International Journal of Innovative Research and Reviews, 6(1) 51-58

International Journal of Innovative Research and Reviews
ISSN: 2636-8919
Website: www.injirr.com
doi:
Research paper, Short communication, Review, Technical paper

REVIEW ARTICLE

Drugs and Natural Products Used in COPD

Ahmet KARAL[1,*] Hülya ÇELİK[1]

[1] *Ağrı İbrahim Çecen University, Faculty of Pharmacy Ağrı, Turkiye*
[2] *Ağrı İbrahim Çecen University, Faculty of Pharmacy Department of Pharmaceutical Technology Ağrı, Turkiye*

** Corresponding author E-mail: hycelik@agri.edu.tr*

HIGHLIGHTS

> Studies on drugs and natural products used in the treatment of COPD are presented.
> Studies aimed to guide future studies on drugs and natural products used in the treatment of COPD were reviewed.
> While this review study declares the success of the studies examined, it also sets a precedent for future studies.

ARTICLE INFO

Received : 11.18.2021
Accepted : 03.26.2022
Published : 07.15.2022

Keywords:
COPD
COPD drugs
Natural products

ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD), with its most general definition, is a disease represent by the formation of inflammation in the air-ways due to harmful particles and bronchoconstriction and irreversible enlargement and destruction of the lung sacs. Factors causing COPD include inhalation of tobacco or tobacco-like substances, environmental exposures, genetic factors, chemicals and air pollution. The drugs used in the treatment of COPD aim to reduce the breathing of patients, acute exacerbations and inflammation. While bronchodilator drugs, which are among the drugs used in treatment, prevent constriction, anti-inflammatory drugs act by reducing inflammation. It is also used in natural products such as ginger, mint and eucalyptus in the treatment of COPD. New methods are being improved for the treatment of COPD with the researches and studies conducted in recent years. In addition, new drugs are tried in treatment. More effective methods and drugs continue to be discovered for the treatment of COPD. Early diagnosis is of great importance in the treatment of COPD. Despite these, there is no cure for COPD.

Contents

1. Introduction 52
2. COPD 52
2.1. Drugs Used in the Treatment of COPD 52
2.2. Bronchodilator Drugs 52
2.3. Beta-2 agonist Drugs 52
2.4. Anticholinergics 53
2.5. Methylxanthines 54
2.6. Anti-inflammatory Drugs 54
2.7. Corticosteroids 55
2.8. Phosphodiesterase-4 Inhibitors 55
2.9. Antibiotics 55
2.10. Sputum Extractors (Mucolytics) 56
3. Natural Products Used in COPD Treatment 56
4. Conclusion 56
Acknowledgment 56
References 57

Cite this article Karal A, Çelik H. Drugs and Natural Products Used in COPD. *International Journal of Innovative Research and Reviews (INJIRR)* (2022) 6(1) 51-58
Link to this article: http://www.injirr.com/article/view/88

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a lung disease. The word chronic is used to denote the prolonged duration of this disease, while the word obstructive is used to denote obstruction of the bronchi. The result is a disease with the inflammatory response of the lungs to certain gases and particles. In-formed and irreversible disease can be obtained and some of the symptoms are treatable [1].

This disease, which threatens millions of people around the world, is an important cause of mortality and morbidity. COPD has a significant share in the health expenditures of countries, and at the same time, it has a negative effect by reducing the workforce of countries. According to 2010 data, COPD disease is 384 million worldwide and the global prevalence of this disease has been determined to be 11.7%. One out of every 4-5 people in the world population over the age of forty has COPD. According to the data of the World Health Organization (WHO), approximately 3 million people die each year from this disease. More than 90% of deaths due to COPD are experienced in developing countries [2].

Although COPD is a disease that cannot be completely eliminated, palliative treatment is possible. COPD patients should not use tobacco and products containing tobacco, and should not be in environments where these products are used. There are some applications to control COPD. quitting tobacco and products containing tobacco, reducing environmental or air pollution, and avoiding chemicals. Purpose of COPD treatment; To reduce the symptoms of the disease, to prevent the progression of the disease, to make exercise a part of daily life, to increase the quality of life of the patient, to prevent other disease-related health problems and COPD attack [3].

Examples of bronchodilators which is include certain drugs used in the treatment of chronic obstructive pulmonary disease; beta-2 agonists, anticholinergics and methylxanthines, as anti-inflammatory; antibiotics, mucolytics, phosphodiesterase-4 inhibitors, corticosteroids, inhaled aerosols and dry powder inhalers, as well as natural products; Eucalyptus oil, peppermint and ginger can be given [4].

2. COPD

COPD is characterized by the occurrence of irreversible enlargement and damage in the air sacs in the lung, while the airways narrow with the formation of an inflammatory response due to harmful gases and particles in the respiratory tract, which usually progresses [5].

Although smoking has been shown to be the most important cause of COPD, there are other factors that can cause or advance COPD, including genetic risk and environmental exposures. COPD can be caused by excessive exposure to certain dusts, chemicals, and indoor or outdoor air pollution in the workplace. Some people who smoke do not develop COPD. Some people who do not smoke can develop COPD; this suggests that genetic factors play a role in who develops and does not develop COPD [6].

2.1. Drugs Used in the Treatment of COPD

For the treatment of COPD in smokers, it is necessary to quit smoking first. Medications may also be given to pre-vent flare-ups that cause COPD symptoms. Some general classes of medication include dilating the airways (bronchodilators), reducing swelling in the airways (steroids), or treating infections (antibiotics). In some people, COPD can also cause low oxygen levels in the blood. If this occurs, oxygen therapy can be given to the person [6]. Early detection of COPD and keeping it away from its factors is the most effective treatment in the disease. These drugs are also necessary to improve the quality of life and reduce the progression of the disease [7].

2.2. Bronchodilator Drugs

Bronchodilators are drugs that reduce respiration by relaxing the smooth muscles in the airways and make breathing easier by widening the airways. They are drugs that are often used to treat long-term conditions where the airways can narrow and become inflamed. These drugs are bronchial asthma, allergic diseases associated bronchospasm in use is available [8].

2.3. Beta-2 agonist Drugs

The effect of beta-2 agonists is to relax airway smooth muscle by stimulating beta-2 adrenergic receptors that increase cAMP and produce functional antagonism against bronchoconstriction. There are short-acting and long-acting beta-2 agonists. Short-acting agonists show their effect in 4 to 6 hours, while long-acting agonists show their effect in 12 hours [9].

Salbutamol: It is a short-acting, selective beta-2 adrenergic receptor agonist used in COPD disease. Anticholinergic drugs such as Ipratropium; It can be used in a powerful combination with corticosteroids such as fluticasone. It is 29 times more selective for beta-2 receptors than beta-1 receptors and provides higher specificity for pulmonary beta receptors compared to beta-1 adrenergic receptors found in the heart. Hypersensitivity to salbutamol; Hyper-sensitivity to milk proteins, intravenous salbutamol or salbutamol tablets should not be used for the prevention of preterm labor pains that are not complicated by conditions such as placenta previa, ante-partum hemorrhage or pregnancy toxemia [10]. Salbutamol is used for acute attacks of bronchospasm caused by chronic bronchitis and obstructive pulmonary disease (COPD), bronchial asthma, chronic bronchopulmonary diseases [11].

Fenoterol: It is a short-acting sympathomimetic agent with bronchodilator activity used in COPD disease. It can be used in combination with ipratropium. It activates the enzyme adenylate cyclase that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cAMP) by stimulating beta-2-adrenergic receptors in the lungs. Increased cAMP concentrations re-lax bronchial smooth muscle, relieve bronchospasms and reduce the release of inflammatory cell mediators, especially from mast cells. Chest pain, dizziness, dry mouth, tiredness, flu-like symptoms, headache, high or low blood pressure, high blood sugar level, insomnia, muscle cramps, nausea, irritability, rapid heartbeat, seizures, due to fenoterol use shivering is one of the side effects that can be seen [12].

Levalbuterol: Levalbuterol is a short-acting sympathomimetic beta-2 adrenergic receptor agonist with bronchodila-tor activity in COPD. It binds to beta-2 adrenergic receptors in bronchial smooth muscle and activates intracellular adenyl cyclase, an enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cAMP). Increased cAMP levels lead to activation of protein kinase A, which causes relaxation of bronchial smooth muscle, which reduces intracellular ionic calcium concentrations and inhibits myosin phosphorylation. Increased cAMP concentrations also inhibit the release of inflammatory mediators, particularly from mast cells. Nervousness, dizziness, tremor, sleep problems, headache, nausea, hypertension, dry mouth, increased cough, or runny nose may occur [13, 14].

Terbutalin: It is an ethanolamine derivative with a selective beta2-adrenergic binding bronchodilation and tocolytic action. It leads to intracellular activation of adenyl cyclase and subsequent increase in cyclic AMP (cAMP) production via a trimeric G protein. Increased levels of cAMP inhibit the relaxation of bronchial and vascular smooth muscle mediated by the activation of protein kinase A, which phosphorylates proteins in the control of muscle tone, and causes inhibition of the release of immediate hypersensitivity mediators from cells, particularly mast cells. cAMP also helps to relax the airway muscles by stopping the release of calcium ions from the intracellular stores, reducing the calcium entry into the cells. Terbutaline increases mu-cociliary clearance by decreasing the release of inflammatory cell mediators [15, 16].

Formoterol: It is a long-acting beta-adrenergic receptor agonist with bronchodilator activity locally in the lungs used in COPD disease. Anticholinergic drugs such as aclidinium, glycopyrronium; It can be used in combination with corticosteroids such as budezonide, beclamethasone and mometasone. It selectively binds to beta-2 adrenergic receptors in bronchial smooth muscle, thereby stimulating intracellular adenyl cyclase, an enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cAMP). Increased cAMP levels in bronchial smooth muscle tissue relaxes bronchial smooth muscle, relieves bronchospasms, improves mucociliary clearance, and opens airways by reducing the release of mediators from inflammatory cells, especially from mast cells [17, 18].

Arformoterol: It is a long beta-2 adrenergic agonist and the active enantiomer of formoterol with bronchodilator activity is inhaled effectively as a sympathomimetic and bronchodilator in chronic obstructive cases. Arformoterol is selectively compatible and able to activate beta-2 adrenergic receptors in bronchiolar smooth muscle, preferentially and activates adenosine triphosphate, causes adenine cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate to ATP s-3', 5'-adenosine monophosphate (monophosphate). Increased intracellular cAMP levels cause smooth muscle and inflammation mediators from mast. This finally heals the breaths arformoterol [19, 20].

Indacaterol: It is a new bronchodilator drug used in COPD disease. It is available in combination with glycopyrronium. It stimulates adrenergic beta-2 receptors in the smooth muscles of the respiratory tract. By causing the muscles to relax, it expands the airways that narrow in COPD. It has a long-lasting effect, because it has high affinity for lipid re-lease sites in the respiratory tract and is slow to separate from receptors. It acts very quickly due to its high intrinsic activity. Its pharmacological effects catalyze the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cAMP), resulting in stimulation of adenyl cyclase, and increased cyclic AMP levels cause relaxation of bronchial smooth muscle. The most common side effect with indacaterol use is cough [21, 22].

Olodaterol: It is a new long-acting beta2-adrenergic agonist that acts by binding and activating beta2-adrenergic receptors in the lungs. It is used in combination with tiotropium. Beta2-adrenergic receptors mediate smooth muscle relaxation and bronchodilation through downstream L-type calcium channel interaction. Activation of the receptor activates adenylate cyclase, stimulating the G protein that catalyzes the formation of cAMP and protein kinase A. The increase of the two molecules causes bronchodilation by relaxation of airway smooth muscles. Bronchodilators help relieve symptoms such as coughing, shortness of breath, and sputum production. Indicated for use in chronic bronchitis, emphysema and chronic obstructive pulmonary disease. Despite similarities in symptoms, olodaterol is not indicated for the treatment of acute COPD exacerbations or for the treatment of asthma [23, 24].

Salmeterol: It is a selective, long-acting beta-2 adrenergic agonist with bronchodilator activity. The long, lipophilic side chain of salmeterol binds to the exoside near the beta-2 adrenergic receptors. The binding in the exoside allows it to bind and dissociate continuously with the receptor, thus providing a long duration of action. This agent stimulates intracellular adenyl cyclase to catalyze the conversion of adenosine triphosphate to cyclic-3',5'-adenosine monop-hosphate. Increased cAMP levels cause relaxation of bronchiolar smooth muscle, bronchodilation, and increased bronchial respiration. Salmeterol is a long-acting beta-2 adrenergic receptor agonist drug for the treatment of asthma and the chronic obstructive pulmonary disease COPD. It is indicated for the prevention of bronchospasm and maintenance of airflow obstruction and the prevention of exacerbations of chronic obstructive pulmonary disease. Salmeterol was first described in the literature in 1988. The structure of salmeterol is similar to that of salbutamols with an aralkyloxy-alkyl substituent on the amine [25].

2.4. Anticholinergics

Anticholinergic agents are bronchodilators used in the treatment of obstructive airway diseases such as chronic obstructive pulmonary disease (COPD). By blocking muscarinic receptors in airway smooth muscle they work. By discovering different muscarinic receptor subtypes, it is possible to develop more selective anticholinergics. In clinical use, Ipratropium bromide, oxitropium bromide and tiotropium bromide are very poorly absorbed when administered by inhalation. All of these active ingredients with a wide therapeutic range are safe and well tolerated by patients. Side effects are generally mild and, as characteristic of all anticholinergic inhalations, include dry mouth and

occasional coughing. Clinical inhaled anticholinergic agents are used for the routine treatment of stable COPD and acute exacerbations [26, 27].

Ipratropium bromide: Ipratropium is a synthetic derivative of anticholinergic atropine. It is administered by inhalation, which produces a local effect. Fenoterol and salbutamol can be used in combination. Ipratropium antagonizes the effects of the muscarinic acetylcholine receptor on parasympathetic, postganglionic, effector-cell junctions. This effect causes inhibition of the parasympathetic nervous system in the airways and inhibits its function. The function of the parasympathetic system in the airway is to create bronchial secretions and bronchoconstriction, and there-fore, blocking this effect may lead to an increase in the diameter of the airways and less secretion. Indicated as a bronchodilator in the treatment of chronic bronchitis, emphysema and chronic obstructive pulmonary disease [28–30].

Oxitropium bromide: It is an anticholinergic substance that acts as a bronchodilator in the treatment of asthma and chronic obstructive pulmonary disease [31]. Oxitropium bromide is a quaternary derivative of scopolamine. The bronchodilating effect of oxitropium is similar to that of ipratropium bromide, but oxitropium has a longer duration. Parasympathetically antagonizes the muscarinic acetylcholine receptor. It prevents the airway narrowing and bronchial secretions of the parasympathetic system [32].

Aclidinium bromide: Acetylcholine is a synthetic anticholinergic drug that binds to muscarinic receptors long-acting, competitively and reversibly. It is available in combination with formoterol. Its effects on the respiratory tract cause bronchodilation via the M3 receptor in smooth muscle. It prevents the bronchoconstriction effects caused by acetylcholine. It is indicated for the long-term treatment of chronic bronchitis, aclidinium bromide, emphysema, and chronic obstructive pulmonary disease bronchospasm. Side effects include blurred vision, dry eyes and mouth, constipation, decreased sweating, urinary retention, tachycardia, impotence, palpitations, restlessness and anxiety [33, 34].

Glycopyrronium bromide: It is an anticholinergic, synthetic with quaternary ammonium structure, which binds competitively to the muscarinic acetylcholine receptor. Concomitant use of formoterol and indacaterol is available in combination. It acts like other antimuscarinic agents, inhibiting the action of acetylcholine on smooth muscle. These peripheral cholinergic receptors are located in autonomic effector cells of smooth muscle, cardiac muscle, atrioventricular node, sinoatrial node, exocrine glands. Thus, it reduces the volume and free acidity of gastric secretions and controls excessive tracheal, pharyngeal and bronchial secretions. It has been approved by the FDA for use as a standalone treatment for chronic obstructive pulmonary disease [35].

Tiotropium bromide: It is a long-acting, antimuscarinic bronchodilator used in the treatment of chronic obstructive pulmonary disease (COPD) and asthma, a quaternary ammonium derivative of atropine. It is used in combination with Olodaterol. Tiotropium acts as an antagonist to M3 muscarinic receptors in the respiratory tract and acts as a bronchodilator by preventing mucus secretion in order to show smooth muscle relaxation and bronchodilation activity [36, 37].

Umeclidinium: It is a long-acting cholinergic antagonist that can be used for symptoms of chronic obstructive pulmonary disease (COPD). It is available as a once-daily in-halation monotherapy or as a fixed-dose combination pro-duct with the long-acting beta2-agonist vilanterol. Umeclidinium has similar affinity to subtypes of M1 to M5 muscarinic receptors. By blocking the highly unloaded M3 muscarinic receptor in the airway smooth muscles of the lungs, it prevents the binding of acetylcholine, thus preventing constrictions and opening the airways. Continuous use clinically has demonstrated significant improvements in lung function [38].

2.5. Methylxanthines

They have been used in chronic obstructive pulmonary diseases for a long time. With the participation of β2-agonist and anticholinergic drugs in the treatment, it has started to be used less. Their mechanism of action has not been fully determined even today; It is suggested that they are effective by mechanisms such as phosphodiacterase inhibition, antagonizing the adenosine receptor, increasing adrenaline secretion, and inhibiting inflammatory mediator and intracellular calcium release. Important side effects of methylxanthines are nausea, vomiting, headache, restlessness, gastro-esophageal reflux, diuresis, arrhythmia, and epileptic attacks [39, 40].

Theophylline: Xanthine, a natural alkaloid derivative; It is obtained from *Coffea Arabicave* and *Camellia sinensis* plants. After theophylline enters the body, it increases the anti-inflammatory effects of glucocorticoids in COPD as a phosphodiesterase inhibitor, adenosine receptor blocker and histone deacetylase activator. It antagonizes adenosine by regulating the intracellular distribution and flow of calcium. Physiologically, it relaxes bronchial smooth muscles and causes bronchodilation. It is used orally. It is used to treat bronchospasm in COPD and asthma diseases [41].

Aminophilin: It is a derivative of methylxanthine and theophylline. It is a combination of drugs containing aminophilin, theophylline and ethylenediamine. Aminophylline relaxes smooth muscles, especially bronchial muscles. It increases the levels of second messenger cAMP or cGMP in the cell by inhibiting cAMP or cGMP phosphodiesterases. Like other theophyllines, it is indicated for the treatment of lung diseases such as chronic bronchitis, aminophylline asthma and COPD [42].

2.6. Anti-inflammatory Drugs

The general name of substances that reduce inflammation and edema is anti-inflammatory [43]. Inflammation is the hallmark of chronic obstructive pulmonary disease (COPD), an increased or abnormal inflammatory immune response resulting from environmental stressors such as smoking, alcohol, stress, allergies, insomnia, extreme physical fatigue, and food sensitivities. Therefore, suppression of the inflammatory response is the right approach to the treatment of COPD. The anti-inflammatory treatments currently available provide little or no benefit to people with COPD and can have harmful effects. Recently, it has largely focused on the inhibition of recruitment and activation of

inflammatory cells and the antagonism of their products. There are many anti-inflammatory approaches to the treatment of COPD. The first approach is phosphodiesterase inhibitors, which provide additional clinical benefit as a single agent or as adjunctive therapy to long-acting bronchodilators. The second approach includes new strategies using drugs such as statins and macrolides. A third potential app-roach involves novel agents whose mechanisms of action are closely related to the mechanisms and pathophysiology of COPD [44, 45].

2.7. Corticosteroids

It helps to reduce the number of exacerbations and improve the quality of life in chronic obstructive pulmonary disease. It is recommended to be used in severe and very severe chronic obstructive pulmonary disease to prevent chronic inflammation in its pathogenesis. Corticosteroids improve lung function and hypoxemia and shorten recovery time, reducing the risk of relapse, treatment failure, and hospital stay [40, 46].

Beclometasone dipropionate: Beclomethasone dipropionate is a synthetic glucocorticoid dipropionate ester with anti-inflammatory and immunomodulatory properties. It is rapidly activated by hydrolysis of an active monoester 17 monopropionate (17-BMP), which is a corticosteroid prod-rug and mediates anti-inflammatory effects. Beclomethasone dipropionate is used as an inflammatory for a variety of ailments such as COPD, asthma, dermatoses, and allergic rhinitis. In the treatment of COPD, beclamethasone dipropionate is used as a triple dose combination of formoterol fumarate and glycopyrronium bromide [47].

Fluticasone: A synthetic glucocorticoid available in the form of Fluticasone furoate and Fluticasone propionate. These drugs can be used as inhalers for various prophylaxis, as well as for the treatment of inflammatory and itchy dermatoses and asthma. Fluticasone, which has anti-inflammatory, anti-allergic and antipruritic effects, is a synthetic trifluorinated glucocorticoid receptor agonist. It activates lipocort by binding to the receptor. It triggers a series of reactions by taking part in the synthesis of inflammatory mediators such as lipocortin, leukotrienes and prostaglandins, and inhibits cytosolic phospholipase A2, stopping the transcription of cyclooxygenase 2, which is necessary for prostaglandin production. It is used in combination with a fluticasone and salmetarol or combined with tiotropium and fluticasone to prevent COPD exacerbations in high-risk COPD patients [48, 49].

Budesonide: A glucocorticoid that reduces COPD exacerbations, is indicated in the prophylaxis of asthma, and treats inflammatory conditions of the lungs and intestines such as Crohn's disease and ulcerative colitis. Budesonide provides inhibition and restriction of neutrophil apoptosis; they inhibit phospholipase A2; They inhibit NF-Kappa B and inflammatory transcription factors; Anti-inflammatory genes such as interleukin-10 provide support. Budesonide and Formoterol are used alone or in combination with other drugs in the treatment of asthma and COPD [50, 51].

Prednisolone: It works to treat chronic obsessive pulmonary disease as well as respiratory disorders and other diseases and reduce inflammation. Although its exact mechanism of action is unknown, its use helps to relax and heal the airways, making it more resistant to bronchospasms. It also protects or increases receptors for inhaled bronchodilators [52].

2.8. Phosphodiesterase-4 Inhibitors

Phosphodiesterase-4 (PDE4) inhibitors are anti-inflammatory agents used in the treatment of COPD. The main effect of PDE4 inhibitors is to reduce inflammation by inhibiting the breakdown of intracellular cyclic AMP. PDE4 inhibitors have more side effects than inhaled medications for COPD. The most common side effects are diarrhea, loss of appetite, nausea, abdominal pain, sleep disturbance, weight loss, and headache [53].

Roflumilast: The phosphodiesterase-4 (PDE-4) inhibitor in lung cells PDE4 roflumilast is very effective in the treatment of chronic obstructive pulmonary disease (COPD) exacerbations Chronic bronchitis reduces moderate to severe exacerbations in patients with very severe COPD treated with systemic corticosteroids. The beneficial effects of roflumilast in patients with a history of hospitalization for an acute exacerbation are substantial [54, 55].

Cilomilast: It is a drug developed for the treatment of chronic obstructive pulmonary disease (COPD) and asthma, which are respiratory diseases. It is used orally by acting as a selective Phosphodiesterase-4 inhibitor. The drug has proven effective in treating COPD, but is not used due to its poor side effect profile [56].

2.9. Antibiotics

Antibiotics are very important drugs used in the treatment and prevention of bacterial infections. The Latin word antibiotic means "against life" [57]. The most common causes of exacerbations of Chronic Obstructive Pulmonary Disease are tracheobronchial infections (bacterial, viral and atypical bacteria) and air pollution. The most common bacteria that cause exacerbations are *H. Influenza*, S. Pneumoniae, *M. Catarrhalis*. Bacterial infections are prevented and increases in exacerbations are prevented with sensitive antibiotics [58].

Tetracycline: It is an antibiotic that can be used orally in acute exacerbations of COPD, especially infections caused by *M. Catarrhalis*. However, it develops resistance against being used in severe patients with minimal respiratory re-serve. Although tetracyclines are effective against M. catarrhalis and *H. Influenzae*, they are less effective against penicillin-resistant S. Pneumonia [59].

Chloramphenicol: It is a highly effective antibiotic in COPD exacerbations. It prevents exacerbations to a great extent, especially in patients with severe exacerbations. It is highly effective against the main pathogen *H. Influenzae*. Concentration in bronchial secretions exceeds 50% of concurrent serum concentrations. As it is known, there is a rare bone marrow toxicity [60].

Macrolide antibiotics: Erythromycin is not used in acute exacerbations of COPD due to its low activity against *H. influenzae*. Roksithromycin, azithromycin and clarithromycin have high pharmacokinetic and antibacterial

activity. Azithromycin is the most cultivated macrolide antibiotic against *H. Influenzae*. Its advantages are that it is app-lied once a day and it increases compliance with three days of administration, and decreases the frequency of recurrence in long follow-ups. Clarithromycin has only moderate activity against *H. Influenzae* [59].

2.10. Sputum Extractors (Mucolytics)

In normal people, about 100 ml of mucus is produced per day. The mucus layer that covers the windpipes protects the lungs from particles and microorganisms in the breathing air. Mucus secretion is carried down the throat and swallowed with saliva. Mucus secretion production increases abnormally due to different reasons. Excessive amount of mucus blocking the respiratory tract is thrown out with cough in the form of sputum. If breakthrough does not occur, there will be difficulties in breathing. Patients with COPD may sometimes find it difficult to expel sputum. Difficulty removing sputum causes exhausting coughs and shortness of breath. In this case, mucolytics that facilitate sputum production can be used. Mucolytics can soften and liquefy dark sputum, thereby facilitating their removal from the lungs by coughing [3].

Erdosteine: Erdosteine regulates the production of mucus in the respiratory tract and increases mucociliary transport while regulating its viscosity and increasing the amount of sputum. Erdosteine inhibits the effects of free radicals from cigarette smoke. It is safe and well tolerated in patients with chronic obstructive pulmonary disease (COPD). Erdosteine and amoxicillin are administered together in chronic obstructive pulmonary patients with acute infective exacerbation [61].

N-acetylcysteine: It is a mucolytic and antioxidant class drug that can affect lung function, airway clearance and inflammatory pathway in the treatment of COPD. Sulfhydryl groups may, for reduced glutathione precursors and acts directly as scavengers of reactive oxygen species, which regulate the redox state in the cells and affects the way that control inflammation. As a mucolytic drug, it helps to reduce dyspnea and improve lung function by clearing the bronchi by reducing the viscosity of sputum [62].

3. Natural Products Used in COPD Treatment

Eucalyptus oil: Obtained from the eucalyptus tree. Eucalyptol, which is the major active ingredient, is naturally produced as cyclic ether and monoterpenoid. Eucalyptol is a mouthwash and antitussive ingredient. It is indicated in airway mucus hypersecretion, asthma and COPD through anti-inflammatory cytokine inhibition. Eucalyptol reduces inflammation and pain when applied topically. It helps to relieve congestion and expel phlegm in chronic obstructive pulmonary disease [63, 64].

Ginger: Derived from the *Zingiber officinale* plant. It helps the body to express air by helping break down mucus in COPD and asthma. It also improves circulation in the lungs and reduces inflammation [65].

Thyme: It is obtained from the Thymus vulgaris plant. Oregano essential oil contains poplarrol, which has antimicrobial properties. It is useful in the treatment of respiratory tract infections that are disturbing for COPD patients. It helps reduce inflammation in the bronchial mucous membranes and helps clear the bronchial passages of mucus [66].

Mint: It is a herbal natural product with Latin "Mentha Piperita". The peppermint plant contains the active ingredient menthol and provides relaxation in the respiratory muscles of menthol. In COPD patients, an expectorant, helping to clear excess mucus from the lungs, making it easier to breathe [67].

Panax ginseng: There are studies showing that the use of P. ginseng reduces inflammation and shortness of breath in the lungs, reduces the number of attacks and the time of attacks in COPD patients. Only antibiotics were given to 37 of 75 patients with chronic bronchitis, while the other 38 patients received antibiotics and 100 mg Panax Ginseng extract. In addition, it was observed that the group using Panax Ginseng recovered faster and more effectively [68].

Reishi Mushroom (Ganoderma Lucidum): This mushroom, also called the immortality mushroom, has been used in Far Eastern medicine for centuries. It increases immunity and contributes to the body's self-renewal. Reishi Mushroom has been used in COPD patients because of its acceleration of the healing of infections and its protective properties against infections [69].

Echinacea: Used in large amounts in upper respiratory tract infections, Echinacea is an intense vitamin C store. Not only against bacteria, but also against influenza, cold, COPD, etc. It is known to be very effective in diseases [70].

4. Conclusion

In this study, we discussed the drugs and natural products used in the treatment of COPD. We examined the mechanisms by which drugs affect the disease in chronic obstructive pulmonary disease. Bronchodilator drugs used in the disease act on receptors and facilitate breathing by preventing narrowing of the airway. Anti-inflammatory drugs make breathing more comfortable by preventing inflammation in the respiratory tract.

Since COPD is not a completely preventable disease, drug therapies and supportive herbal natural products are used to prevent the disease from progressing to worse outcomes altogether. Drugs are sometimes used in combination to increase their effects, and sometimes they are used alone. Nowadays, new methods are tried to be developed to obtain more effective and specific drugs.

New drugs have been developed in recent studies. In addition, new techniques and treatment methods are being tried. COPD prophylaxis and early diagnosis are of great importance for COPD. Frequent exacerbations of advanced COPD disease greatly increase mortality rates. Treating the disease early reduces the mortality rate. Despite these, it is a disease that cannot be treated completely. There is no specific treatment for COPD yet.

Acknowledgment

This study was prepared from Ahmet Karal's Research Project Thesis.

References

[1] Kalender E. *KOAH Hastalarina Eczaci Tarafindan İlaç Eğitimi Verilmesinin Klinik Parametrelere ve Yaşam Kalitesine Etkisinin Değerlendirilmesi [Evaluation of the Effect of Drug Education by Pharmacists on Clinical Parameters and Quality of Life in COPD Patients]*. Master Thesis. Ankara University. Ankara (2013).

[2] Mapp CE, Boschetto P, Maestrelli P, Fabbri LM. Occupational Asthma. *Am. J. Respir. Crit. Care Med* (2005) **172**(3):280–305. doi:10.1164/rccm.200311-1575SO.

[3] *KOAH Nasıl Tedavi Edilir? [How to Cure COPD?]* (2022). Available from: https://www.koahhastalaridernegi.org/.

[4] Arseven O, Öngen G, Müsellim B, Okumuş G. *Türkiye'de Temel Akciğer Sağlığı Sorunları ve Çözüm Önerileri [Basic Lung Health Problems in Turkey and Solution Suggestions]* (2010).

[5] Vestbo J. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease GOLD executive summary. *Am. J. Respir. Crit. Care Med* (2013) **187**(4):347–365. doi:10.1164/rccm.201204-0596PP.

[6] Günay S, Sariaydin M, Demırcı N. KOAH tedavisinde yeni bronkodilatörler ve kombinasyonları [New bronchodilators and their combinations in the treatment of COPD]. *Tuberk. Toraks* (2016) **64**(3):240–245. doi:10.5578/tt.10267.

[7] Tekin E, Bayraktar M, Sanalp Menekşe T, Bayramoğlu A. Treatment Management in Acute Exacerbation of COPD in the Emergency Department: Dilemma in Oxygen Therapy. *International Journal of Innovative Research and Reviews* (2020) **4**(2):23–29.

[8] Almadhoun K, Sharma S. Bronchodilators. *StatPearls* (2021).

[9] Higgins BG, Powell RM, Cooper S, Tattersfield AE. Effect of salbutamol and ipratropium bromide on airway calibre and bronchial reactivity in asthma and chronic bronchitis. *Eur. Respir. J* (1991) **4**(4):415–420.

[10] *Salbutamol," National Center for Biotechnology Information* (2020). Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Salbutamol.

[11] Morgan D, Paull J, Richmond B, Wilson-Evered E, Ziccone S. Pharmacokinetics of intravenous and oral salbutamol and its sulphate conjugate. *Br. J. Clin. Pharmacol* (1986) **22**(5):587–593. doi:10.1111/j.1365-2125.1986.tb02939.x.

[12] Fenoterol in Turkish. *Fenoterol in Türkiye* (2022).

[13] *Levalbuterol," National Library of Medicine National Center for Biotechnology InformationPubChem CID 123600*. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Levalbuterol.

[14] Levalbuterol CONCENTRATE Vial For Nebulizer - Uses, Side Effects, and More. *WebMD* (XXXX).

[15] Cooperberg A, Breckenridge SM, Arbelaez AM, Cryer PE. *Terbutaline and the Prevention of Nocturnal Hypoglycemia in Type 1 Diabetes* (2008). doi:10.2337/dc08-0520.

[16] Riether C. Stimulation of β2-adrenergic receptors inhibits calcineurin activity in CD4+ T cells via PKA-AKAP interaction. *Brain. Behav. Immun* (2011) **25**(1):59–66. doi:10.1016/j.bbi.2010.07.248.

[17] Anderson G. Formoterol: pharmacology, molecular basis of agonism, and mechanism of long duration of a highly potent and selective β2-adrenoceptor agonist bronchodilator. *Life Sci* (1993) **52**(ue 26):2145–2160. doi:10.1016/0024-3205(93)90729-M.

[18] Salomon JJ. Beta-2 Adrenergic Agonists Are Substrates and Inhibitors of Human Organic Cation Transporter 1. *Mol. Pharm* (2015) **12**(8):2633–2641. doi:10.1021/mp500854e.

[19] Hanania NA. The safety and efficacy of arformoterol and formoterol in COPD. *COPD J. Chronic Obstr. Pulm. Dis* (2010) **7**(1):17–31. doi:10.3109/15412550903499498.

[20] Donohue JF. Arformoterol and salmeterol in the treatment of chronic obstructive pulmonary disease: A one year evaluation of safety and tolerance. *Ther. Adv. Respir. Dis* (2008) **2**(2):37–48. doi:10.1177/1753465808089455.

[21] P. L, C R, Kagan M, Dain J. Metabolism and Pharmacokinetics of Indacaterol in Humans. *Drug Metab. Dispos. Sept* (2012) **40**(9):1712–1722. doi:10.1124/dmd.112.046151.

[22] Naline E, Trifilieff A, Fairhurst RA, Advenier C, Molimard M. Effect of indacaterol, a novel long-acting β2-agonist, on isolated human bronchi. *Eur. Respir. J* (2007) **29**(3):575–581. doi:10.1183/09031936.00032806.

[23] Deeks ED. Olodaterol: A review of its use in chronic obstructive pulmonary disease. *Drugs* (2015) **75**(6):665–673. doi:10.1007/s40265-015-0371-4.

[24] Koch A. *International Journal of COPD Dovepress Lung function efficacy and symptomatic benefit of olodaterol once daily delivered via Respimat ® versus placebo and formoterol twice daily in patients with gOlD 2-4 COPD: results from two replicate 48-week studies* (2014). doi:10.2147/COPD.S62502.

[25] Cazzola M, Testi R, Matera MG. of Salmeterol. *Drug Dispos* (2002) **41**(1):19–30.

[26] Barnes PJ. The role of anticholinergics in chronic obstructive pulmonary disease. *Am. J. Med. Suppl* (2004) **117**(12):24–32. doi:10.1016/j.amjmed.2004.10.018.

[27] Gross NJ. Anticholinergic agents in asthma and COPD. *Eur. J. Pharmacol* (2006) **533**(1–3):36–39. doi:10.1016/j.ejphar.2005.12.072.

[28] Drugbank. *Ipratropium*. Available from: https://go.drugbank.com/drugs/DB00332.

[29] *Ipratropium Bromide (Code C29128*: NCI Metathesaurus.

[30] Rehder KJ. Adjunct therapies for refractory status asthmaticus in children. *Respir. Care* (2017) **62**(6):849–865. doi:10.4187/respcare.05174.

[31] Oxitropium bromide. *Wikipedia* (2022).

[32] Frith C, A. P, Jenner B, Dangerfield R, Atkinson J, Drennan. Oxitropium bromide: dose-response and time-response study of a new anticholinergic bronchodilator drug. *Chest* (1986) **89**(2):249–253. doi:10.1378/chest.89.2.249.

[33] *Aclidinium*. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548832/. doi:Liver.

[34] Cazzola M, Mario CP. Aclidinium bromide for the treatment of chronic obstructive pulmonary disease. *Expert Opin. Pharmacother* (2013) **14**(9):1205–1214.

[35] Glycopyrronium. *DrugBank*.

[36] Price F, D. S, A., Cerasoli. Biochemical properties, pharmacokinetics and pharmacological response of tiotropium in chronic obstructive pulmonary disease patients. *Expert Opin. Drug Metab. Toxicol* (2009) **5**(4):417–424. doi:10.1517/17425250902828337.

[37] Tiotropium Bromide (Code C84608. In: *NCI Metathesaurus. CL449040*.

[38] Decramer M. Bronchodilation of umeclidinium, a new long-acting muscarinic antagonist, in COPD patients. *Respir. Physiol. Neurobiol* (2013) **185**(2). doi:10.1016/j.resp.2012.08.022.

[39] Incalzi RA, Gemma A, Marra C, Muzzolon R, Capparella O, Carbonin P. Chronic obstructive pulmonary disease: An original model of cognitive decline. *Am. Rev. Respir. Dis* (1993) **148**(2):418–424. doi:10.1164/ajrccm/148.2.418.

[40] İlvan A. Kronik Obstrüktif Akciğer Hastalığı Alevlenmesinde Farmakolojik Tedavi [Pharmacological Treatment in Chronic Obstructive Pulmonary Disease Exacerbation]. *Solunum Dergisi* (2009) **0**(324):14–17.

[41] Theophylline (Code C872. *NCI Metathesaurus* **C0039771**.

[42] Aminophylline. *National Library of Medicine National Center for Biotechnology Information* (2022).

[43] *Anti-inflammatory* (2022). Available from: https://tr.wikipedia.org/static/images/mobile/copyright/wikipedia-wordmark-tr.svg,

[44] Cazzola M, Page CP, Calzetta L, Matera MG. Emerging anti-inflammatory strategies for COPD. *Eur. Respir. J* (2012) **40**(3):724–741. doi:10.1183/09031936.00213711.

[45] V. J, Loukides D, Bartziokas K. *Novel Anti-Inflammatory Agents in COPD: Targeting Lung and Systemic Inflammation* **14** (2013). 235–245. doi:10.2174/1389450111314020008.

[46] Sezer L, Kart M. *KOAH tedavisinde inhale kortikosteroidler [Inhaled corticosteroids in the treatment of COPD]* (2013). 24–30.

[47] Barnes PJ. Anti-inflammatory actions of glucocorticoids: molecular mechanisms. *Clin. Sci* **94**(6):557–572. doi:10.1042/cs0940557.

[48] *Fluticasone*: National Institutes of Health National Library of Medicine National Center for Biotechnology Information (2022).

[49] F. I. Jadwiga A. Wedzicha, M.D., M.D. DB, M.D. KR, M.D. JV, M.D. D, Nicolas Roche MD, et al. Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD. *N Engl J Med* (2016) **374**:2222–2234. doi:10.1056/NEJMoa1516385.

[50] *Budesonide*: National Institutes of Health National Library of Medicine National Center for Biotechnology Information (2022).

[51] Roth A, G. W, A. N, L., Thalén. High-performance liquid chromatographic determination of epimers, impurities, and content of the glucocorticoid budesonide and preparation of primary standard. *J. Pharm. Sci* (1980) **69**(7):766–770. doi:10.1002/jps.2600690705.

[52] *Prednisolone for COPD*: COPD NEWS TODAY (2022).
[53] Rabe KF. Update on roflumilast, a phosphodiesterase 4 inhibitor for the treatment of chronic obstructive pulmonary disease. *Br. J. Pharmacol* (2011) **163**(1):53–67. doi:10.1111/j.1476-5381.2011.01218.x.
[54] *Roflumilast*. Available from: https://go.drugbank.com/drugs/DB01656. doi:Online.
[55] Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet* (2009) **374**(9691):685–694. doi:10.1016/S0140-6736(09)61255-1.
[56] *Cilomilast*. Available from: https://go.drugbank.com/drugs/DB03849. doi:online.
[57] Turkish Medicines and Medical Devices Agency, Department of Rational Drug Use. *Antibiyotik Nedir ? [What is antibiotic?]* (2022). Available from: http://www.akilciilac.gov.tr/?page_id=1009.
[58] Sayıner L, A. M. Türk Toraks Derneği akut bronşit ve KOAH ve bronşektazi alevlenmelerinde antibiyotik tedavisi uzlaşı raporu [Turkish Thoracic Society Consensus Report on Antibiotic Treatment in Acute Bronchitis and COPD and Bronchiectasis Exacerbations]. *Türk Toraks Derg* (2009) **10**(7):3–7.
[59] Bakır M. Günümüzde KOAH Akut Alevlenmelerinde Antibiyotik Seçimi [Antibiotic Choice in Acute Exacerbations of COPD Today]. *Flora* (2003) **8**.
[60] Ball P. Epidemiology and treatment of chronic bronchitis and its exacerbations. *Chest* (1995) **108**(2 SUPPL):43–52. doi:10.1378/chest.108.2_Supplement.43S.
[61] Erdosteine. *DrugBank*.
[62] Sadowska AM, Verbraecken J, Darquennes K, Backer W. The role for N-acetylcysteine in the management of COPD. *Int. J. Chron. Obstruct. Pulmon. Dis* (2006) **1**(2):425–434. doi:10.2147/copd.2006.1.2.99.
[63] Bastos V. Inhaled 1,8-cineole reduces inflammatory parameters in airways of ovalbumin-challenged guinea pigs. *Basic Clin. Pharmacol. Toxicol* (2011) **108**(1):34–39. doi:10.1111/j.1742-7843.2010.00622.x.
[64] Worth H, Schacher C, Dethlefsen U. Concomitant therapy with Cineole (Eucalyptole) reduces exacerbations in COPD: A placebo-controlled double-blind trial. *Respir. Res* (2009) **10**:1–7. doi:10.1186/1465-9921-10-69.
[65] Çifci A. Ginger (Zingiber officinale) prevents severe damage to the lungs due to hyperoxia and inflammation. *Turkish J. Med. Sci* (2018) **48**(4):892–900. doi:10.3906/sag-1803-223.
[66] GREEN RJ. *Natural therapies for emphysema and COPD: relief and healing for chronic pulmonary disorders*: Inner Traditions/Bear & Co (2007).
[67] McKay DL, B J. IA Review of the Bioactivity and Potential Health Benefits of Peppermint Tea (Mentha piperita L. *Phyther. Res* (2006) **20**:619–633. doi:10.1002/ptr.1936.
[68] Scaglione F, Weiser K, Alessandria M. Effects of the standardised ginseng extract G115® in patients with chronic bronchitis: A nonblinded, randomised, comparative pilot study. *Clin. Drug Investig* (2001) **21**(1):41–45. doi:10.2165/00044011-200121010-00006.
[69] Eo SK, Kim YS, Lee CK, Han SS. Antiviral activities of various water and methanol soluble substances isolated from Ganoderma lucidum. *J. Ethnopharmacol* (1999) **68**(1–3):129–136. doi:10.1016/S0378-8741(99)00067-7.
[70] Isbaniah F, Wiyono WH, Yunus F, Setiawati A, Totzke U, Verbruggen MA. Echinacea purpurea along with zinc, selenium and vitamin C to alleviate exacerbations of chronic obstructive pulmonary disease: Results from a randomized controlled trial. *J. Clin. Pharm. Ther* (2011) **36**(5):568–576. doi:10.1111/j.1365-2710.2010.01212.x.