytokines including TNF-α and IL-1 than free AG [106]. A recent study reported that liposomal delivery of paclitaxel triggers apoptosis of drug-resistant cancer cell by targeting mitochondria. These liposomes deliver the drug directly to the tumor site, interfere with the mitochondrial function, and facilitate the cell apoptosis [114]. Shahiwala and Mishra reported that liposomal-mediated levonogestrel delivery prolonged the effective concentration of drug in plasma, and pulmonary delivery also reduces the systemic side effects of the drug [115].

5.2 Polymeric nanoparticles

Currently, researchers have focused on nanotechnological processes involving medicinal plants, which have developed a number of modern delivery systems, including polymeric nanoparticles. Polymeric nanoparticles are made from biodegradable and biocompatible polymers that can easily be targeted and hence can be used for controlled drug delivery [116, 117]. Polymeric nanoparticles are colloidal suspensions that monitor the release of drugs, aiming them at specific locations. Polymeric nanoparticles can enhance the solubility of the constituents, decrease the effective dose, and improve drug absorption. These nanoparticles offer several advantages like they are stable, nontoxic, noninflammatory, nonimmunogenic, and target specific tissues [118–120]. The characteristics of particles like size, zeta potential, and drug releases can be adjusted by selecting various polymer lengths, surfactants, and organic solvents during synthesis. Polymeric nanoparticles can be synthesized from natural or artificial polymers. Natural polymers are preferred as they can carry more than one active constituent and can reside in body for longer timings lesser side effects, etc. [119]. They are intensively investigated using various important pulmonary drugs due to their biocompatibility, surface modification ability, and sustainable release properties [34].

Das et al. and his team prepared *Phytolacca decandra* root extract as well as Poly (lactide-*co*-glycolide) encapsulated nanoparticles of *P. decandra* extract. They tested both the extract and nanoparticles on mice and on A549 cells for lung carcinoma. They showed that nanoencapsulation of drug improves drug bioavailability and produced stronger chemopreventive action against lung carcinoma [121]. In another study, methanolic extract of *Ocimum sanctum* has been loaded into polymeric nanoparticles, which shows stronger antimicrobial action against various pathogens such as *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* [122].

Majumdar et al. entrapped luteolin into a polymeric NPs to improve its solubility, bioavailability, and systemic delivery and evaluated the anticancer activity by using H292 lung cancer cells. The results revealed that polymeric NPs has significant anticancer activity against lung cancer cell line in comparison with the free luteolin [122a].

5.3 Solid lipid nanoparticles

Solid lipid nanoparticles composed of the lipid (0.1%–30% w/w) dispersed in the aqueous solution of surfactant (0.5%–5% w/w) as stabilizing agent [123]. The range of mean diameter SLN is between 40 and 1000 nm [124]. SLN prepared with the good quality of excipients provides physical stability and chemical stability for active molecule, controlled release, and enhanced bioavailability of the active molecule and safety [125]. However, SLN is reported having low drug loading capacity and leakage of active molecules in storage [126]. Lipid nanoparticles have many benefits for pulmonary application of the loaded drug. Acceptability of SLN can be ensured in the airways, nontoxic with biodegradable lipids, and homogeneous endogenous

degradation of the products [127]. SLN can be easily encapsulated into particles or aerosolized into droplets with optimum aerodynamical qualities to ensure the delivery of active compound on target site of lung. Furthermore, SLN has quick onset of action due to the nanosized particles compared with large particles [128, 129]. Adhesion, retention, and accumulation of SLN in lungs may lead to sustained and enhanced therapeutic effects to provide patient satisfaction and long dosing interval. Hence, SLN can play a vital role in the treatment of diseases associated with the respiratory system and targeted drug delivery.

In China, Yuxingcao injection is a most prescribed Chinese Traditional Medicine that is used for pneumonia, pulmonary and renal infections, malignant pleural effusion, and refractory hemoptysis. It is an aqueous distillate of *Herba Houttuyniae* (Yuxingcao in Chinese). However, these injections were banned by the government due to the adverse drug reactions associated with its administration. Therefore, to reduce ADRs of the injection, SLNs of three different particles sizes loaded with Yuxingcao essential oil were prepared for its sustained delivery in lungs by high-shear homogenization technique. In vitro release study revealed enhanced sustained release of drug up to 48 h. Intratracheal administration of SLN to rats prolonged the pulmonary retention up to 24 h and also increased AUC values in comparison with Yuxingcao injection. Hence, SLNs may provide sustain inhalation delivery and enhanced bioavailability. It can also be a promising inhalable carrier for the single-dose application [130].

Curcumin is reported to have significant antiinflammatory activity. However, its poor bioavailability and fast metabolization limited its use as an effective medicine. Therefore solid lipid nanoparticles loaded with curcumin SLNs were prepared and evaluated its therapeutic efficacy by using ovalbumin (OVA)-induced allergic rat model. SLN is prepared by using solvent injection method. The release profile of SLNs suggested sustained release of curcumin after initial burst. Pharmacological activity suggested that SLN significantly inhibiting the expression of T-helper cytokines (interleukin-4 and interleukin-13) in bronchoalveolar lavage fluid compared [131].

Ferulic acid is phenolic in nature used as a phytonutrient reported to have good anticancer activity. Merlina et al. prepared PLGA NPs of ferulic acid (FA) to improve its bioavailability at the target site and evaluated against NCI-H460, nonsmall cell lung carcinoma cell lines for its anticancer activity. The results of the in vitro study revealed that nanoparticles have better anticancer effect in comparison to the free ferulic acid [132].

Camptothecin, quinoline-based alkaloid, is effective against the variety of cancer cells because it inhibits the topoisomerase-I. However, chemical stability and poor stability are the major challenges to establish it as a potent chemotherapeutic agent. Therefore, Castillo et al. prepared PEG-coated and non-PEG-coated camptothecin encapsulated iron oxide superparamagnetic NP by using iron coprecipitation method and evaluated against H460 lung cancer cell line for its anticancer activity. However, no significant variation was observed between camptothecin encapsulated PEG-coated and non-PEG-coated NPs. However, NP enhanced the anticancer activity of camptothecin in comparison to the free camptothecin [133].

Verma et al. developed aerosol of magnetic core-shell nanoparticles encapsulated with quercetin and evaluated for antiproliferative activity against the A549 lung cancer cells. Furthermore the surface of the magnetic core-shell nanoparticles was coated by using PLGA to improve the dispersion of quercetin in the aqueous media, to enhance the stability against oxidation, and to ensure biocompatibility of the nanoparticles. The biocompatibility of prepared nanoparticles was evaluated by applying in vitro and in vivo studies. The results showed significant antiproliferative activity of magnetic core-shell nanoparticles loaded with quercetin against the A549 cells [134].

6 Future prospects

The advancement in the field of nanotechnology and development of NDDS incorporated with herbal therapeutic agents have emerged as valuable system [135]. This enhances the biological activity and circumvent the challenges associated with herbal medicines. However, challenge remains the same, which is the implementation of this technology in clinical therapies [136]. Clinical trials to evaluate the interaction of these nanosized system with biological activity of our body presents the current problems and highlights the challenge of translating this technology into therapies [137]. The major challenges associated with this NDDS involves the scaling-up of these therapeutic techniques to market level for its commercialization and developing of multifunctional system that can act on different biological system and meet the therapeutic requirements [138]. Few additional challenges includes the probing of nanoparticles to improve their targeting efficiency and meet the requirements of international standards related to their biocompatibility and toxicity [139, 140].

7 Conclusion

Over the years, herbal medicines have gained the attention of both doctors and patients for its therapeutic value and very few side effects in comparison with modern medicines. For targeted and effective treatment, herbal drugs can be developed in modern dosage form and enhance their efficiency in upright direction. Along with this, scientists are looking for different ways to render the components of herbal medicine to reduce the repetitive administration of phototherapeutic drugs and increase its compliance among the patients. Novel drug delivery system has emerged as the viable solution for delivering herbal ingredients. Application of NDDS not only reduces the repetitive administration of drug and overcome noncompliance but also improves the bioavailability, solubility, and permeability and reduces the toxic effect of these therapeutic agent. Lately, scientists working pharmaceutical industries have taken the paradigm shift toward designing novel drug delivery system for herbal drugs via scientific approaches. These efforts will enable the researchers to gain the interest of remaining market. Still many challenges are associated with herbal drugs

which require solutions such as conducting of clinical trials of these herbal drugs, improvement of biological assays for standardization, development of toxicological assay, determining of animal models for safety and toxicity assessment, reviewing of the absorption site and toxicity of herbal drug, and lastly the regulatory aspects of these herbal drugs. Therefore development of the novel drug delivery system incorporated with herbal drugs has a great potential and valuable impact in the society, Moreover, this approach can also implement at industrial scale.

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