

 <p>ISSN NO. 2320-5407</p>	<p>Journal Homepage: -<a href="http://www.journalijar.com">www.journalijar.com</a></p> <p><b>INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)</b></p> <p>Article DOI:10.21474/IJAR01/10350 DOI URL: <a href="http://dx.doi.org/10.21474/IJAR01/10350">http://dx.doi.org/10.21474/IJAR01/10350</a></p>	 <p>INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR) ISSN 2320-5407 Journal Homepage: <a href="http://www.journalijar.com">http://www.journalijar.com</a> Article DOI:10.21474/IJAR01/10350</p>
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## REVIEW ARTICLE

### MECHANISM OF CIGARETTE SMOKE - INDUCED CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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#### Manuscript Info

##### Manuscript History

Received: 27 November 2019

Final Accepted: 30 December 2019

Published: January 2020

##### Key words:-

Chronic Obstructive Pulmonary Diseases (COPD), Cigarette Smoke (CS), Lung, Oxidative Stress, Inflammation, Airway-Remodeling

#### Abstract

Chronic Obstructive Pulmonary Diseases (COPD) is currently the third leading cause of death worldwide. COPD causes great burden to society by contributing in morbidity and productivity loss. Cigarette smoking is the primary reason for COPD in smokers. In spite of the several initiatives of the national and international public health organizations for quitting smoking, number of smokers are increasing in low- and middle-income countries continuously. For the prevention and morbidity management of this treatable disease, understanding of the pathogenic events orchestrated by cigarette smoke (CS) is required. In smokers, COPD is caused by the constant exposure of lung to harmful components of CS. Oxidative stress plays the central role in CS-induced COPD pathogenesis in smokers along with other important components of COPD pathogenesis, such as lung injury, lung inflammation, protease-antiprotease imbalance, small airway remodeling and apoptosis. In this review we tried to briefly summarize the mechanisms behind the CS-induced pathogenesis for COPD which follow a complex network of events.

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#### Introduction:-

Cigarette smoking plays a pivotal role in non-communicable diseases (NCDs) which are major contributors to the total number of global deaths. Chronic obstructive pulmonary diseases is one of the leading mortality contributor among all NCDs (Eriksen et al 2015). According to US Surgeon General Reports, cigarette smoking is the major cause of Chronic Obstructive Pulmonary Diseases (USDHHS 2004). There are more than one billion smokers in the world (Mendis et al 2011) and the number is still increasing, with the epidemic shifting to the developing world (Mendis et al 2011, Laniado-Laborín 2009). The majorities (about 80%) of the world's smokers live in low and middle-income countries (Laniado-Laborín 2009). Global prevalence of adult tobacco smoking was almost 22% in 2010 (WHO Global status report NCDs 2014). Smoking of manufactured cigarette is the most convenient and globally practiced way of tobacco consumption (Mendis et al 2011) and used by 90% of current smokers (WHO Global status report NCDs 2014). Respiratory tract and lung are the primary organs to be exposed to cigarette smoke (CS). From lung, CS enters the bloodstream and gets access to almost every organ of the human body.

Chronic obstructive pulmonary disease (COPD) is currently the third leading cause of death worldwide (WHO: Global health estimate 2016). It was predicted that COPD will cause 7.8 % of global death by 2030 (Mathers and Loncar 2006). Besides mortality, COPD attributes morbidity, productivity loss, and presents a great burden to both

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individual patients and the healthcare system. COPD was projected as the 7th leading cause of disability-adjusted life year (DALY, a WHO-recommended measure of disease burden) in 2030 (Mathers and Loncar 2006). As the most important risk factor for COPD, cigarette smoking accounts for approximately 90% of COPD cases (Peto et al 1992). Smoking causes about 80% of all deaths from COPD (USDHHS 2014). Smokers are 12 to 13 times more likely to die from COPD than nonsmokers (USDHHS 2014).

Although the easiest way to prevent such loss from cigarette smoking is to stop cigarette smoking, it seems an unachievable task in present situation. In spite of several initiatives to spread the awareness about smoking related health hazards, number of smokers are increasing day by day in the middle- and low-income countries. Increase in taxes on cigarettes and forming law against smoking in public places have not change the mind of smokers so far. In this scenario prevention of cigarette smoke induced pathogenesis by molecular way is the only way to stop the harm in smokers. To achieve such goal and to develop newer and effective drug against these diseases, one must understand the pathogenic events caused by smoking at molecular level. This understanding will also help to answer the pertinent question that which specific chemical compound(s) amidst the complex mixture of cigarette CS is actually responsible for triggering the initiation of molecular reactions leading to COPD. In this review we tried to summarize the mechanisms behind the CS-induced pathogenesis for COPD which follow a complex network of events. For finding newer preventive and intervention measures, understanding of the disease pathogenesis is the primary requirement in this field of research.

#### **Pathogenesis of cigarette smoke-induced Chronic Obstructive Pulmonary Disease (COPD):**

Chronic obstructive pulmonary disease (COPD) is a common disease. It is caused by the constant exposure of lung to harmful particles and gases from environment. They induce abnormalities in alveolus and respiratory tract of lung. This ultimately leads to limitation of airflow with constant difficulties in respiration which are the basic characteristics of COPD. Timely medical intervention can prevent and treat this particular condition (Vogelmeier et al 2017). As the name suggests, COPD refers to a group of chronic pulmonary diseases such as emphysema and chronic bronchitis which cause airflow obstruction in the lung leading to troubled breathing (CDC: COPD prevention framework 2011). In emphysema, air sacs of the lung are damaged leading to enlarged airspace and breathlessness. On the other hand, chronic bronchitis is characterized by a regular cough and sputum production for at least a trimester a year for minimum two consecutive years.

Scientists tried to understand the pathogenesis of CS-induced COPD by using different suitable animal model (Churg et al 2008). Emphysematous lung damage is the major prominent phenotypic establishment in COPD patient. It was extensively studied using these models (USDHHS 2010). However, as sputum production is hard to monitor, an animal model for studying chronic bronchitis is difficult to establish (Churg et al 2008). In vivo model systems of CS-induced emphysema are used to vary in the cigarettes used, the species used, the manner in which CS is delivered, and assessment of the dose of smoke actually reaching the animals. Standard research cigarettes are generally used, and the exposure is produced by directing smoke from a single cigarette to the nose of the animal restrained in a single body compartment or by exposing groups of animals that are free to move in a chamber in which CS is put into the atmosphere (USDHHS 2010). Oxidative stress from exposure to CS has a prominent role in the pathogenesis of the COPD. Oxidative stress is also interrelated to the other components of COPD pathogenesis, such as lung injury, lung inflammation, protease-antiprotease imbalance, small airway remodeling and apoptosis (USDHHS 2010). In this review we will discuss about the specific mechanistic components of CS-induced COPD pathogenesis.

#### **CS-induced Oxidative Stress in lung:**

Exogenous oxidants from inhaled CS play the central role in oxidative stress-induced lung injury in smokers (Rahman and MacNee 1998). The lung as an environmentally exposed organ has well evolved enzymatic and nonenzymatic antioxidant systems to protect the airways and alveoli against both exogenous and endogenous oxidants. However, the balance between oxidant and antioxidant shifts unfavorably towards oxidative stress in smokers who develop COPD. The reason behind this shift is either due to the presence of an excess of oxidants or a decreased level or function of antioxidants (USDHHS 2010). In normal physiologic condition, the relative rate of production and removal of ROS is well controlled (Gutteridge 1994). Thus, in normal condition antioxidants rapidly remove the reactive oxygen species (ROS) and thereby preventing them from inducing cellular dysfunction and eventual cell death. Superoxide dismutase (SOD), catalase (Kinnula and Crapo 2003), glutathione (GSH) redox system (Rahman and MacNee 2000) and thioredoxin system (Arner and Holmgren 2000) are the major enzymatic antioxidant system of lung.

**CS-induced lung epithelial injury:**

The structural integrity of the lung is contributed by the airway epithelial cells which produce mucus, defensins, matrix proteins, lipid molecules, inflammatory mediators, cell surface receptors, and antioxidants. Scientific studies observed that the epithelial cell lining of lung plays an important role in its defense from noxious foreign particles. Upon the exposure of CS-derived ROS, these cells in airway immediately response (Mercer et al 2006). In *in vivo* studies, it was found that CS-induced lung injury primarily initiates with increased permeability of epithelial lining (Li et al 1994) leading to an increased influx of inflammatory cells in lung airway epithelial layer (Martin et al 1998).

**CS-induced lung inflammation:**

COPD is often characterized by the increased inflammatory response in the lungs (Hogg 2004). CS-induced oxidative stress is believed to be the responsible mechanism for the initiation and enhancement of lung inflammation which plays a major role in COPD. Lung inflammation is augmented by ROS of CS by various physiological ways, such as releasing inflammatory mediators IL-8 (Profita et al 2003), increased production of redox-sensitive transcription factors (NF- $\kappa$ B and AP-1), activation of different signaling pathways such as C-JUN N-terminal kinase, extracellular signal-regulated kinase and p38 mitogen-activated protein kinase (Rahman and MacNee 1998). I- $\kappa$ B bound cytosolic inactive NF- $\kappa$ B is activated by oxidant-induced I- $\kappa$ B kinase. NF- $\kappa$ B regulates the gene expression of various inflammation mediators by binding to its consensus sites in nucleus leading to inflammation. In the patients of COPD, translocation of NF- $\kappa$ B to the nucleus and its nuclear binding are increased in the airway macrophages and airway epithelial cells of the lung (Di Stefano et al 2002). As the resulting inflammation further increases oxidative stress, a harmful physiological cycle is generated where increased oxidative stress and augmented inflammation perpetuate each other (USDHHS 2010).

**CS-induced protease-antiprotease imbalance:**

CS-induced oxidative stress and lung inflammation both play a significant role in the process leading towards the protease-antiprotease imbalance which is considered to be the central piece of the classic theory of emphysematous lung damage (USDHHS 2010). Proteases involved in this mechanism of matrix degradation are metalloproteases, serine proteases and cysteine (USDHHS 2010). Metalloproteases, including MMP-9 and MMP-12 (Parks and Shapiro 2000), can degrade elastin (Churg et al 2008). In COPD patient, infiltrated inflammatory cells upon activation release protease. On the other hand oxidants from CS and other sources inactivate antiprotease such as AAT. These two events ultimately lead towards protease-antiprotease imbalance. In the condition of protease-antiprotease imbalance, protease starts to degrade matrix. Some *in vitro* studies suggested that oxidative stress of lung in COPD patient is further increased by the protease as it induces the release of ROS from lung epithelial cells (Aoshiba et al 2001).

**CS-induced small airway remodeling (SAR):**

A lung tissue has repair mechanism against the potential injuries from the inhaled substances. Tissue remodeling is such a well-controlled mechanism of repair. Upon the continuous CS-induced oxidative stress and lung inflammation, the remodeling system becomes deregulated in smokers (Hogg 2004). Remodeling of small airways plays a significant role in smoker's airflow obstruction by thickening the airway walls (Hogg 2004). This tissue remodeling leads to airway fibrosis, emphysema, and pulmonary hypertension (Postma and Timens 2006). Collagen deposition is associated SAR-induced narrowing of the airway (Hogg 2004). SAR has a strong association with FEV1 (Hogg 2004).

**CS-induced apoptosis:**

Apoptosis of alveolar endothelial cells was emerged to be a leading phenomenon towards the initiation of emphysematous lung damage in smokers (Kasahara et al 2001). Airway lymphocytes (Majo et al 2001) and stimulated peripheral blood leukocytes (Hodge et al 2003) from patients with COPD also show increased apoptosis. There is strong evidence supporting the role of oxidative stress in apoptosis (Tuder et al 2003).

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