Oxidative stress is also known to induce histone acetylation and methylation of promoter region leading to change in gene expression. The lysine residue in amino termini of histone3 (H3) and histone4 (H4) can undergo several modifications including acetylation and methylation. Histone acetylation induces transcriptional activation whereas decreased acetylation causes transcriptional repression [39]. Oxidative stress affects the activity and function of histone deacetylase enzyme (HDAC) which plays an important role in histone acetylation. Several studies showed that oxidative stress induces HDAC enzyme resulting in overexpression of genes in cancer [37]. Oxidative stress also affects histone methylation either by inducing the activity of DNA methylase enzyme or by decreasing production of SAM. Methylation of histone is associated with both transcription activation and repression of gene [40]. Hence, oxidative stress leads to changes in epigenetics by histone modification and DNA methylation which in turn modulates the expression of genes leading to chronic diseases such as cancer.

5 Gene–Environment Interaction in Oxidative Stress-Induced Pathologies

Oxidative stress induced by different environmental stimuli modulates the transcription of various genes which results in different chronic diseases in human beings including cardiovascular diseases, COPD, cancer, and neurodegenerative diseases. Some of these diseases are discussed below.

5.1 Pesticide-Induced Pathologies

Pesticides are commonly used chemicals intended to kill the pests, vectors of diseases, in agricultural field and enhance the agricultural production. However, excessive and indiscriminate use has led to dissemination in the environment – soil, water, and air – which adversely affects the human health. Several studies have reported that long-term exposure to even lower amount of pesticides leads to chronic diseases such as cancer [41], cardiovascular [42], and neurodegenerative diseases [43]. The toxic effect of pesticides such as organophosphates, organochlorines, pyrethroids, thiazines, and paraquat is mainly due to their ability to induce oxidative stress [44].

Pesticides induce oxidative stress in exposed cells by the following mechanisms:

1. Pesticides cause production of ROS either as by-products during pesticide metabolism or due to mitochondrial dysfunction. When pesticide enters inside the body, they get metabolized by several detoxifying enzymes such as NADPH-cytochrome P450 reductase, xanthine oxidase, and NADH-ubiquinone oxidoreductase. The by-product of this metabolism results in production of secondary free radicals, e.g., paraquat (PQ) metabolism leads to generation of paraquat mono-cation which further gets reoxidized to generate paraquat di-cation and oxygen radicals as shown in the equation resulting in redox imbalance [45]:

$$PQ^{2+} + e^{-}\,CYP450 \longrightarrow PQ^{+}$$

$$PQ^{+} + O_2 \longrightarrow PQ^{2+} + O_2^{\bullet -}$$

   Some of the pesticide such as rotenone causes mitochondrial dysfunction by blocking ubiquinone binding site of complex-I of electron transport system and prevents transport of electrons from complex-I to ubiquinone, and free electrons react with oxygen generating free radicals [46].
2. Pesticides also cause change in antioxidant homeostasis. Long-term exposure to pesticides such as organophosphates leads to decrease in antioxidant enzymes such as SOD and CAT which are first line of defense against oxidative stress [47]. As a result exposed cells fail to neutralize generated ROS, leading to enhanced stress.
3. Glutathiones (GSH) are the most important intrinsic defense system that directly scavenges free radicals. Decrease in GSH level has been observed in liver, brain, kidney, and spleen of rat exposed to organophosphate pesticides [48].

Pesticides cause decrease in level of GSH either by direct oxidation of GSH to glutathione disulfide (GSSG), by causing decreased level of glutathione reductase (GR) enzyme, or by oxidation of NADPH. GR needs NADPH as a substrate for reduction of oxidized GSSG to its reduced and active form, GSH:

$$GSSG + NADPH + H^{+} \xrightarrow{GR} 2GSH + NADP^{+}$$

Paraquat herbicide is reported to cause oxidation of NADPH and hence prevent regeneration of GSH in the cells resulting in decrease GSH/GSSG ratio and redox imbalance. Although depletion of NADPH activates pentose phosphate pathway by feedback mechanism that leads to restoration of NADPH, this results in continuous redox cycling between paraquat and oxygen, resulting in formation of $O_2^{\bullet -}$ [48]. Further, since GSH plays important role in regeneration of other antioxidants such as ascorbic acid and alpha-tocopherol, decreased GSH level may prevent their regeneration as well. Pesticides thus decrease antioxidant defense of the body leading to oxidative stress.

4. Pesticides such as organophosphates, synthetic pyrethroid, and carbamates may also increase the lipid peroxidation activity in erythrocytes cell [49]. Initial generation of ROS by detoxifying enzyme results in lipid peroxidation which further generates lipid-free radicals resulting in increased oxidative stress. Organophosphates are reported to induce peroxidative damage of biological membrane resulting in accumulation of lipid peroxidation products [48].
5. Pesticide-induced oxidative stress is also determined by extent of exposure and genetic polymorphism in pesticide metabolizing enzymes such as paraoxanase-1 (PON-1), pseudo or butyryl cholinesterase (BCHE), and GST, which play an important role in metabolizing organophosphates. Different polymorphic forms of PON-1 enzyme such as PON1-192RR, PON1−108TT, and PON1−909CC occur which are associated with lower PON-1 activity, which lead to pesticide toxicity and induction of oxidative stress. Short-term exposure to organophosphates in PON1-192RR genotype leads to increase in GPx and CAT as an adaptive mechanism against oxidative stress. Long-term exposure of organophosphate in PON1-192RR genotype results in lower SOD activity making them susceptible to oxidative stress. GSTs are another class of polymorphic enzyme that play protective role by deactivating oxygen free radical upon exposure to pesticide. Short-term exposure in GSTM1 null genotype was found to be associated with decrease in SOD level making them susceptible to oxidative stress. Hence, polymorphic gene encoding PON1 and GSTs are important determinants of organophosphate pesticide-induced oxidative stress [44]. These evidences indicate that the extent of pesticide-induced oxidative stress depends on the type of polymorphism in metabolizing enzyme genes, which in turn impacts the expression as well as activity of antioxidant enzymes.

Pesticides cause generation of oxidative stress in the cells which activates redox-sensitive transcription factors such as NF-kB which in turn transcribes numerous genes of pro-inflammatory enzymes, chemokines, and cytokines [45]. These mediators increase inflammation and tissue damage which results in diseases such as cancer, neurodegeneration, and cardiovascular diseases (Fig. 3). Increased peroxidation of membrane lipids, membrane receptor, and membrane-bound enzyme can also alter function, structure, and fluidity of membrane leading to pathogenesis. Brain tissues are more prone to pesticide-induced oxidative stress since they are rich in polyunsaturated fatty acids which easily undergo peroxidation leading to neural degeneration diseases such as Parkinson [50].

Several investigations are underway to establish the link between pesticides and diseases and their causative mechanism [51]. Such studies may lead to novel approaches for prevention and treatment of pesticide- induced diseases. Nevertheless, owing to high toxic effect of pesticides on human health, a number of pesticides have been banned and use of less toxic pesticides is encouraged.

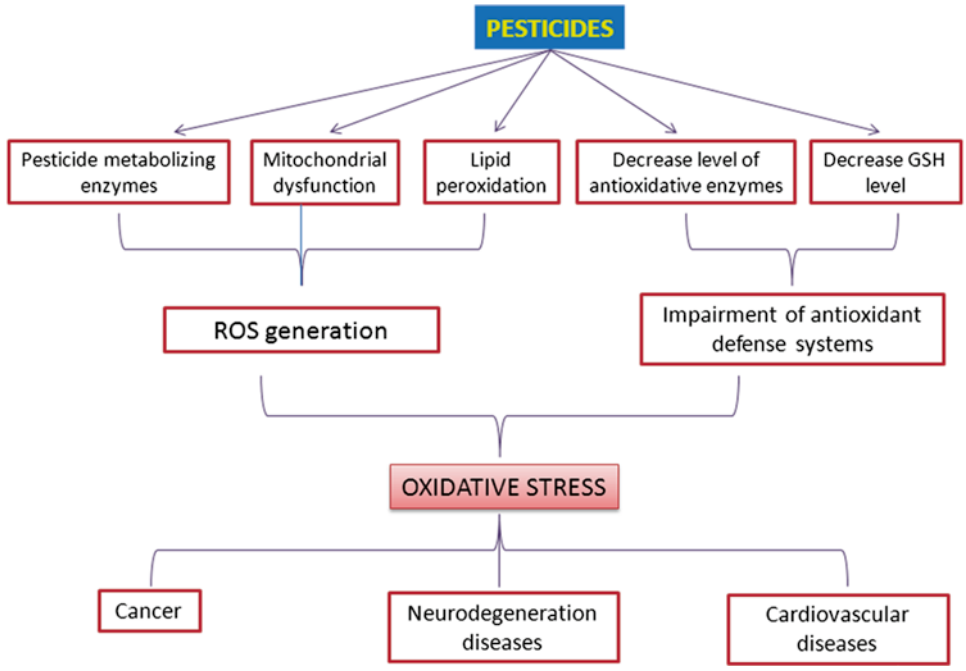

Fig. 3 Summary of pesticide-induced oxidative stress leading to chronic diseases

5.2 Cardiovascular Disease

Cardiovascular diseases (CVD) are the leading cause of mortality and morbidity worldwide [52]. CVD include many diseases related to heart and blood vessels, e.g., coronary heart disease, ischemic heart disease, atherosclerosis, hypertension, cardiac hypertrophy, cardiomyopathies, and congestive heart failure [53]. A disturbance in redox homeostasis in the body may result in failure at genetic transcription level due to the exposure to various environmental factors that could lead to development of CVD [54]. Although it is well known that environmental factors such as smoke, poor diet, diabetes, and aging increase oxidative stress, the relationship between oxidative stress, genes, and CVD remains complex. The possible mechanisms of gene–environment interaction-induced oxidative stress in CVD are important to understand for better therapeutic strategies.

Cigarette smoke, a common environmental factor associated with increased oxidative stress, is linked with oxidation of low-density lipoprotein (LDL) resulting in formation of oxidized low-density lipoprotein (oxLDL), which is implicated in plaque formation in coronary artery [54–56]. Smoking also causes vascular endothelial damage which leads to inflammation followed by an increase in the expression of cell adhesion molecules. The important cellular sources of oxidative stress in cardiovascular system upon exposure to environmental oxidants include enzymes Nox, xanthine oxidoreductase (XOR) and nitric oxide synthetase (iNOS), and mitochondrial enzyme such as mitochondrial uncoupling protein (UCP) [57, 58].

Tobacco smoke containing metabolites are converted into ROS by enzyme such as myeloperoxidase [59]. ROS besides causing oxidation of LDL forming oxLDL also activate more ROS-producing machinery such as Nox which further lead to generation of more oxLDL [60]. In endothelial cells, oxLDL bind to lectin-like oxidized low-density lipoprotein receptor 1 (LOX-1) encoded by OLR 1 gene [61, 62]. An adaptor protein, TRAF3IP2, interacts with active LOX-1 and binds to inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ) upon