Summary and Conclusions
Diverse interactions between genetic factors and the environmental factors most likely explain individual susceptibility or resistance to the respiratory disorders like COPD induced by environmental pollutants. The investigation of heritable susceptibility to disease is an effort to associate disease phenotype with underlying genotype. The variations in genes can be used as markers in genome wide association mapping studies to identify the related disorder susceptibility loci. The \textit{CYP1A1}, \textit{CYP1A2}, \textit{GSTP1}, \textit{mEPHX} and \textit{CYBA} are the five candidate genes of substantial importance for the susceptibility to the COPD. The present thesis tried to explore the possible association of the five candidate genes with COPD. We also tried to decipher the disease complexity by using mice model exposed to acute cigarette smoke, the main causing factor for COPD to reveal the disease pathogenesis at histological, biochemical and molecular levels. Beside that we also investigate the involvement of the above genetic variants in the susceptibility to another pulmonary disorder, HAPE, related to high altitude. The major conclusions of the work are as follows.

In Chapter 2 plasma LPO, GSH levels, GPx, CAT activities, BMI and FEV1\% predicted were analyzed for individual and interactive causal effects. The patients had increased LPO and decreased antioxidants. Of note are the correlations of oxidative stress markers with BMI and FEV1\% predicted; LPO inversely and GSH, GPx, CAT positively correlated with both BMI, and FEV1\% predicted in the patients. Further, a positive correlation existed between BMI and FEV1\% predicted in COPD. The overall findings suggest that the COPD patients are vulnerable to oxidative stress and have impaired status of oxidant-antioxidants balance. Our findings strengthened the intimate relationship of oxidative status with BMI and lung function in severity of the disease. Even the direct correlation between BMI and FEV1\% predicted is an indication of aggravated pathophysiology.

Chapter 3 deals with genetic studies and is divided into two parts to describe the detoxification and oxidative stress markers. In part \textsuperscript{1}\textdegree, the genetic variants I105V, A114V of \textit{GSTP1} and Y113H, H139R of \textit{mEPHX} were investigated for possible association, individually or in combination with COPD and their contribution to oxidative stress markers such as MDA, GSH, GPx and airflow obstruction. Patients
were over-represented by the alleles 105V, 114V of *GSTP1* and 113H, 139H of *mEPHX* and the haplotypes of same alleles i.e. 105V–114V and 113H–139H. Moreover, there was marked over-representation of combination of genotypes, I105I+A114A of *GSTP1* in controls; whereas, the combinations with 105V/114V alleles of *GSTP1* and the homozygotes H113H+H139H of *mEPHX* in patients. Patients had significantly elevated MDA level and decreased GSH level & GPx activity. Of note, the genotypes, I105V/V105V, A114V/V114V of *GSTP1* and Y113H/H113H of *mEPHX* associated with increased MDA level, decreased GSH level and lower FEV1% predicted in patients; so was the correlation of these biomarkers and lung function with the combinations of the genotypes. Consequently, the findings pointed towards the role of alleles 105V/114V of *GSTP1* and 113H/139H of *mEPHX* and the combination of genotypes with same alleles in association with imbalanced oxidative stress and lung function, signifying the importance in COPD.

In part II\textsuperscript{nd} of Chapter 3, we examined the oxidative stress associated gene polymorphisms 462Ile/Val, 3801T/C of *CYP1A1*, −3860G/A of *CYP1A2* and −930A/G, 242C/T of *CYBA* individually or in combination and their contribution to oxidative stress markers by measuring MDA, CAT, GSH and GPx. Patients were over-represented by the alleles 462Val, 3801C of *CYP1A1* and −930G, 242C of *CYBA* and consequently the haplotypes i.e. 462Val:3801C, 462Val:3801T and 930G:242C. Similarly, *CYP1A1* and *CYP1A2* haplotypes, 462Val:3860G and 462Val:3801T:3860G were significantly over-represented. The same alleles associated genotypes combinations within and between genes were more prevalent in patients. Of note, the genotypes, 462Ile/Val+Val/Val, 3801TC+CC of *CYP1A1* and −930AG+GG of *CYBA* associated with increased MDA level, decreased CAT activity and GSH level in patients. The *CYP1A1* 462Ile/Val, 3801T/C and *CYBA* −930A/G, 242C/T polymorphisms emerged as noteworthy variants, showing association with COPD. Therefore, the identified alleles, its haplotypes and the genotypes combination associated with imbalanced oxidative stress, signifying the importance in the disease.

In Chapter 4 we examined the association of genes involved in maintaining redox balance such as NADPH oxidase and *GSTP1* with HAPE (another pulmonary
disorder) by analyzing the polymorphisms −930A/G, 242C/T of NADPH-oxidase \( p22phox \) and 105I/V, 114A/V of \( GSTP1 \) individually and in combination. LPO levels were estimated and correlated with individual genotype and genotypes combinations of these polymorphisms. Genotype distribution of −930A/G, 242C/T and 105I/V polymorphisms differed significantly between the two groups. The haplotypes G-C of \( p22phox \) and 105V-114A of \( GSTP1 \) were significantly over-represented in HAPE-p. HAPE-p had significantly elevated LPO levels, which correlated with GG, CC, 105VV and 114VV genotypes. Interaction between any two polymorphisms of the two genes revealed over-representation of most of the minor-alleles associated genotypes combinations in HAPE-p, which correlated with significantly elevated LPO levels. Additionally, HAPE-p were also over-represented by the four genotypes combination GG+CC+105VV+114VV, which correlated with elevated LPO levels. The findings pointed towards the conclusion that the alleles −930G/242C of \( p22phox \) and 105V/114V of \( GSTP1 \), their haplotypes and genotypes combinations associated with imbalanced oxidative stress and susceptibility to HAPE.

In Chapter 5 the acute-term CS exposure to mice revealed the molecular complexity of disease pathogenesis at biochemical (detoxification and endogenous antioxidant enzymes) and molecular levels (RNA, Protein and DNA levels) using various techniques including histopathology, biochemical estimation, RT-PCR, Western Blotting and Comet assay. Most of the detoxifying and oxidative status genes upregulated in terms of their expression as well as their enzyme activities in CS exposure group, however, the expression and activity/levels returned to near normal in NAC treated as compared to CS group, although it remained higher as compared to C group. The study concludes that the deleterious effect of CS in acute exposure is due to higher expression and activity/levels of oxidants than that of antioxidants.