

14

Respiratory Conditions

Adolfo Andrade-Cetto¹ and Jorge García-Alvarez²

Department of Cell Biology, School of Sciences, National Autonomous University of Mexico, Mexico

14.1 Introduction

14.1.1 The respiratory system

Breathing is one of the essential functions of living beings, in which gas exchange is necessary to obtain energy and maintain active metabolism in all tissues. The respiratory system consists of very specialized structures, including the nasal cavity, pharynx, larynx, trachea, bronchi, bronchioles and lungs, and facilitates the passage of oxygen from the air into the body, where it is then captured by the bloodstream. Erythrocytes are essential components of the blood that capture, transport and distribute oxygen from the lungs to the body's cells. Subsequently, these cells capture carbon dioxide to remove it from the body via a process that is essentially the reverse of oxygen uptake.

In the lung, the alveolar epithelium is the respiratory unit and is characterized by two types of cell: type I pneumocytes and type II pneumocytes. Type I pneumocytes are flat cells with a nucleus protruding into the alveolar surface, whereas type II pneumocytes have rounded edges and surface microvilli and secrete surfactant liquid, a phospholipid layer that coats the alveoli. The alveolar epithelium represents the interphase between the oxygen introduced from outside and the blood capillaries. This respiration unit is therefore a very thin, rapidly permeable and widely vascularized diffusion barrier, and this structural organization allows gas exchange through diffusion between the blood and air containing oxygen (Petechuk, 2004).

14.1.2 Respiratory diseases

Similar to other systems, the respiratory system requires a delicate balance to maintain homeostasis, and the environment largely determines the proper functioning of such systems. When maintenance functions are carried to the limit, control mechanisms are overwhelmed and disease ensues, which can adversely affect an individual's quality of life and ultimately

a nation's economy. The World Health Organization (WHO, 2014) has classified respiratory diseases into groups. This classification is the international standard used to classify mortality and morbidity, and the impact on the public health and social security strategies of most countries. The groups are:

- A. Diseases affecting the upper respiratory tract (nasal cavity, pharynx, larynx, etc.) due to microorganisms.
- B. Diseases affecting the lower respiratory tract (bronchi, bronchioles), further divided into those that are caused by microorganisms and caused by external agents (e.g. cigarette smoke).
- C. Conditions in the alveoli caused by chronic particles that may be present on a daily basis or acute inhalation of a toxin/irritating substance.
- D. Diseases that alter the structure of the alveoli, preventing gas exchange.

The diseases include the following:

- A. Acute upper respiratory tract infections: colds, sinusitis, pharyngitis, tonsillitis, tracheitis and epiglottitis.
Influenzas and pneumonia: H1N1 influenza, viral pneumonia and pneumonia caused by bacteria such as *Haemophilus influenzae*.
Other diseases of the upper respiratory tract: allergic rhinitis, chronic rhinitis, chronic sinusitis and chronic laryngitis tonsillitis.
Infections of the upper respiratory tract: acute bacterial rhino sinusitis.
- B. Acute lower respiratory infections: acute bronchitis and acute bronchiolitis.
Lower respiratory tract chronic diseases: bronchitis, emphysema, chronic obstructive pulmonary disease (COPD) and asthma.
- C. Lung diseases caused by external agents: pneumoconiosis caused by inhalation of organic and inorganic particles such as silica, asbestos, actinomycetes and fungal spores.
- D. Other respiratory diseases principally affecting the interstitium: pulmonary edema, pulmonary eosinophilia and idiopathic pulmonary fibrosis.
Suppurative and necrotic conditions of the lower respiratory tract: gangrene and necrosis of lung abscesses with and without pneumonia.
Other pleural diseases: pleural plaque pneumothorax.
Other diseases of the respiratory system: acute and chronic respiratory failure, apnea and lung collapse.

14.1.3 Common cold

The common cold is an infectious disease caused by rhinovirus and adenovirus, which causes an inflammatory reaction in the nasal passage. It mainly affects the nose and throat, causing discomfort. The most common feature is the persistent nasal discharge with sneezing, which can last for several days; infection usually resolves without treatment. In children it is more common and increases in periods of cold, cough and nasal congestion gets worse at night and nasal discharge may last for more than three days. It is very difficult to differentiate bacterial infections. The most notable difference is that viral infection improves spontaneously in 7 to 12 days, and nasal discharge is watery and clear (although it may change over time). For bacterial infections, nasal discharge is usually thicker, purulent and mucoid (Grief, 2013).

14.1.4 Influenza

Influenza is a debilitating disease caused by viruses that infect the upper respiratory tract (nose, throat, bronchi and lungs). The infection is often accompanied by fever, headache, runny nose, nasal congestion, joint pain and muscular pain, although these symptoms may vary according to age. Influenza viruses are spherical, with a coat consisting mainly of hemagglutinin, and have a diameter of 80–120 nm. The main types of influenza viruses are influenza A, B and C. Influenza A viruses are usually transmitted between birds and mammals, and can cause death. Influenza B viruses are found only in humans, while the C viruses are not very common, but can also cause disease. Type A viruses are classified depending on two coat proteins, hemagglutinin and neuraminidase, which are present in varying amounts (Gopinath *et al.*, 2014).

14.1.5 Acute lower respiratory tract infections: acute bronchitis

Acute bronchitis is caused by inflammation of the bronchial tree and affects both adults and children without chronic lung disease. These infections are caused by agents that circulate in the environment on a seasonal basis and are also responsible for causing respiratory infections of the upper airway, including rhinovirus, coronavirus and adenovirus. Acute bronchitis is characterized by the presence of acute cough, which worsens as the disease progresses. The pulmonary secretions (sputum) in bronchitis cases are purulent but do not necessarily indicate bacterial infection. Fever may also be present (Wenzel and Fowler, 2006).

14.1.6 Other diseases of the upper respiratory tract: allergic rhinitis and rhinitis

Allergic rhinitis is an inflammatory disorder of the nasal mucosa induced by a reaction mediated by immunoglobulin E (IgE) in subjects sensitized by an allergen. This condition is characterized by sneezing, runny nose, nasal congestion and nasal itching, and is usually accompanied by redness, watering and itchy eyes. These symptoms can lead to physical and mental complications, including sleep disorders and bad breath, in children and adolescents, which may result in inefficient performance in daily activities. In some cases, allergic rhinitis is associated with asthma (Schatz, 2007).

Rhinitis mainly affects the nose and throat, although it can spread to the larynx. The most common feature of rhinitis is a persistent nasal discharge or cough (or both), which lasts more than 10 days. In children, nasal congestion and cough worsen at night, and nasal discharge may last for more than 3 days. It is very difficult to distinguish bacterial from viral rhinitis, although the most notable difference is that viral rhinitis improves spontaneously within 7 to 12 days, and the nasal discharge is watery and clear (but may change over time). In contrast, bacterial rhinitis is associated with nasal discharge that is usually thicker, purulent and mucoid (Wald *et al.*, 1981; Meltzer *et al.*, 2006).

14.1.7 Chronic lower respiratory tract diseases: COPD

COPD is a preventable and treatable disease with significant extrapulmonary effects. This disease is characterized by a typically progressive chronic airflow limitation associated with

an abnormal inflammatory response to the inhalation of toxic particles or gases. Patients with COPD may develop emphysema, chronic bronchitis, bronchiolitis and cardiovascular disorders with hypertension. COPD is associated with high morbidity and mortality rates, and the main risk factor for this disease is inhaling cigarette smoke as a result of tobacco addiction (smoking). The pathologic progress of COPD is mainly measured by airflow obstruction, showing a decreased expiratory volume. The damage is progressive and irreversible, and is associated with an abnormal inflammatory response followed by destruction of the lung parenchyma (Markewitz *et al.*, 1999; Thorley and Tetley, 2007).

14.1.8 Lung diseases caused by external agents: hypersensitivity pneumonitis

Hypersensitivity pneumonitis, also known as extrinsic allergic alveolitis, is a disease caused by an exaggerated inflammatory immune response in the bronchioles and lung alveoli to inhaled antigen particles present in the environment. A wide variety of antigens have been described, but the most common are organic particles such as fungi, bacteria, animal proteins and chemical compounds of lower molecular weight that function as haptens and bind to albumin to create an antigenic particle. Hypersensitivity pneumonitis is subdivided into acute and chronic hypersensitivity pneumonitis. The acute phase is characterized by fever, chills, sweating, headache and nausea. These symptoms last for a few hours and may be accompanied by coughing and dyspnea (shortness of breath when performing daily activities). If these problems persist, cough and dyspnea become more severe over the course of days or weeks after exposure. When the disease becomes chronic, the symptoms described above are accompanied by fatigue and weight loss (Selman, 2004).

14.1.9 Other respiratory diseases principally affecting the interstitium: idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis is a chronic and lethal disease. As its name suggests, this disease is of unknown etiology and primarily affects older adults between 50 and 70 years of age. In most patients, disease progression is slow and the median survival is estimated at 2 to 5 years after diagnosis. In addition, this disease currently has no cure. Clinical manifestations are often characterized by progressive dyspnea, accompanied by cough and lung volume reduction with subsequent deterioration of gas exchange. These alterations are due to damage to the alveolar epithelium and lead to abnormal connective tissue remodelling. This phenomenon is the result of fibroblast proliferation, which leads to the loss of gas exchange between the alveolar epithelium and blood capillaries (Selman *et al.*, 2001).

14.1.10 Suppurative and necrotic lower respiratory tract conditions: pneumonia with necrosis

Pneumonia with necrosis is a rare complication of lung infections caused by bacterial agents, such as *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae* and *Klebsiella pneumoniae*, or fungi such as *Aspergillus*. In these infections, necrotic foci form in localized areas and may be accompanied by other complications such as pulmonary abscess and gangrene, in which the lung tissue is destroyed. During this disease, thrombosis occurs in

larger blood vessels and plays a role in pathogenesis. Patients with these complications show symptoms that often accompany infection, such as dyspnea, cough commonly accompanied with fluids, fever, chest pain and loss of consciousness. Risk factors include advanced age with habits of alcoholism, smoking, diabetes mellitus, chronic lung disease or liver disease. However, appropriate use of broad-spectrum antibiotics can result in successful treatment. In more severe cases with gangrene, surgical procedures may be required (Penner *et al.*, 1994; Norte *et al.*, 2012).

14.1.11 Other pleural diseases: pleural plaque

Pleural plaques are dense and fibrotic lesions that occur in the parietal pleura, which is the tissue lining the lungs that enables their extension. These lesions are detected by thorax X-ray or computed tomography (CT) scan, and their size varies from a few millimetres to a centimetre. These plaques are very common in people who were exposed to asbestos or silica but have also been observed in unexposed individuals. Pathologically, the lesions are mainly composed of avascular and acellular collagen fibres, with only a few fibroblasts present between the fibres. These lesions limit the extension of the lung during the breathing process, and this disease is therefore characterized by breathlessness. This symptom may also be accompanied by coughing and tightness in the chest (Clarke *et al.*, 2006).

14.1.12 Other diseases of the respiratory system: acute respiratory failure

Acute respiratory failure can develop rapidly, within minutes to hours, and is more common in infants than adults. Respiratory failure can have various causes, and most of the fatalities are observed in developing countries. Malnutrition in children under 5 years of age is a major risk factor for this condition, as these children are likely to develop chronic fatigue and subsequent respiratory failure. Another risk factor is severe chronic anemia, which prevents the efficient transport of oxygen (Balfour-Lynn *et al.*, 2014).

Traditional plant-based medicines have long been used to treat respiratory conditions, mainly for the relief of associated symptoms such as cough, sneezing or rhinitis. They have a number of pharmacological actions relevant to treat diseases of both the upper and lower respiratory tract, including asthma, sinusitis, rhinitis and others. In addition to their traditional use, phytomedicines and even isolated compounds from plants play an important role in treating respiratory conditions and as supportive measures in more serious diseases such as: bronchitis, emphysema and pneumonia (Heinrich *et al.*, 2012). They are now sold in many pharmacies worldwide.

Ethnopharmacological research in countries where people mainly depend on traditional medicine for the treatment of respiratory diseases provides an excellent strategy to discover new plant species or new compounds to treat respiratory conditions, as exemplified by the species discussed in the following sections.

14.2 Case studies

Medicinal plants are used worldwide to treat respiratory conditions, and some useful natural products used to treat respiratory problems, such as codeine or ephedrine, are now included in manufactured products. Indeed, the modern literature provides several examples of how plants

serve both as important components of traditional medicines and new phytotherapeutic agents found in over-the-counter medications.

Many plant preparations have been studied clinically but have not been developed as phytomedicines. In a review of clinical trials of phytomedicines used in otorhinolaryngology and pulmonology, currently under development as potential novel medications, Ghazi-Moghadam *et al.* (2012) reported that species such as *Lycopersicon esculentum* Miller yielded a bioactive naringenin chalcone shown to inhibit the release of histamine from mast cells during the initial phase of inflammation. In addition, this plant compound decreased the level of eosinophils and eosinophil cationic proteins in patients with mild to moderate perennial allergic rhinitis. A herbal tablet formulated with *Cinnamomum zeylanicum* Nees, *Malpighia glabra* L. and *Bidens pilosa* L. was shown to significantly reduce nasal symptoms and inhibit the release of prostaglandin D2 in patients with allergic rhinitis. In Japan, *Rubus chingii* var. *suavissimus* (S. K. Lee) L. T. Lu is used for the treatment of allergic rhinitis, and a randomized, double-blind, placebo-controlled study reported that this plant improved patients' nasal symptoms. *Nigella sativa* L., a plant used in Middle Eastern and Mediterranean regions, has been reported to have anti-inflammatory and anti-allergic effects, which are mediated by changes in the phagocytosis and killing activity of polymorphonuclear leucocytes, leukotriene synthesis and inhibition of histamine release. In particular, patients treated with its fatty oil for 30 days showed significant improvements of nasal signs and symptoms. Furthermore, this plant was shown to function as a histamine antagonist and inhibitor of the histamine receptor; a placebo-controlled trial reported that treatment of asthmatic patients with an extract of this plant for 3 months improved symptoms and pulmonary function tests. The extracts of *Pelargonium sidoides* DC from Southern Africa also are used widely in the treatment of respiratory tract infections, acute rhino sinusitis and bronchitis, and are now a well-established element in European phytotherapy with licensed products widely available. The antimicrobial and anti-inflammatory activity of this botanical drug is based on inducing the release of tumor necrosis factor (TNF)- α and increased activity of natural killer (NK) cells. Following a therapeutic dose of 30 drops three times per day for at least 7 days, patients show significant improvements in the symptoms of common cold and acute bronchitis. The leaves of *Eucalyptus globulus* Labill are reported to possess antibacterial activity against oral bacteria, and extracts in chewing gum have been shown to significantly inhibit plaque formation, inflammation and bleeding of the gingiva. The main active principle is the monoterpene cineol. *Andrographis paniculata* (Burm. f.) Ness. (Acanthaceae) is an important medicinal plant widely used in Chinese traditional medicines and mentioned in ancient scriptures of Ayurveda. The prevention and treatment of uncomplicated upper respiratory tract infections in adults and children stand out because there is considerable clinical evidence to back up such uses (Joseph, 2014), extracts of the plant present a consistent inhibitory effect on the secretion of influenza virus, regulated on expressed and secreted activation of normal T cells (Wang and Liu, 2014).

The following section covers brief but more detailed examples of species that have already been developed into phytomedicines.

14.2.1 *Althaea officinalis* L. Malvaceae

Medicinal plants with antitussive effects and a broad-spectrum effect function to reduce coughing through demulcent action, by removing the irritation (expectorant) or by depressing the cough reflex.

The medicinal use of *Althaea officinalis* (marshmallow root) has been documented in Europe since Roman times. It is traditionally used as a demulcent and emollient to treat irritation of the

oral and pharyngeal mucosa and associated dry cough (European Medicines Agency, 2009). In the Middle Ages the species was prescribed by Lonicerus and Matthiolus as an expectorant and diuretic. Today the roots are collected in the autumn from plants not less than 2 years old.

The demulcent effects of *A. officinalis* are due to its high content of polysaccharide hydrocolloids, which form a protective coating on the oral and pharyngeal mucosa to soothe local irritation and inflammation (Shah *et al.*, 2011). This botanical drug is also indicated for the treatment of acute or chronic bronchitis and dry cough. Specifically, a formulation is used as a gargle to treat inflammation of the mucous membranes of the mouth and throat. Ten to 15 g of the root are mixed with 150 ml of cold water and stirred for 90 minutes prior to application.

The root extract and the isolated polysaccharide were tested at oral doses of 50–100 mg/kg body weight for treatment of cough induced by mechanical stimulation, and the results were compared with those obtained for *Althaea* syrup (1000 mg/kg), prenoxidiazine (30 mg/kg), dropropizine (100 mg/kg) and codeine (10 mg/kg). Both the extract and isolated polysaccharide significantly reduced the intensity and the number of cough efforts from the laryngopharyngeal and tracheobronchial areas. Polysaccharides from this plant also exhibited statistically significant cough-suppressing activity, which was noticeably higher than that of the control drug. In particular, the greatest antitussive activity was observed with the polysaccharide containing the highest proportion of the uronic acid constituent (Al-Snafi, 2013).

Mucilage polysaccharides contain 5–11% mucilage and consist of a mixture of colloiddally soluble polysaccharides, particularly acid arabinogalactans, rhamnans, arabans, glucans and acidic heteropolysaccharides, including D-galactose, L-rhamnose, D-glucuronic acid and D-galacturonic acid (European Medicines Agency, 2009).

14.2.2 Codeine and noscapine

These compounds occur naturally in opium (*Papaver somniferum* L.) and are clearly derived from local and traditional knowledge but are currently produced using a semi-synthetic process. In particular, 3-methylmorphine is used for its antitussive properties. This drug is on the WHO's list of essential medicines. Codeine sulfate causes respiratory depression, in part by a direct effect on the brainstem respiratory centres. It depresses the cough reflex through direct effects on the cough centre in the medulla. Noscapine is a benzyl isoquinoline alkaloid also isolated from opium. It is used for its cough-suppressing effects, and the agonist is the σ -receptor (Kamei, 1996).

14.2.3 *Echinacea purpurea* (L.) Moench and *Echinacea angustifolia* DC.

These species are mentioned in the European Pharmacopoeia as a support treatment for flu-like infections and recurrent infections of the upper respiratory tract. It is known that these plant extracts activate the immune system and anti-inflammatory reactions through the up-regulation of TNF- α . In one double-blind study that included 100 patients with acute flu-like infections, patients received 30 ml of an *Echinacea* preparation or placebo and after 2 days the dose was reduced to 15 ml/day. Eight cold symptoms (lethargy, limb pain, headache, rhinitis, cough, sore throat and pharyngeal redness) were rated for severity using a semi-quantitative scoring system (WHO, 1999c).

In a double-dummy controlled trial, the effects of a combined *Echinacea* and sage spray were compared to a chlorhexidine/lidocaine combination for the treatment of sore throat, and 60%

of patients in each group became symptom-free after 3 days with no significant difference between these two combinations (Ghazi-Moghadam *et al.*, 2012). The main compounds present in *E. purpurea* are chicoric acid, caffeic acid and two immuno-stimulatory polysaccharides (PSI and PSII). PSI was identified as 4-O-methyl glucurono-arabinoxylan (composed mainly of glucuronic acid and the sugars arabinose and xylose), while PSII was shown to be an acidic arabino rhamnogalactan (mainly composed of the sugars arabinose, rhamnose and galactose). In a meta-analysis from 2006 the authors concluded that the standardized extracts of Echinaceae were effective in the prevention of the symptoms of the common cold after clinical inoculation (Rhinovirus). In a review of randomized controlled trials Linde *et al.* (2009) found that the available Echinacea products differ greatly in terms of chemical composition and plant part used, and that the majority of these products have not been tested in clinical trials. They therefore suggested that alcoholic and pressed juice preparations that are based primarily on the aerial parts of *E. purpurea* might have the best evidence base and have beneficial effects on cold symptoms in adults if treatment is started early.

14.2.4 *Ephedra sinica* Stapf. (Ephedraceae)

Medicinal plants with antitarrhal effects are used to reduce excessive discharge from mucous membranes. These plant medicines are particularly useful for nasal and sinus congestion and mucosal edema, and they can also reduce airway hypersensitivity.

For over 5000 years the Chinese have used ephedra medicinally. It is listed as one of the original 365 medicinal plants from the classical 1st century AD text on Chinese herbalism by Shen Nong. Chinese traditional medicinal uses include the alleviation of sweating, lung and bronchial constriction, water retention, coughing, shortness of breath, common cold and fevers without sweat (WHO, 1999a). ESCOP recommend the plant to treat nasal congestion due to hay fever, allergic rhinitis, acute coryza, common cold and sinusitis.

The main active constituents of ephedra, including ephedrine and pseudoephedrine, are potent bronchodilators and sympathomimetic drugs that stimulate α -, β 1- and β 2- adrenoceptors to relax the bronchial muscles. Ephedrine, like other sympathomimetics with α -receptor activity, causes vasoconstriction and blanching when applied topically to nasal and pharyngeal mucosal surfaces. In addition, the continued prolonged use of these preparations (3 days) may cause rebound congestion and chronic rhinitis. Part of ephedrine's peripheral mechanism of action is related to the release of norepinephrine, with rapidly repeated doses being less effective owing to the depletion of norepinephrine stores. Ephedrine is also a potent stimulator of the CNS, and the effects of this drug may last for several hours after oral administration. Furthermore, the use of this botanical drug can produce side effects such as nervousness, tremor, sleeplessness, loss of appetite and nausea. The plant has a risk of abuse, and for this reason products sold as over-the-counter herbal medicines or dietary supplements are now banned in most countries (WHO, 1999a).

A recent study (Yen *et al.*, 2014) evaluated the traditional medicine Yakammaoto, which for more than 2000 years has been used to treat flu-like symptoms in China and Japan. This preparation containing nine ingredients, including *Ephedra sinica*, was evaluated for its effects on coxsackie virus B4 (CVB4), which causes flu-like symptoms and life-threatening diseases such as pneumonia. These authors concluded that Yakammaoto showed antiviral activity against CVB4-induced cellular injuries in the airway mucosa, preventing viral attachment, internalization and replication.

14.2.5 *Thymus vulgaris* L. (Lamiaceae)

Antitussive drugs are used to control coughing, particularly in patients with a dry, nagging, unproductive cough.

Thymus vulgaris is indigenous to southern and Central Europe, although it is currently a pan-European species that is cultivated in Europe, America and other parts of the world. The plant has been used traditionally to treat coughs due to colds, bronchitis, laryngitis and tonsillitis. The leaves and flowers are indicated for the treatment of irritable and whooping cough, catarrh of the upper respiratory tract, bronchial catarrh, the supportive treatment for tussis, and for mouthwashes and gargles used to lessen inflammation of the mouth (WHO, 1999b).

The principal components of this plant (including chemo varieties) are thymol and carvacrol (up to 64% of the oil), along with linalool, p-cymol, cymene, thymene, α -pinene, apigenin, luteolin, 6-hydroxyluteolin glycosides and di-, tri- and tetra-methoxylated flavones (WHO, 1999b). Its expectorant properties, which function via a bronchospasmolytic effect, have been demonstrated in animal and *in vitro* experiments and were attributed to the compounds thymonin, cirsilineol and 8-methoxycirsilineol. An extract containing 0.072% thymol was also shown to antagonize contractions of isolated guinea pig trachea. Furthermore, extracts of this plant showed activity against *Mycobacterium tuberculosis* strain H37Rv, *Klebsiella pneumoniae* and *Diplococcus pneumoniae*. In clinical studies, *T. vulgaris* also showed activity against non-productive cough resulting from uncomplicated respiratory infections. In particular, 93.5% of 154 children treated with 15–30 ml of syrup containing 97.6 mg of thyme fluid extract showed improved cough intensity in cases presenting bronchial catarrh (ES COP, 2003).

14.3 Conclusions

Respiratory conditions have been treated with medicinal plants since ancient times and there are many examples of plants that are effective in treating the main symptoms of catarrh, cough, sneezing, etc. Since these conditions can be recognized easily by traditional healers, medicinal plants have been commonly used for their treatment. For cases in which the origin of the disease cannot be recognized (by healers), as in a respiratory viral infection, the traditional medicine seldom targets the virus itself but rather treats the symptoms, which is often sufficient to achieve patient recovery. In more serious diseases, such as pulmonary fibrosis, emphysema or influenza, traditional medicine has a more limited action, but it can still play an important role as supportive treatment.

A variety of natural products are used to treat respiratory ailments, including saponins, chalcones, monoterpenes, phenolic compounds and alkaloids. In particular, the alkaloids codeine, noscapine and ephedrine are used in many prescriptions, although a specific pharmacological action has not yet been correlated to a certain class of compound.

It is important to note how traditional medicines used for centuries in Europe are currently being developed as phytomedicines. Moreover, traditional preparations that are still used in the Americas (Mesoamerica and Brazil as examples), China, India and Africa can provide new medicinal plants for the treatment of respiratory conditions. As an example; in many lesser developed countries a major concern is tuberculosis, and there are quite a few R&D activities focusing on medicinal plants for such conditions. Thus new ethnopharmacological studies can lead us to find new species to target this bacterial infection.

Traditional medicines have provided us with phytomedicines and natural products for the treatment of respiratory ailments. For this reason ethnopharmacological field studies in countries where traditional medicine still plays an important role could lead us to discover new therapeutic agents that can be developed in a more global way as new phyto-medicines or isolated compounds.

Acknowledgments

Thanks to Dr Prof. Michael Heinrich for his help in editing the manuscript. This work was partially supported by grants from DGAPA, PAPIIT (project IN214413) and CONACyT CB-0151264.

References

- Al-Snafi, A. E. (2013) The pharmaceutical importance of *Althaea officinalis* and *Althaea rosea*: A review. *International Journal of PharmTech Research*, **5**, 1378–1385.
- Balfour-Lynn, R.E., Marsh, G., Gorayi, D., *et al.* (2014) Non-invasive ventilation for children with acute respiratory failure in the developing world: literature review and an implementation example. *Pediatric Respiratory Reviews*, **15**, 181–187.
- Clarke, C.C., Mowat, F.S., Kelsh, M.A. and Roberts, M.A. (2006) Pleural plaques: a review of diagnostic issues and possible non asbestos factors. *Archives of Environmental and Occupational Health*, **61**, 183–192.
- ESCOP (2003) *Monographs*. Thieme, Norfolk, 556 pp.
- European Medicines Agency (2009) *Evaluation of Medicines for Human Use. Assessment report on Althaea officinalis L. Radix*, document reference MEA/HMPC/98718/2008, London.
- Ghazi-Moghadam, K., Inançli, H.M., Bazazy, N., *et al.* (2012) Phytomedicine in otorhinolaryngology and pulmonology: Clinical trials with herbal remedies. *Pharmaceuticals*, **5**, 853–874.
- Gopinath, S.C., Tang, T.H., Chen, Y., *et al.* (2014) Sensing strategies for influenza surveillance. *Biosensors and Bioelectronics*, **61C**, 357–369.
- Grief, S.N. (2013) Upper respiratory infections. *Primary Care Clinics in Office Practice*, **40**, 757–770.
- Heinrich, M., Barnes, J., Gibbons, S. and Williamson, E. (2012) *Fundamentals of Pharmacognosy and Phytotherapy*, Elsevier-Churchill Livingstone, p. 336.
- Joseph, S.M. (2014). Scientific aspects of the therapeutic use of *Andrographis paniculata* (Kalmegh): A review. *International Journal of Pharmaceutical Sciences Review and Research*, **27**, 10–16.
- Kamei, J. (1996) Role of opioidergic and serotonergic mechanisms in cough and antitussives. *Pulmonary Pharmacology*, **9**, 349–356.
- Linde, K., Barrett, B., Bauer, R., *et al.* (2009) *Echinacea for preventing and treating the common cold (Review)*, The Cochrane Collaboration, Wiley & Sons, p. 104.
- Markewitz, B.A., Owens, M.W. and Payne, D.K. (1999) The pathogenesis of chronic obstructive pulmonary disease. *American Journal of the Medical Sciences*, **318**, 74–78.
- Meltzer, E.O., Hamilos, D.L., Hadley, J.A., *et al.* (2006) Rhinosinusitis: developing guidance for clinical trials. *Otolaryngology Head and Neck Surgery*, **135**, S31–S80.
- Norte, A., Santos, A., Gamboa, F., *et al.* (2012) Necrotizing pneumonia: a rare complication. *Acta Medica Portuguesa*, **25**, 51–55.
- Penner, C., Maycher, B. and Long, R. (1994) Pulmonary gangrene, a complication of bacterial pneumonia. *Chest*, **105**, 567–573.
- Petechuk, D. (2004) *The Respiratory System*, Greenwood Press, Westport, p. 240.
- Schatz, M.A. (2007) A survey of the burden of allergic rhinitis in the USA. *Allergy*, **62** (Suppl. 85), 9–16.
- Selman, M. (2004) Hypersensitivity pneumonitis: a multifaceted deceiving disorder. *Clinical Chest Medicine*, **25**, 531–547.

- Selman, M., King, T.E. and Pardo, A. (2001) Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. *Annals of Internal Medicine*, **134**, 136–151.
- Shah, S.M., Akhtar, N., Akram, M., *et al.* (2011) Pharmacological activity of *Althaea officinalis* L. *Journal of Medicinal Plant Research*, **5**, 5662–5666.
- Thorley, A.J. and Tetley, T.D. (2007) Pulmonary epithelium, cigarette smoke and chronic obstructive pulmonary disease. *International Journal of Chronic Obstructive Pulmonary Disease*, **2**, 409–428.
- Wald, E.R., Milmoie, G.J., Bowen, A.D., *et al.* (1981) Acute maxillary sinusitis in children. *New England Journal of Medicine*, **304**, 749–754.
- Wang, X.G. and Liu, Z.J. (2014) Prevention and treatment of viral respiratory infections by traditional Chinese herbs (Review). *Chinese Medical Journal*, **127**, 344–1350.
- Wenzel, R.P. and Fowler, A.A. (2006) Clinical practice. *Acute bronchitis*. *New England Journal of Medicine*, **355**, 2125–2130.
- WHO (1999a) *Monographs on Selected Medicinal Plants. Herba Ephedrae*, World Health Organization, Geneva/Malta, pp. 145–153.
- WHO (1999b) *Monographs on Selected Medicinal Plants. Herba Thymi*, World Health Organization, Geneva/Malta, 259–266.
- WHO (1999c) *Monographs on Selected Medicinal Plants. Herba Echinaceae purpureae*, World Health Organization, Geneva/Malta, 136–144.
- WHO (2014) *International Classification of Diseases (ICD-10)*, available from <http://www.who.int/classifications/icd/en/>.
- Yen, M.H., Lee, J.J., Yeh, C.F. *et al.* (2014) Yakammaoto inhibited human coxsackievirus B4 (CVB4)-induced airway and renal tubular injuries by preventing viral attachment, internalization, and replication. *Journal of Ethnopharmacology*, **151**, 1056–1063.