JABET
Journal of Advanced Biotechnology and Experimental Therapeutics

REVIEW ARTICLE

J Adv Biotechnol Exp Ther. 2023 Jan; 6(1): 109-122
eISSN: 2616-4760, https://doi.org/10.5455/jabet.2023.d110
Published by www.bsmiab.org

# Epidemiological burden, risk factors, and recent therapeutic advances in chronic obstructive pulmonary disease

**Bakthavatchalam Loganathan Ayilya[1], Rasool Abdul Nazeer[1,*]**

[1]Biopharmaceuticals Lab, Department of Biotechnology, School of Bioengineering, SRM Institute of Science and Technology, Kattankulathur, Tamilnadu, India

[*]**Corresponding author**
Rasool Abdul Nazeer, PhD
Biopharmaceuticals Lab,
Department of Biotechnology,
School of Bioengineering,
SRM Institute of Science and Technology, Kattankulathur
Tamilnadu, India
e-mail: nazeerr@srmist.edu.in

**Academic editor**
Md Jamal Uddin, PhD
ABEx Bio-Research Center, Dhaka 1230, Bangladesh

**Article info**
Received: 13 August 2022
Accepted: 24 September 2022
Published: 25 October 2022

**Keywords**
COPD; Epidemiology; Morbidity; Mortality; Prevalence; Smoking.

## ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a progressive disease that is certainly preventable and treatable and is caused due to the continuous exposure to noxious substances and toxic gases and is characterized by airflow limitation and chronic inflammation in the lungs coupled with persistent symptoms in the respiratory tract leading to obstructive bronchiolitis and parenchymal emphysema. The incidence and progression of COPD is a complicated pathological phenomenon, and the overall severity is due to its exacerbations and comorbidities in individuals. Further, COPD is a major contributor to the global years of life lost and by 2030 it would be the third leading causes of mortality in the world. Also, knowledge on COPD, its associated conditions, and the clinical understanding of the disease date back to the 16th century. The prevalence, morbidity and mortality may vary across the globe based on their exposure to smoking, tobacco, occupational pollutants, indoor pollution, outdoor air pollution, gender, age, and genetic inheritance. Considering the continuous exposure to toxic substances and aging of the general population, the burden and prevalence of COPD are estimated to increase substantially in the coming years. Furthermore, COVID-19 patients with pre-existing COPD conditions suffer from severe disease progression and delay in recovery.



## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a complex disease indicated by persistent symptoms in the respiratory tract and limitation in the airflow, combined with an increased chronic inflammation in the airway tract and lungs due to continuous exposure to toxic substances, gases, and is influenced by a combination of host factors. Inhaling these toxic particles and gases from biomass fuels and cigarette smoke causes lung inflammation and further worsens by destructing the parenchymal tissues and disrupt the natural defense and repair mechanism resulting in emphysema and airway fibrosis [1]. This host of pathological changes often leads to symptoms like difficulty in breathing, cough, dyspnea, and hyper production of sputum [2]. It is a progressive disease which is commonly preventable and treatable, but the overall complications in individuals, morbidity and mortality are often due to the exacerbations and comorbidities [3]. COPD is characterized by parenchymal destruction, i.e., emphysema and disease of the small airways i.e., obstructive bronchiolitis [4].

There are several potential risk factors for COPD. For some individuals, the fundamental cause is inefficient lung function in early adulthood, for others it is the accelerated loss of forced expiratory volume in the first second (FEV1) with age, and for some others it may be both. Independent of FEV1 trajectory, smoking is strongly related to the progression of disease, the development of emphysema, and a poor prognosis. In Western nations, never-smokers' experiences with COPD are considerably

more favorable. Due to factors such as biomass exposure and tuberculosis sequelae, underdeveloped nations may suffer from a kind of COPD characterized by more severe airway pathology and less emphysema than developed nations. [5]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has declared that smoking cigarettes and tobacco are high risk factors in high-income countries, with occupational exposure and indoor cooking adding to the significant risk factors in low-income countries [6]. Also, genetics contribute to the complexity of COPD by determining the clinical phenotype when genetic abnormalities are combined with a specific exposure for a certain period [7].

COPD is the major contributor to the years of life lost globally, with significant mortality numbers, it was ranked third in the world in 2010 and is estimated to be the fourth highest cause of mortality and fifth in terms of the COPD disease burden by 2030 [1,8-9]. The most prevalent COPD phenotype is the result of several interconnected factors, the most prominent of this is active smoking [10]. However, it is not established that all smokers acquire COPD, implying that some intrinsic or extrinsic elements have a role in the progression of clinical illness. Also, COPD patients have significant clinical heterogeneity [11]. Also, it is well understood that individuals with distinct COPD traits differ distinctively [12], including the disease onset, early phases, and their disease progression [13]. Furthermore, the existence of comorbidities in elderly adults, such as diabetes, cardiovascular disease, lung cancer and osteoporosis has been shown to impact the course of COPD in individual patients [14]. Various minor factors like the loss of pulmonary function during the early days, social and psychological aspects of a patient, as well as clinical delays have made the early diagnosis of COPD complicated [15]. There has been a lot of studies worldwide about the epidemiological aspects of COPD, but they are confined to different geographical locations. This study is focused on analyzing and compiling the epidemiological burden of COPD and its risk factors at various geographical locations across the globe. This paper also reviews the recent therapeutic advancements for COPD.

## ORIGIN AND HISTORY OF COPD

Some of the earliest evidence to the description of the disease dates back to the 16$^{th}$ century when a condition of emphysema was described as the 'voluminous lungs' [16]. 19 cases of 'turgid lungs' due to the air was described by Morgagni [17] and Samuel Johnson's emphysematous lungs was illustrated in 1789 by Baille [18-19]. In 1814, the clinical understanding of chronic bronchitis and its association to COPD were described by Badham, who referred to the prime symptoms, chronic cough with a hyper secretion of mucus as 'catarrh' and referred chronic bronchitis and bronchiolitis to 'disabling disorders' [20]. William Briscoe, during the '9th Aspen Emphysema Conference' is thought to have coined and initiated the term 'COPD' in a discussion. COPD is now used to indicate a rapidly rising health hazard [21]. 'The Central Institute of Brackish water Aquaculture (CIBA) Guest Symposium' held in 1959 and 'the American Thoracic Society Committee on Diagnostic Standards' held in 1962 [22-23] are the two landmark meetings that defined COPD and its components, which led the foundation for the definitions framed thereafter.

The knowledge of the pathogenesis of the disease evolved over the years and in 1993, as a part of the new national health initiative, The Lung Division of the National Heart, Lung, and Blood Institute (NHLBI) was launched and 'The National Lung Health Education Program (NLHEP)' was established to investigate the developments in COPD. Further, in 2001, the World Health Organization (WHO) and NHLBI jointly

launched GOLD to spread awareness of the severity of the disease and to facilitate early diagnosis and treatment [24]. This was followed by the formation of 'the European Respiratory Society (ERS)' and 'the American Thoracic Society (ATS)' in 2004 for COPD guidelines [25].

Charles Fletcher [26] dedicatedly studies the natural history of COPD by recognizing the risk factors of smoking and the abrupt decline rate of FEV1 in susceptible smokers in his efforts of disabling symptoms which led to the scientific foundation for the cessation of smoking at various phases of the disease [27]. Also, Burrows *et al.,*[28] described the phenomenon when patients with high slump having the worst prognosis as "The Horse Racing Effect". This discovery also stressed on the significance of early detection and clinical intervention. During the early course of the disease, the complex biochemical and cellular reactions in the small airways and alveoli get damaged and lose elastic recoil [29] and the lungs expand and FVC increases resulting in early physiological changes that can be easily identified with the help of Spirometry [28]. It is also established that the clinical signs are often developed during the moderate and advanced phases of COPD [30].

## BURDEN OF COPD

COPD is considered as one of the primary factors for morbidity and mortality in the world and causes an ever increasing social and economic burden [9] and the key points are highlighted in Figure 1. The prevalence, morbidity and mortality of COPD may vary across the globe based on the conditions the different populations are exposed to [31]. Mostly, tobacco smoking is a most important cause for the prevalence of COPD although, other factors like occupational exposure, indoor and outdoor air pollution contribute significantly to many countries [32]. Upon considering the continuous exposure to toxic substances and aging of the world population, the burden and prevalence of COPD is estimated to rise substantially of the coming decades [8].

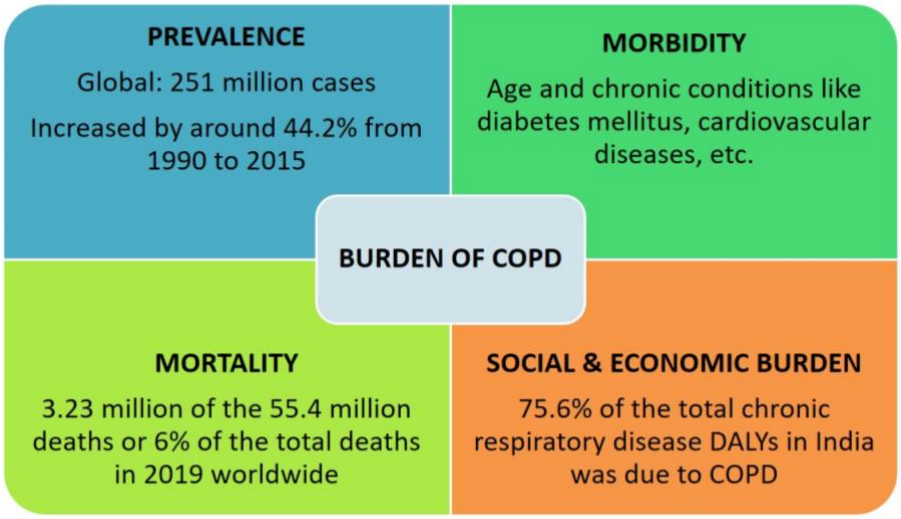


**Figure 1**. Burden of COPD.

## Prevalence

COPD's prevalence in the globe increased by around 44.2% from 1990 to 2015 [33]. In the year 2016, 'The Global Burden of Disease Study' reported an estimated COPD prevalence of around 251 million [34]. Various meta-analysis and systematic reviews were conducted over the years which revealed a pooled COPD prevalence from 37 studies to be 7.6% and 8.9% from 26 estimated spirometrics [35]. Similarly, in a study conducted in over 28 countries between the years 1990 and 2004, the COPD prevalence was found to be high among ex-smokers and smokers when compared to the non-smokers over 40 years of age. Also, it was found to be comparatively more in men than women [35].

The Burden of Obstructive Lung Disease (BOLD) program uses standardized pre- and post-questionnaire and retrieved data from various spirometric studies to analyze the prevalence and risk of COPD across the world population over 40 years of age spread across 38 countries of which nine countries are still under study [3]. BOLD reported a grade 2 or higher overall prevalence of 10.1%, 11.8% among male and 8.5% among the female with a prevalence of 3-11% among non-smokers [36]. Among the low and middle-income countries, the prevalence of COPD was 9.2% [37]. According to WHO (2021), they contribute to over 90% of the deaths due to COPD [34]. Also, meta-analysis estimates reported a prevalence of 10.6 in population of over 30 years in LMICs [38]. In India, the reported number of COPD cases spiked from 28.1 million in 1990 to a striking 55.3 million in 2016 and the prevalence from 3.3% to 4.2%. Also, in 2016, the DALY rates and age standardized COPD prevalence were maximum in less developed low Epidemiological transitional level (ETL) states of Uttar Pradesh and Rajasthan in India [39]. The prevalence, DALYs and severity of COPD among the world population is summarized in Table 1.

**Table 1.** Prevalence, DALYs and severity of COPD among the world population [40-42]

| Items | Male | Female | Overall |
|---|---|---|---|
| Global prevalence (in million) | 267·4 (214·6–330·2) | 267·4 (214·6–330·2) | 391·9 (312·6–487·9) |
| Global prevalence % | 14·1% (11·3–17·4) | 6·5% (5·1–8·2) | 10·3% (8·2–12·8) |
| Proportion of all cause DALYs % | 3.22% (2.93-3.49) | 3.33% (2.95-3.71) | 3.27% (2.96-3.56) |
| DALY rate per 100000 | 1128.21 (1045.99-1202.19) | 1007.37 (916.25-1088.81) | 1068.02 (994.47-1135.50) |
| Proportion of all cause deaths % | 5.89% (5.50-6.20 | 5.51% (5.00-5.91) | 5.72% (5.43-5.97) |
| Death rate per 100000 | 46.68 (43.62-49.25) | 36.99 (33.63-39.85) | 41.85 (39.64-43.96) |
| Percentage of population with mild COPD | 8.63% (6.75–10.52) | 4.68% (3.65–5.72) | 7.06% (5.90–8.21) |
| Percentage of population with moderate COPD | 8.61% (6.68–10.54) | 5.48% (4.25–6.71) | 6.58% (5.41–7.74) |
| Percentage of population with severe to very severe COPD | 2.62% (1.85–3.39) | 1.27% (0.97–1.57) | 1.61% (1.30–1.92) |

In India, a cross sectional study was conducted for the people above 30 years of age between 2000 and 2020. The data revealed that the prevalence of COPD among the Indian population aged over 30 years was over 7 percent [43].

## Morbidity and mortality

Morbidity includes conditions of physician intervention, emergency department visits and hospitalization. Since the database from these parameters are less reliable and not readily available compared to that of the mortality data, studies indicate that COPD morbidity increases with age [44-45] and COPD patients develop comorbidities at a very young age [46]. Other chronic conditions like diabetes mellitus, cardiovascular diseases, etc., also contribute to the morbidity in COPD patients [47].

In 2011, COPD was considered as the third highest cause of overall death in the United States. COPD, on being a progressive disease in the respiratory tract accounted to 3 million deaths which was 6% of overall deaths globally in the year 2012 [3], 3.2 million

deaths which was 5.7% in 2017 [48] and 3.23 million of55.4 million deaths or 6% of total deaths in 2019 worldwide with over 90% deaths from the low and middle-income countries. COPD was ranked as the second most prevalent cause of death in 2017 and it had already exceeded the WHO's prediction of the disease to be the third leading cause of death in 2030 [34]. With the increase in smoking in many developing countries, and the increase in the age of the population in high income countries, the COPD prevalence will increase in the upcoming 40 years and by 2060, it is predicted that there would be 5.4 million annual deaths due to COPD and its associated conditions. Further, the significant increase in the death rate due to COPD can be attributed to expanding the epidemic of smoking, reduced mortality rates due to other conditions like heart attack and stroke, increase in age of the population in high income countries and relatively low disease control measures in developing countries.

### Social and economic burden

In 2016, India contributed to 32% of the overall DALYs due to chronic respiratory diseases in the world and 75.6% of the total DALYs of the respiratory disease in India were due to COPD. This disproportionately high disease burden and huge health loss in India, particularly in the low epidemiological transition level states emphasize the need for more convergent policy interventions to investigate the significant disease burden in India. Compared to the global average, the DALYs per case of COPD in India was higher by 1.7 times in 2016, where even most states in the country had higher DALY rates in comparison with most other places with similar Socio-demographic Index worldwide [39].

In the European Union, out of the overall annual budget for health, around 6% is estimated to be allotted for respiratory diseases and around 56% of the allotment (38.6 billion Euros) for respiratory disease is accounted for COPD [49] and it is estimated to be $32 billion and $20 billion as the cost of COPD in the United States [50]. Previous studies suggest that the impact in the Indian economy in terms of indirect and direct medical expenditure was reported to be significantly high (direct medical cost: approximately Rs. 29,885 ± 11,995.33, or US$300–500; direct nonmedical cost: approximately Rs. 7,441.25 ± 2,228.90, or US$90–155) and is also associated with loss of daily wages for a significant time period [51-52]. Negative relations of COPD were found when using clean fuel and a better economic condition of the families [53].

## RISK FACTORS OF COPD

COPD mortality rates have declined in recent years, and anti-smoking initiatives have succeeded in some western nations. Nevertheless, the demographic influence of ageing on the increasing world population and increase in smoke and air pollution in Asia, will make to COPD a never settling problem in the 21st century [54]. In the year 2016, high risk factors were identified as air pollution which contributed to 53.7%, tobacco usage which contributed to 25.4% and occupational exposure which contributed to 16.5% of the total DALYs due to COPD in India [39]. Although several longitudinal studies have been carried out to monitor the disease progression, the current understanding of the potential risk factors for COPD (Figure 2) is still incomplete in many aspects. Exposure to biomass fuel, active and passive smoking, tobacco smoke, exposure to occupational dust, pollution and increasing age have all been linked to COPD among Indians [43].

### Smoking and air pollution

Though smoking is the primary risk factor for COPD, studies have proved the prevalence of COPD and airflow limitations among non-smokers too [36] but the non-smokers have comparatively lesser symptoms and milder systemic inflammation compared to smokers [55]. On the other hand, even for frequent smokers, less than 50% develop COPD in their lifetime [56]. Cigar, pipe, waterpipe [57] and marijuana [58] are other types that are equally important risk factors of COPD. Environmental tobacco smoke or passive smoking also leads to increased lung burden of the inhaled toxic gases leading to the development of COPD [59]. Second-hand smoking and other factors were understood to play a major role when a study in Uttar Pradesh, India by Mahmood *et al.*,[60] reported a striking 56.5% of the patients were non-smokers.

According to WHO report, outdoor air pollution affects 1 billion, biomass fuel exposure affects around 2 billion people and 1 billion people in the globe are at the risk of second-hand smoking. With reference to census 2010, over 65% of the population in India live in rural areas where biomass fuels are used in the form of wood, animal dung and crops and the effluent release in the living environment results in a significant population getting exposed to biomass fuels [61]. Also, in a similar study conducted in India, over half the recorded COPD cases were from the industrial area. The industrial areas show overall high prevalence (5.6 to 9.4 cases per thousand) of COPD and non-industrial areas showed low (0 to 0.9 per thousand) prevalence [62].

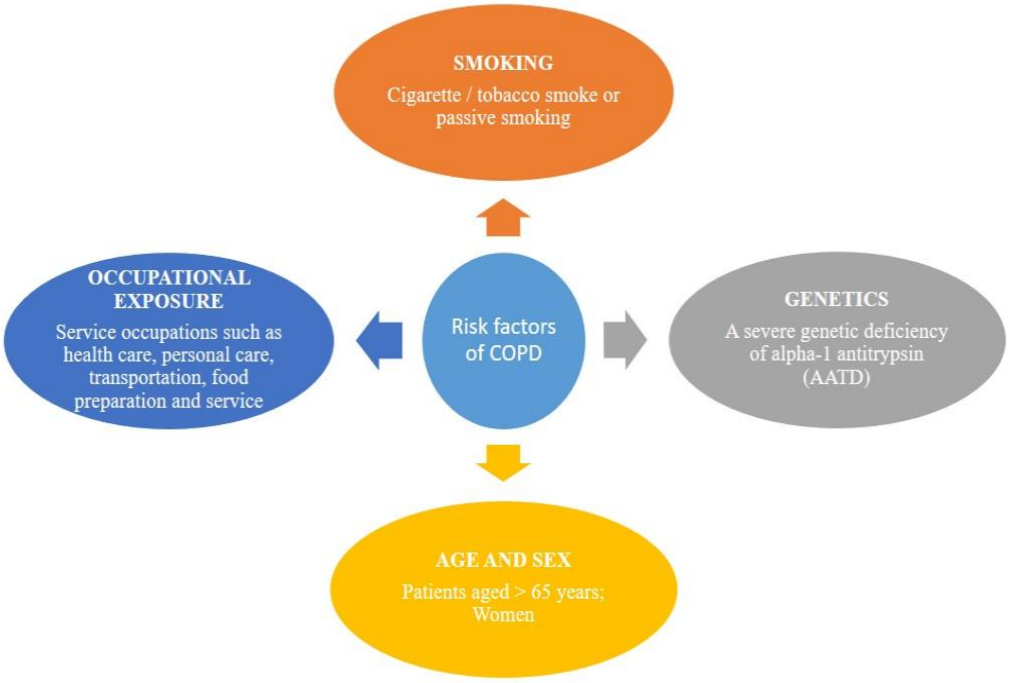


**Figure 2.** Risk factors of COPD.

### Age and sex

There has always been an increase in the clinical investigations of aged population in studies related to COPD. 'Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE)' and 'COPD Gene cohorts' data studies revealed that the patients aged over 65 years were reported to have worst lung function, needed frequent oxygen therapy due to low exercise tolerance and high risk for comorbidities compared to the younger population [63]. During 2004-2011, the self-reported doctor

diagnosed cases of COPD among adults aged 4 to 70 years had an overall average annual prevalence of 4.18% and the trend increased with age [64]. This is also in accordance with the reports from the 'Behavioral Risk Factor Surveillance System' study in 2011 among US adults, which ranged from 6.6% for adults of age 45 years to 12.1% for adults aged around 70 years [65]. Also, a meta-analysis of over 123 research studies across the globe reported a prevalence rate of 11.4% among adults over 30 years old [38]. In a field survey conducted among a population of 44387 in Bangalore, India, there was a prevalence of 4.36% and it was found to increase with age.

Population based studies in India revealed a COPD prevalence of 2-22% among men and 1.2-19% among women [66]. Early diagnosis of COPD patients < 55 years reported 66% predominance in the female and demonstrated that it is strongly associated with maternal smoking in maternal COPD cases [67]. Among the patients with critical emphysema, early onset of COPD and GOLD stage IV COPD, more female with comparatively few pack-years of smoking have radiographic emphysema compared to that of male [68] and older women have more severe COPD and dyspnea than older men [69]. Also, in another study conducted by Busch *et al.*,[70], younger women suffer severe dyspnea and limitation in airflow with an exacerbation of 1.53 higher Odds ratio than young men. This can be attributed to high wall area percentage and low luminal area, airway thickness and internal diameter in women compared with male smokers [71].

Additionally, since the female COPD Gene longitudinal data suggests that they have increased risk of more acute respiratory diseases irrespective of other covariates [72] women are prone to a high risk for developing COPD and exacerbations. On the other hand, low bone mineral density and vertebral fractures associated with steroid usage, pack years of smoking, age, smoking status, radiographic emphysema, and exacerbations highlight high risk than female smokers [73].

**Occupational exposure**

COPD is characterized by airflow restriction, respiratory symptoms, and comorbidities associated with exposure to harmful particles and gases. Exposure to vapors, gases, dust, and fumes (VGDF) in the workplace is one of these factors, and hence adds to the classification of "occupational" COPD. Specifically for inorganic dust, this link has been confirmed through epidemiological investigations. In population-based investigations, occupational exposure to VGDF accounts to 14% which is an essential factor to consider [74]. Numerous studies have proven the biological validity of this connection. According to Balmes et al.,[75], occupational exposure attributes to around 15% of COPD cases. The increased prevalence of the disease was associated with service occupations such as health care, personal care, transportation, food preparation and service [76]. Further, women in these occupations are at 2 to 4-fold more risk compared to that of men [77]. Exposure to gases, fumes, dusts and vapors in various industries and occupation have been studied to be associated with COPD among the working population [76][78]. Prolonged exposure of silica dust and coal among the miners [75][79], organic and inorganic dust and other particles among agricultural workers [80] result in high mortality and morbidity rates of COPD. Among women, the increased prevalence of COPD can be attributed to the biological differences, environmental tobacco smoke and occupational exposure [81].

A study among the US workers of age between 40 and 70 years belonging to different occupational groups was carried out to determine the prevalence and odds ratio of COPD among various occupational groups. The overall prevalence was reported as 4.2%

with healthcare workers with highest odds of COPD, followed by hotels and service workers. Variation by occupations further confirms the occupational exposure contributing to the disease significantly [64]. Smoking-adjusted risk of COPD development was observed to be increased by occupational particle exposure, according to the study by Grahn et al., [82]. The exposure-response relationships for diesel exhaust, gypsum and insulation, and welding fumes were all favorable. COPD was also associated to high levels of exposure to asphalt/bitumen and other organic substances. For men, the population attributable fraction for COPD induced by occupational particle exposure was 10.6%, whereas for women it was 6.1%. A reduction in these exposures is essential to avoid future COPD occurrences.

### Genetic factors

A severe genetic deficiency of alpha-1 antitrypsin (AATD) is documented as the genetic risk factor of COPD [83]. Although the genetic risk factor of COPD is attributed to a very minor population, it is very crucial to understand the interaction of the environmental factors and genetics. In a systematic review conducted from 20 studies in the European population, AATD PiZZ genotype was recorded in 0.12% of the COPD patients and was prevalent 1 in 408 and 1 in 1274 in Northern and Eastern Europe respectively [84]. In a study comprising 439 255 participants, it was discovered that a polygenic risk score comprised of millions of variants with low genome-wide significance had significant associations with incident COPD. People with a high genetic risk for COPD may be more susceptible to the effects of smoking [85]. Among the smokers and siblings of patients with COPD, a prominent family risk of limitation in airflow was observed by [86] and this proves the risk of environmental exposure in genetics. Genes encoding glutathione S-transferase and matrix metalloproteinase 12 (MMP-12) were found to be associated with reduced lung function [87] and genetic loci with COPD with phenotypes $FEV_1$ or $FEV_1/FVC$ and markers near hedgehog interacting protein (HHIP), alpha-nicotine acetylcholine receptors and many other genes are under investigation on their involvement in COPD [88-89].

## ADVANCES IN DRUG DEVELOPMENT FOR COPD

Maintenance therapies for Chronic Obstructive Pulmonary disease (COPD) including various pharmacological treatments focuses on alleviating symptoms and reducing the risk of disease progression, exacerbation, and mortality. Often, pharmacological interventions can lead to variable responses from COPD patients due to the disease heterogeneity. From precision in pharmacological approach to optimizing treatment based on the information from integrated clinical and biomarker, the treatment options for COPD had evolved over the years. Studies conducted by many researchers have provided optimal evidence for using combination treatments at various levels [90]. The pressing need for pharmacological treatments for exacerbations and dyspnea and symptom specific treatment approach to alleviate risks and reducing symptoms and its frequencies, improving health and exercise tolerance was recommended by the GOLD [91]. On the other hand, there is no medication for COPD that can improve the lung function in the long time and there is no strong clinical evidence to support the same till date.

Pharmacological therapy can be tailored to individuals possessing diverse pathophysiological mechanisms using biomarkers [92]. Vaccinations are early preventive strategies. Pharmacological therapy is based on the severity of lung

impairment and symptoms such as cough, sputum production, dyspnea, and exacerbation levels [93]. Around 37 generic drugs belonging to the class of medications including Anticholinergics, Bronchodilators, Inhaled Corticosteroids (ICS), Beta2-Agonist, Antimuscarinic drugs, Methylxanthines, Phosphodiesterase-4 inhibitors, Anti-inflammatory agents and Mucolytic agents are commonly used across the world [93] and some are furnished in Table 2. Though most drugs are effective in relieving symptoms, some demonstrate adverse side effects, which in turn highlight the need for more natural bioactive compounds with comparatively lesser side effects.

**Table 2**. Pharmacological therapies for COPD.

| S. No | Class of medication | Action | Generic name of the drug | Ref. |
|---|---|---|---|---|
| 1. | Bronchodilators (Beta2-Agonist) | Increases FEV1 by relaxing the airway smooth muscle. Stimulates beta2-adrenergic receptors to increase cyclic AMP and works against bronchoconstriction. | Formoterol, Salmeterol | [94] |
| 2. | Antimuscarinics | Blocks the effect of acetylcholine on M3 muscarinic receptor against bronchoconstriction of airway smooth muscles | Tiotropium, Umeclidinium | [95] |
| 3. | Methylxanthins | Act as non-selective phosphodiesterase inhibitor | Theophyllin, Aminophylline | [96] |
| 4. | Inhaled corticosteroids (ICS) | Used to control exacerbations in COPD patients | Fluticasone, Budisonide, Prednisolone | [97] |
| 5. | Combination bronchodilator therapy | Shortacting Beta2-Agonist / short-acting muscarinic antagonists (SABA/SAMA) | Formoterol and tiotropium | [98] |
| | | Long acting Beta2-Agonist / long-acting muscarinic antagonists (LABA/LAMA) | Formoterol/aclidinium, Formoterol/glycopyrronium | |
| | | LABA/ICS | Salmeterol/fluticasone, Formoterol/budesonide | |
| 6. | Triple therapy | LABA/LAMA/ICS | Fluticasone/umeclidinium/vilanterol | [99] |
| 7. | Phosphodiesterase-4 (PDE4) inhibitor | Reduces inflammation by inhibiting the breakdown of intercellular cyclic AMP | Roflumilast | [100] |
| 8. | Antibiotics, mucolytic and antioxidant agents | Targets anti-inflammatory pathways | Azithromycin, Simvastatin, Erdosteine, Carbocysteine, N-acetylcysteine | [101] |

## Anti-COPD compounds from natural sources

Nine bioactive compounds screened from marine brown algae (*Ecklonia cava, Ishige foliacea, Ishige okamura, Undariopsis peteseniana* and *Hizikia fusiformis*) and Apo9 1 fucoxanthinoneisolated from *Undariopsis peteseniana* exhibit superior protection against the cytotoxicity induced by the cigarette smoke in cultured airway human epithelial cells by preventing cigarette smoke-induced apoptosis, DNA damage and mitochondria-derived ROS production but the activities were not demonstrated *in vivo*[102]. Astaxanthin, a xanthophyll carotenoid with natural reddish-orange pigment widely present in abundance in marine organisms such as algae, crab, shrimp, krill, and salmon possess potent antioxidant properties and is proved to be the best among other carotenoids and vitamin E. It suppresses cigarette smoke induced emphysema in mice by increasing the Nrf2 and HO-1 expression in the lung [103]. Though this compound was successful *in vitro* and in in murine model of COPD, the study had limitations like the concentration of astaxanthin in the blood of the mice and the bioavailability was not known and the optimal concentration of astaxanthin is yet to be studied for effectiveness.

Brevenal from a marine dinoflagellate, *Karenia brevis* reduces pro-inflammatory mediators while still preserving anti-inflammatory secretion from the cells on many cell lines which was proposed as a potential anti-inflammatory drug for mucociliary

clearance [104]. However, an *in vivo* trial would prove significant in proving the physiological effect of the compound without compromising on the healing response of the immune system.3,3′-dimethyellagic acid-4-O-sulfate and Jaboticabin-two polyphenols from Jaboticaba exerted anti-inflammatory activities, with a potential to treat COPD on cell lines but the studies are yet to be confirmed with animal models [105]. Naringenin, a natural flavanone from dormant peach *Prunus persica* flower buds, consumable by human, abundantly present in citrus fruits and vegetables with diverse bioactivity, was proposed to show potential pharmacological activities against multiple pathological stages of COPD [106]. Though the bioactivity of this flavanone was extensively studied *in vitro* as well as *in vivo*, it needs more clinical study to support its effect on human, which is limited by its poor aqueous solubility and bioavailability in human and needs an effective drug delivery system. The potentially promising anti-COPD compounds were predominantly studied from plant source and very few from marine algae, were more of phenolic compounds and flavanones with limited bioavailability and heavier for gastric absorption and requires stronger supporting evidence based *in vivo* studies.

## CONCLUSION

COPD incidence and disease progression is a complicated pathological phenomenon, and it involves a host of pathological processes. The overall severity, morbidity and mortality of the disease is due to the exacerbations and related comorbidities in individuals. COPD being a major contributor to the global years of life lost, it is projected to be the third leading cause of mortality in the world by 2030. Prevalence, morbidity, and mortality of the disease exhibit may vary across the globe based on their factors like exposure to smoking, tobacco, occupational pollutants, indoor and outdoor air pollution, age, gender, and genetic inheritance. Considering the continuous exposure to toxic substances and aging of the general population in the world, the burden and prevalence of COPD is estimated to increase substantially soon. On the other hand, it is also necessary to include research on the severe disease progression and delayed recovery in the COVID-19 patients with pre-existing COPD conditions at various levels.

## ACKNOWLEDGEMENT

Both the authors would like to thank the management of SRM Institute of Science and Technology, Chennai, TN, India for their support.

## AUTHOR CONTRIBUTIONS

Formal analysis, data acquisition, writing original draft: BLA; Validation, conceptualization, writing-reviewing, editing, analysis, supervision: RAN. All authors have read and approved the final version of the manuscript.

## CONFLICTS OF INTEREST

There is no conflict of interest among the authors.

## REFERENCES


[1] Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. 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.

[2] Riley CM, Sciurba FC. Diagnosis and outpatient management of chronic obstructive pulmonary disease: a review. JAMA. 2019; 321(8):786-797.

[3] Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2021. Global strategy for the diagnosis, management and prevention of COPD. Proceedings of the Global Initiative for Chronic Obstructive Lung Disease.

[4] Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Am J Respir Crit Care Med. 2017; 195(5):557-582.

[5] Lange P, Ahmed E, Lahmar ZM, Martinez FJ, Bourdin A. Natural history and mechanisms of COPD. Respirology. 2021; 26(4): 298-321.

[6] Brusselle GG, Joos GF, Bracke KR. New insights into the immunology of chronic obstructive pulmonary disease. Lancet. 2011; 378(9795):1015-1026.

[7] Silverman EK, Spira A, Paré PD. Genetics and genomics of chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2009; 6(6):539-542.

[8] Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006; 3(11):e442. doi: 10.1371/journal.pmed.0030442.

[9] Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012; 380(9859):2095-2128.

[10] Han MK, Agusti A, Calverley PM, Celli BR, Criner G, Curtis JL, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med. 2010; 182(5):598-604.

[11] Dobnhoest AC. Respiratory insufficiency. Lancet, 1955; 265(6876):1185-1187.

[12] Han MK, Tayob N, Murray S, Woodruff PG, Curtis JL, Kim V, et al. Association between emphysema and chronic obstructive pulmonary disease outcomes in the COPDGene and SPIROMICS cohorts: a post hoc analysis of two clinical trials. Am J Respir Crit Care Med. 2018; 198(2):265-267.

[13] Labaki WW, Martinez CH, Martinez FJ, Galbán CJ, Ross BD, Washko GR, et al. The role of chest computed tomography in the evaluation and management of the patient with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2017; 196(11):1372-1379.

[14] Negewo NA, Gibson PG, McDonald VM. COPD and its comorbidities: impact, measurement and mechanisms. Respirology. 2015; 20(8):1160-1171.

[15] Jones RC, Price D, Ryan D, Sims EJ, von Ziegenweidt J, Mascarenhas L, et al. Opportunities to diagnose chronic obstructive pulmonary disease in routine care in the UK: a retrospective study of a clinical cohort. Lancet Respir Med. 2014; 2(4):267-276.

[16] Bonet T. Sepulchretum sive anatonia pructica ex Cadaveribus Morbo denatis, proponens Histoa's Observations omnium pené humani corporis affectuum, ipsarcomoue Causas recorditas revelans. Geneva (Switzerland): Pierre Chouet.1679.

[17] Morgagni GB. The seats and causes of disease. Investigated by anatomy; in five books, containing a great variety of dissections, with remarks. Translated by Alexander B, Miller A, Caldwell T. London: Johnson and Payne. 1769.

[18] Baillie M. The morbid anatomy of some of the past important parts of the human body divided into 10 fasciculi. London: W. Blum. R. and Co.1799.

[19] Bishop PJ. Samuel Johnson's lung. Tubercle, 1959; 40:478–81.

[20] Badham C. An Essay on Bronchitis: With a Supplement Containing Remarks on Simple Pulmonary Abscess, Etc. Callow.1814.

[21] Briscoe WA, Nash ES. The slow space in chronic obstructive pulmonary disease. Ann N Y Acad Sci. 1965; 121(3):706-722.

[22] Ciba Guest Symposium. 1959. Terminology, definitions, and classification of chronic pulmonary emphysema and related conditions. Thorax. 14:286–99

[23] Donald KW. Identification of asthma. Chairman's opening remarks. Ciba Found Study Group. 1971; 38:1-4.

[24] Petty TL. The history of COPD. Int J Chron Obstruct Pulmon Dis. 2006; 1(1):3–14.

[25] Celli BR, MacNee WATS, Agusti AATS, Anzueto A, Berg B, Buist AS, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004; 23(6):932-946.

[26] Fletcher CM. The natural history of chronic bronchitis and emphysema. An eight-year study of early chronic obstructive lung disease in working men in London.1976.

[27] Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE, Lung Health Study Research Group*. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med. 2005; 142(4):233-239.

[28] Burrows B, Knudson RJ, Camilli AE, Lyle SK, Lebowitz MD. The "horse-racing effect" and predicting decline in forced expiratory volume in one second from screening spirometry. Am Rev Respir Dis. 1987; 135(4):788-793.

[29] Petty TL, Silvers GW, Stanford RE. Mild emphysema is associated with reduced elastic recoil and increased lung size but not with air-flow limitation. Am Rev Respir Dis. 1987; 136(4):867-871.

[30] Mannino DM, Gagnon RC, Petty TL, Lydick E. Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988-1994. Arch Intern Med. 2000; 160(11):1683-1689.

[31] Lange P, Celli B, Agustí A, Boje Jensen G, Divo M, Faner R, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. N Engl J Med. 2015; 373(2):111-122.
[32] Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet. 2009; 374(9691):733-743.
[33] GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Respir Med. 2020; 8(6): 585 -596.
[34] World Health Organization. Chronic Obstructive Pulmonary Disease (COPD) Fact Sheet. World Health Organization. 2021. Available at Chronic obstructive pulmonary disease (COPD) (who.int) [Accessed on 04 February, 2022]
[35] Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. Eur Respir J, 2006; 28(3):523–32.
[36] Lamprecht B, McBurnie MA, Vollmer WM, Gudmundsson G, Welte T, Nizankowska-Mogilnicka E, et al. BOLD Collaborative Research Group. COPD in never smokers: results from the population-based burden of obstructive lung disease study. Chest. 2011; 139(4):752-763.
[37] World Health Organization. 2017. Available at Chronic respiratory diseases (who.int) [Accessed 9 February 2022].
[38] Adeloye D, Chua S, Lee C, Basquill C, Papana A, Theodoratou E, Nair H, et al. Global Health Epidemiology Reference Group (GHERG). Global and regional estimates of COPD prevalence: Systematic review and meta–analysis. J Glob Health. 2015; 5(2):020415.
[39] India State-Level Disease Burden Initiative CRD Collaborators. The burden of chronic respiratory diseases and their heterogeneity across the states of India: the Global Burden of Disease Study 1990-2016. Lancet Glob Health. 2018; 6(12):e1363-e1374. doi: 10.1016/S2214-109X(18)30409-1.
[40] Varmaghani M, Dehghani M, Heidari E, Sharifi F, Moghaddam SS, Farzadfar F. Global prevalence of chronic obstructive pulmonary disease: systematic review and meta-analysis. East Mediterra Health J. 2019;25(1): 47-57.
[41] Soriano JB, Kendrick PJ, Paulson KR, Gupta V, Abrams EM, Adedoyin RA, et al. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet Respiratory Medicine. 2020;8(6): 585-596.
[42] Adeloye D, Song P, Zhu Y, Campbell H, Sheikh A, Rudan I.et al. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis. The Lancet Respiratory Medicine. 2022; 10(5):447-458.
[43] Verma A, Gudi N, Yadav UN, Roy MP, Mahmood A, Nagaraja R, et al. Prevalence of COPD among population above 30 years in India: A systematic review and meta-analysis. J Glob Health. 2021; 11.
[44] Quach A, Giovannelli J, Chérot-Kornobis N, Ciuchete A, Clément G, Matran R, et al. Prevalence and underdiagnosis of airway obstruction among middle-aged adults in northern France: The ELISABET study 2011–2013. Respir Med. 2015; 109(12): 1553-1561.
[45] Menezes AMB, Perez-Padilla R, Jardim JB, Muiño A, Lopez MV, Valdivia G, et al. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. Lancet. 2005; 366(9500):1875-1881.
[46] Divo MJ, Celli BR, Poblador-Plou B, Calderón-Larrañaga A, de-Torres JP, Gimeno-Feliu LA, et al. EpiChron—BODE Collaborative Group. Chronic Obstructive Pulmonary Disease (COPD) as a disease of early aging: Evidence from the EpiChron Cohort. PLoS One. 2018; 13(2).
[47] Chen W, Thomas J, Sadatsafavi M, FitzGerald JM. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. Lancet Respir Med. 2015; 3(8):631-639.
[48] Li X, Cao X, Guo M, Xie M, & Liu X. Trends and risk factors of mortality and disability adjusted life years for chronic respiratory diseases from 1990 to 2017: systematic analysis for the Global Burden of Disease Study 2017. BMJ. 2020; 368.
[49] Gibson GJ, Loddenkemper R, Lundbäck B, Sibille Y. Respiratory health and disease in Europe: the new European Lung White Book. Eur Respir J. 2013; 42(3):559-563.
[50] Guarascio AJ, Ray SM, Finch CK, Self TH. The clinical and economic burden of chronic obstructive pulmonary disease in the USA. ClinicoEconomics and outcomes research: Clinicoecon Outcomes Res. 2013; 5:235.
[51] Lakiang T, Nair NS, Ramaswamy A, Singhal U. Economic impact of chronic obstructive pulmonary disease: A cross-sectional study at teaching hospital in South India. J Family Med Prim Care. 2018; 7(5):1002.
[52] Londhe J, Mudliar K, Powar K, Dhadge N, Gaikwad S, Modi M, et al. Direct and indirect costs of COPD treatment in Pune city, India. 2019.
[53] Roy MP. Socio-demographic factors of COPD mortality in India. Clinical Epidemiology and Global Health, 2020; 8(3), 939-942.
[54] López-Campos JL, Tan W & Soriano JB. Global burden of COPD. Respirology. 2016; 21(1):14-23.
[55] Thomsen M, Nordestgaard BG, Vestbo J, Lange P. Characteristics and outcomes of chronic obstructive pulmonary disease in never smokers in Denmark: a prospective population study. Lancet Respir Med. 2013; 1(7):543-550.
[56] Rennard SI, Vestbo J. COPD: the dangerous underestimate of 15%. Lancet. 2006; 367(9518):1216-1219.
[57] Günen H, Tarraf H, Nemati A, Al Ghobain M, Al Mutairi S, Bacha ZA. Waterpipe tobacco smoking. Tuber Toraks, 2016; 64(1):94-96.
[58] Tan WC, Lo C, Jong A, Xing L, FitzGerald MJ, Vollmer WM, et al. Marijuana and chronic obstructive lung disease: a population-based study. CMAJ. 2009; 180(8):814-820.
[59] Yin P, Jiang CQ, Cheng KK, Lam TH, Lam KH, Miller MR, et al. Passive smoking exposure and risk of COPD among adults in China: the Guangzhou Biobank Cohort Study. Lancet. 2007; 370(9589):751-757.
[60] Mahmood T, Singh RK, Kant S, Shukla AD, Chandra A, Srivastava RK. Prevalence and etiological profile of chronic obstructive pulmonary disease in nonsmokers. Lung India. 2017; 34(2):122.

[61] Salvi S, Barnes PJ. Is exposure to biomass smoke the biggest risk factor for COPD globally? Chest. 2010; 138(1):3-6.
[62] Sharma AK, Kalra OP, Saini NK, Kelkar H. Pilot study of chronic obstructive pulmonary disease in an industrial town in India. J Health Pollut. 2019; 9(21).
[63] Parulekar AD, Martinez C, Tsai CL, Locantore N, Atik M, Yohannes AM, et al. Examining the effects of age on health outcomes of chronic obstructive pulmonary disease: results from the genetic epidemiology of chronic obstructive pulmonary disease study and evaluation of chronic obstructive pulmonary disease longitudinally to identify predictive surrogate endpoints cohorts. J Am Med Dir Assoc. 2017; 18(12):1063-1068.
[64] Doney B, Hnizdo E, Syamlal G, Kullman G, Burchfiel C, Martin CJ, Mujuru P. Prevalence of chronic obstructive pulmonary disease among US working adults aged 40 to 70 years: National Health Interview Survey Data 2004 to 2011. J Occup Environ Med. 2014; 56(10):1088.
[65] Centers for Disease Control and Prevention (CDC). Current cigarette smoking prevalence among working adults--United States, 2004-2010. MMWR Morb Mortal Wkly Rep. 2011; 60(38):1305-1309.
[66] Jindal SK, Aggarwal AN, Gupta D. Disease and Its Association with Smoking. Indian J Chest Dis Allied Sci, 2001; 43:139-471.
[67] Foreman MG, Zhang L, Murphy J, Hansel NN, Make B, Hokanson JE, et al. COPD Gene Investigators. Early-onset chronic obstructive pulmonary disease is associated with female sex, maternal factors, and African American race in the COPD Gene Study. Am J Respir Crit Care Med. 2011; 184(4):414-420.
[68] Hardin M, Foreman M, Dransfield MT, Hansel N, Han MK, Cho MH, DeMeo D. Sex-specific features of emphysema among current and former smokers with COPD. Eur Respir J. 2016; 47(1):104-112.
[69] Sørheim IC, Johannessen A, Gulsvik A, Bakke PS, Silverman EK, DeMeo DL. Gender differences in COPD: are women more susceptible to smoking effects than men? Thorax. 2010; 65(6):480-485.
[70] Busch R, Han MK, Bowler RP, Dransfield MT, Wells JM, Regan EA, Hersh CP. Risk factors for COPD exacerbations in inhaled medication users: the COPD Gene study biannual longitudinal follow-up prospective cohort. BMC Pulm Med. 2016; 10:16-28.
[71] Kim YI, Schroeder J, Lynch D, et al. Gender differences of airway dimensions in anatomically matched sites on CT in smokers. COPD. 2011; 8(4):285-292.
[72] Bowler RP, Kim V, Regan E, Williams AA, Santorico SA, Make BJ, et al. Prediction of acute respiratory disease in current and former smokers with and without COPD. Chest. 2014; 146(4):941-950.
[73] Jaramillo JD, Wilson C, Stinson DJ, Lynch DA, Bowler RP, Lutz S, et al. Reduced bone density and vertebral fractures in smokers. Men and COPD patients at increased risk. Ann Am Thorac Soc. 2015; 12(5):648-656.
[74] Murgia N, Gambelunghe A. Occupational COPD - The most under-recognized occupational lung disease? Respirology. 2022.
[75] Balmes J, Becklake M, Blanc P, Henneberger P. American Thoracic Society Statement: Occupational contribution to the burden of airway disease. Am J Respir Crit Care Med. 2003; 167(5):787-97.
[76] Bang KM, Syamlal G, Mazurek JM. Prevalence of chronic obstructive pulmonary disease in the US working population: an analysis of data from the 1997–2004 National Health Interview Survey. COPD. 2009; 6(5):380-387.
[77] Varkey AB. Chronic obstructive pulmonary disease in women: exploring gender differences. Curr Opin Pulm Med. 2004; 10(2):98-103.
[78] Blanc PD. Occupation and COPD: a brief review. J Asthma. 2012; 49(1):2-4.
[79] Hnizdo E, Vallyathan V. Chronic obstructive pulmonary disease due to occupational exposure to silica dust: a review of epidemiological and pathological evidence. Occup Environ Med. 2003; 60(4):237-243.
[80] Bergdahl IA, Toren K, Eriksson K, Hedlund U, Nilsson T, Flodin R, Järvholm B. Increased mortality in COPD among construction workers exposed to inorganic dust. Eur Respir J. 2004; 23(3):402-406.
[81] Han MK, Postma D, Mannino DM, Giardino ND, Buist S, Curtis JL, Martinez FJ. Gender and chronic obstructive pulmonary disease: why it matters. Am J Respir Crit Care Med. 2007; 176(12):1179-1184.
[82] Grahn K, Gustavsson P, Andersson T, Lindén A, Hemmingsson T, Selander J, & Wieber P. Occupational exposure to particles and increased risk of developing chronic obstructive pulmonary disease (COPD): A population-based cohort study in Stockholm, Sweden. Environ Res. 2021; 200: 111739.
[83] Stoller JK, Aboussouan LS. $\alpha$1-antitrypsin deficiency. Lancet, 2005; 365(9478):2225-2236.
[84] Blanco I, Diego I, Bueno P, Pérez-Holanda S, Casas-Maldonado F, Miravitlles M. Prevalence of $\alpha$1-antitrypsin PiZZ genotypes in patients with COPD in Europe: a systematic review. Eur Respir Rev. 2020; 29(157). doi: 10.1183/16000617.0014-2020.
[85] Zhang PD, Zhang XR, Zhang A, Li ZH, Liu D, Zhang YJ & Mao C. Associations of genetic risk and smoking with incident COPD. Eur Respir J. 2022; 59(2).
[86] McCloskey SC, Patel BD, Hinchliffe SJ, Reid ED, Wareham NJ, Lomas DA. Siblings of patients with severe chronic obstructive pulmonary disease have a significant risk of airflow obstruction. Am J Respir Crit Care Med. 2001; 164(8):1419-1424.
[87] Ding Z, Wang K, Li J, Tan Q, Tan W, Guo G. Association between glutathione S-transferase gene M1 and T1 polymorphisms and chronic obstructive pulmonary disease risk: a meta-analysis. Clin Genet. 2019; 95(1):53-62.
[88] Cho MH, McDonald MLN, Zhou X, Mattheisen M, Castaldi PJ, Hersh CP, et al. Risk loci for chronic obstructive pulmonary disease: a genome-wide association study and meta-analysis. Lancet Respir Med. 2014; 2(3):214-225. doi: 10.1016/S2213-2600(14)70002-5.
[89] Pillai SG, Ge D, Zhu G, Kong X, Shianna K, Need A, et al. Investigators ICGN, Rennard SI, Lomas DA, Silverman EK, Goldstein DB: A genome-wide association study in chronic obstructive pulmonary disease (COPD): identification of two major susceptibility loci. PLoS Genet. 2009; 5(3):e1000421. doi: 10.1371/journal.pgen.1000421.
[90] Singh D. Pharmacological treatment of stable chronic obstructive pulmonary disease. Respirology. 2021;26(7):643-651.

[91] Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD Science Committee report 2019. Eur Respir J. 2019;53:1900164.
[92] Stockley RA, Halpin DMG, Celli BR, Singh D. Chronic obstructive pulmonary disease biomarkers and their interpretation. Am J Respir Crit Care Med. 2019;199:1195–204
[93] Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2022. Global strategy for the diagnosis, management and prevention of COPD. Proceedings of the Global Initiative for Chronic Obstructive Lung Disease.
[94] Ni H, Moe S, Soe Z, Myint KT, Viswanathan KN. Combined aclidinium bromide and long-acting beta2-agonist for chronic obstructive pulmonary disease (COPD). Cochrane Database of Systematic Reviews.2018; 12.
[95] Chapman KR, Wise RA, Scirica BM, Bhatt DL, Daoud SZ, Lythgoe D, Gil EG. Long-acting antimuscarinic therapy in patients with chronic obstructive pulmonary disease receiving beta-blockers. Respiratory research. 2021; 22(1): 1-10.
[96] Shuai T, Zhang C, Zhang M, Wang Y, Xiong H, Huang Q, Liu J. Low-dose theophylline in addition to ICS therapy in COPD patients: a systematic review and meta-analysis. PloS one. 2021; 16(5): e0251348.
[97] Bafadhel M, Singh D, Jenkins C, Peterson S, Bengtsson T, Wessman P, Fagerås M. Reduced risk of clinically important deteriorations by ICS in COPD is eosinophil dependent: a pooled post-hoc analysis. Respiratory research. 2020; 21(1): 1-10.
[98] Suissa S, Dell'Aniello S, Ernst P. Comparative effects of LAMA-LABA-ICS vs LAMA-LABA for COPD: cohort study in real-world clinical practice. Chest. 2020; 157(4): 846-855.
[99] Brusselle GG, Himpe U, Haerens M, Fievez P, Leduc D, Peche R, et al. A Prospective Non-Interventional Study in COPD Patients That Evolve to Fixed LABA/LAMA/ICS Triple Therapy (TRIVOLVE). In TP37. TP037 Physiologic assessment in chronic lung disease. American Thoracic Society. 2021: A2171-A2171
[100] Phillips JE. Inhaled phosphodiesterase 4 (PDE4) inhibitors for inflammatory respiratory diseases. Frontiers in Pharmacology. 2020; 11: 259.
[101] Juergens LJ, Worth H, Juergens UR. New perspectives for mucolytic, anti-inflammatory and adjunctive therapy with 1, 8-cineole in COPD and asthma: review on the new therapeutic approach. Advances in therapy. 2020; 37(5): 1737-1753.
[102] Jang JH, Lee JH, Chand HS, Lee LS, Lin Y, Weathington N, Mallampalli R, Jeon YJ, Nyunoya T. APO-9'-Fucoxanthinone Extracted from Undariopsis peteseniana Protects Oxidative Stress-Mediated Apoptosis in Cigarette Smoke-Exposed Human Airway Epithelial Cells. Marine Drugs. 2016; 14(7): 140.
[103] Kubo H, Asai K, Kojima K, Sugitani A, Kyomoto Y, Okamoto A, Yamada K, Ijiri N, Watanabe T, Hirata K, Kawaguchi T. Astaxanthin Suppresses Cigarette Smoke-Induced Emphysema through Nrf2 Activation in Mice. Mar Drugs. 2019; 17(12): 673.
[104] Keeler DM, Grandal MK, McCall JR. Brevenal, a Marine Natural Product, is Anti-Inflammatory and an Immunomodulator of Macrophage and Lung Epithelial Cells. Marine Drugs. 2019; 17(3): 184.
[105] Zhao DK, Shi YN, Petrova V, Yue GGL, Negrin A, WuSB, D'Armiento JM, Lau CBS, Kennelly EJ. Jaboticabin and Related Polyphenols from Jaboticaba (Myrciaria cauliflora) with Anti-inflammatory Activity for Chronic Obstructive Pulmonary Disease. J Agric Food Chem. 2019; 67(5): 1513-1520.
[106] Chen Z, Chen P, Wu H, Shi R, Su W, Wang Y, Li P. Evaluation of Naringenin as a Promising Treatment Option for COPD Based on Literature Review and Network Pharmacology. Biomolecules. 2020; 10(12): 1644.