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Pesticide-Induced Oxidative Stress and Cancer: Mechanistic Insights and Public Health Implications

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Abstract

Pesticides are widely used in modern agriculture to improve crop yield and prevent pest-related losses. However, increasing epidemiological and experimental evidence links chronic pesticide exposure with cancer development. One of the critical mechanisms implicated in this association is oxidative stress. Pesticides induce excessive reactive oxygen species (ROS) formation overwhelming the antioxidant defense systems and leading to cellular damage, lipid peroxidation, DNA mutation, and ultimately carcinogenesis. ROS-mediated signaling in addition to direct genotoxicity, it also disrupts normal cell cycle regulation, alters gene expression and suppresses tumor suppressor pathways, that leads to facilitating malignant transformation. The co-ordinated behaviour of both enzymatic and non-enzymatic antioxidants, along with its mitochondrial dysfunction that's further aggravates the oxidative imbalance. This review aims to explore the biochemical interplay between pesticide-induced oxidative stress and cancer, with a focus on molecular pathways, types of pesticides involved, antioxidant disruption, and potential biomarkers of exposure and effect. Pesticide exposure and oxidative damage of cell discusses its recent findings from in vitro and in vivo studies that strengthen the causal relationship between them. To mitigate the effect of cancer in the human population, we need to have proper knowledge of these interactions for the betterment of public health surveillance, regulation of policy with more future therapeutic interventions. Pesticide-related cancer risks will be reduced by the greater awareness with sustainable agricultural practices and safer alternatives.

Keywords: Carcinogenesis, Oxidative stress, Pesticides, Public Health, Reactive Oxygen Species (ROS).

1 Introduction

1.1 Global Cancer Burden and Environmental Determinants

With an estimated 20 million new cases and over 9.7 million deaths reported in 2022 alone, that relates to Cancer is one of the leading causes of morbidity and mortality worldwide (Bray et al., 2024). While changing modern lifestyle factors such as tobacco use, alcohol

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consumption, and dietary habits means that the meal timing of humans are well-established contributor to carcinogenesis, growing attention is being paid to environmental exposures to the human population, particularly chemicals and pollutants that individuals may encounter through their occupation or surroundings. Among these, pesticide concentration is becoming a hazardous concern due to their worldwide use in agriculture and public health programs, and their long-term existence in the environment and human tissues (La Merrill et al., 2020).

Due to the rapid development of various industries and agricultural intensification have led to the widespread use of pesticides has occurred globally. It is commonly seen that pesticides have significantly increased food production, but they have also raised public health concerns due to their toxic effects on non-target organisms, including humans (Aktar et al., 2009). Due to long-term exposure to certain pesticides that have been associated with various cancers, such as leukemia, non-Hodgkin lymphoma, breast cancer, lung cancer, and prostate cancer (Alavanja et al., 2004). A key mechanism connecting pesticide exposure to cancer is oxidative stress, a condition resulting from the imbalance between free radicals and the generation of ROS, which ultimately weakens the antioxidant defense capacity of the body (Valko et al., 2007).

1.2 Pesticides and Human Exposure

Pesticides include a broad range of chemical substances designed to kill or repel pests, including insecticides, herbicides, fungicides, rodenticides, and nematicides. These agents are extensively applied in both developed and developing countries to protect crops and prevent post-harvest losses. However, the unintended human exposure, via inhalation, ingestion of residues in food and water, or dermal absorption, has raised considerable public health concerns (Jurewicz & Hanke, 2008). In agricultural regions such as Eastern Uttar Pradesh, India, pesticide use is often poorly regulated. Farmers, usually unaware of the toxicological hazards, use these substances without protective gear, leading to chronic exposure (Sachan et al., 2022). Pesticides can accumulate in fatty tissues, cross biological barriers, and interfere with cellular and metabolic processes. Several epidemiological studies have shown correlations between prolonged pesticide exposure and increased risks of various cancers, particularly hematological malignancies, breast cancer, prostate cancer, and lung cancer (Alavanja et al., 2013; Bassil et al., 2007).

1.3 Oxidative Stress as a Central Mechanism

One of the most widely studied and plausible mechanisms by which pesticides exert carcinogenic effects is through the induction of oxidative stress. Oxidative stress refers to a condition in which the generation of reactive oxygen species (ROS) exceeds the body's antioxidant defense mechanisms. ROS, including superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH), are naturally produced during normal cellular metabolism, particularly during mitochondrial respiration and the activity of cytochrome P450 enzymes (Valko et al., 2007). However, excessive ROS production due to xenobiotic exposure can result in oxidative damage to lipids, proteins, and nucleic acids, triggering genomic instability, a hallmark of cancer (Klaunig et al., 2011).

1.4 Impairment of Antioxidant Systems

Pesticides have been shown to deplete both enzymatic antioxidants, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), and non-enzymatic antioxidants such as vitamin C, vitamin E, and reduced glutathione (GSH). This antioxidant suppression exacerbates oxidative damage and contributes to cellular transformation. For example, exposure to organophosphates like chlorpyrifos has been associated with elevated malondialdehyde (MDA) levels, a marker of lipid peroxidation, and reduced GPx and SOD activities in both animal and human studies (Verma et al., 2007).

1.5 Molecular Link Between Oxidative Stress and Carcinogenesis

ROS (Reactive Oxygen Species) could be facilitated in various forms of DNA breakages, namely 8-hydroxy-2'-deoxyguanosine (8-OHdG) formation, double-strand DNA breaks, and base modifications via several agents. These DNA lesions could lead to mutagenesis if not efficiently repaired. Additionally, ROS (Reactive Oxygen Species) can disrupt cell-cell interaction pathways, which are involved in cellular proliferation, apoptosis, and inflammation, named as NF-κB, MAPK, PI3K/Akt pathways (Klaunig et al., 2011). Long-duration exposure to oxidative stress will create a cellular microenvironment that ultimately leads to malignant transformation and tumor progression. Moreover, pesticides may also act as endocrine-disrupting chemicals (EDCs), which further leads to cancers that relate to hormonal imbalance and receptor-mediated signalling, which causes breast and prostate cancer (Mnif et al., 2011).

1.6 Vulnerable Populations and Regional Relevance

Due to unregulated usage, limitations in health-related literacy, and poor adaptation of safety protocols in India, especially in rural states named as Uttar Pradesh (U.P.), Bihar, and Punjab, pesticide long duration exposure is a pressing concern. Gorakhpur region of eastern Uttar Pradesh, a pesticide-intensive area, some epidemiological studies were conducted to demonstrate significant alterations in oxidative stress markers among cancer patients with pesticide exposure and compared them to non-exposed controls (Ojha et al., 2024). These findings suggested that we have an urgent need for comprehensive assessment and mitigation strategies.

1.7 Aim of the Review

We focus on this complexity with its clinical significance of pesticide-induced oxidative stress and its role in cancer development. This review aims to elaborate:

- Categorize major classes of pesticides and summarize their toxicological profiles.
- Explore the biochemical pathways of oxidative stress induced by pesticide exposure.
- Examine the molecular and cellular mechanisms linking oxidative stress with cancer.
- Highlight key biomarkers of oxidative damage and pesticide exposure in human studies.
- Discuss current epidemiological evidence, particularly from India and the world.
- Outline therapeutic interventions and policy recommendations to mitigate risks.

This comprehensive analysis is crucial and focusing for public health authorities, Doctors, and researchers aiming to find out the major cause of oxidative stress cancer and control the burden of environmentally induced cancers in the context of rapid industrialization and agrochemical dependence.

2 Pesticides: Classification, Routes of Exposure, and Mechanisms of Toxicity

Pesticides are basically a wide class of chemical substances that are applied to the soil for controlling pests that threaten agricultural productivity, public health, and ecological balance. Based on target organism, they are classified as insecticides, herbicides, fungicides, rodenticides, etc., chemical composition (organophosphates, organochlorines, carbamates, pyrethroids, neonicotinoids), and mode of action (acetylcholinesterase inhibitors, mitochondrial electron transport inhibitors, sodium channel modulators) (Akashe et al., 2018). In all classes of pesticides, these two classes of organophosphates and organochlorines have been extensively used in developing countries due to their efficacy and low cost, besides their environmental persistence and high toxicity (Jayaraj et al., 2016; Kaushal et al., 2021). These compounds may further undergo chemical transformation in the environment, producing metabolites that can also show toxic effects (Mnif et al., 2011). Their long duration existed concentration in food, water, and air poses a continuous risk for long-term exposure, particularly in agricultural communities.

Pesticides are a broad group of chemical substances used globally to control pests, weeds, fungi, and other organisms that threaten agriculture and public health. While their role in increasing agricultural productivity is indisputable, the health consequences of prolonged and unregulated pesticide exposure are becoming increasingly apparent. Among these, the link between pesticide exposure and cancer, mediated through oxidative stress and genotoxicity, is particularly concerning. Pesticides encompass a wide range of synthetic and natural chemicals used to control agricultural pests, improve crop yield, and prevent vector-borne diseases. However, chronic exposure to pesticides, particularly in occupational and rural agricultural settings, has been linked to genotoxicity, endocrine disruption, and carcinogenic outcomes in humans (Mostafalou & Abdollahi, 2013).

2.1 Classification of Pesticides

Pesticides are broadly categorized based on their target organisms and chemical composition. Below is a simplified classification:

I. Based on Target Organism:

i. **Insecticides:** Target insects (e.g., organophosphates, carbamates, pyrethroids). Various mechanisms, including mitochondrial disruption and redox imbalance.

ii. **Herbicides:** Target unwanted plants (e.g., glyphosate, paraquat, atrazine). Disrupt aromatic amino acid synthesis in plants.

iii. **Fungicides:** Control fungal infections in crops (e.g., mancozeb, captan). Various mechanisms, including mitochondrial disruption and redox imbalance.

iv. **Rodenticides:** Used against rodents (e.g., warfarin, brodifacoum)

v. **Nematicides:** Target nematodes (e.g., aldicarb)

II. Based on Chemical Composition:

a) **Organophosphates** (e.g., chlorpyrifos, malathion): Inhibit acetylcholinesterase activity, are more acutely toxic, leading to neurotoxicity.
b) **Carbamates** (e.g., carbaryl, aldicarb): Similar mechanism to organophosphates but less persistent.
c) **Organochlorines** (e.g., DDT, endosulfan): Lipophilic, persistent in the environment, disrupt sodium ion channels and bioaccumulate in adipose tissue, causing chronic toxicity.
d) **Pyrethroids** (e.g., cypermethrin, deltamethrin, permethrin): Synthetic analogs of natural pyrethrins; disrupt neuronal sodium channels.
e) **Neonicotinoids** (e.g., imidacloprid): Bind to nicotinic acetylcholine receptors in insects, primarily affecting insects but also raising neurotoxicity concerns in humans.
f) **Phenoxy herbicides** (e.g., 2,4-D): Mimic plant hormones and disrupt cell growth.

Table 1 Classes of Pesticides, Their Examples, Target Organisms, Modes of Action, and Associated Cancer Risks

S. No.	Classes of Pesticides	Examples	Target Organisms	Mode of Action	Associated Cancer	References
1	Organophosphates	Malathion, Parathion, Chlorpyrifos	Insects	Inhibits acetylcholinesterase (AChE)	Leukemia, non-Hodgkin lymphoma	(Alavanja et al., 2013; Bassil et al., 2007)
2	Carbamates	Aldicarb, Carbaryl	Insects	Reversible AChE inhibition	Non-Hodgkin lymphoma	(Bassil et al., 2007; Zahm & Ward, 1998)
3	Organochlorines	DDT, Lindane	Insects	Disrupts sodium channels in neurons	Breast cancer, Liver cancer	(Cohn et al., 2007; *IARC Monographs Evaluate DDT, Lindane, and 2,4-D*, 2015)
4	Pyrethroids	Permethrin, Cypermethrin	Insects	Modifies sodium channel kinetics	Possible endocrine-related cancers	(Heudorf et al., 2004; Saillenfait et al., 2015)

5	Herbicides	Glyphosate, Atrazine	Plants	Inhibits photosynthesis, amino acid synthesis	Non-Hodgkin lymphoma, Prostate cancer	(Blair et al., 1992; *IARC Monographs Volume 112: Evaluation of Five Organophosphate Insecticides and Herbicides*, 2015)
6	Fungicides	Mancozeb, Captan	Fungi	Interferes with mitochondrial respiration	Lymphoma, Thyroid cancer, Testicular cancer	(Cocco et al., 2013; *IARC Monographs Volume 112: Evaluation Of*, 2015)
7	Biopesticides	Bacillus thuringiensis toxins	Insects, Fungi	Targets specific genes or pathways	Not strongly associated	(Glare et al., 2012; US EPA, 2015)
8	Neonicotinoids	Imidacloprid, Thiamethoxam	Insects	Binds to nicotinic acetylcholine receptors (nAChRs)	Possible links to breast cancer, leukemia (limited evidence)	(Authority, 2015; Cimino et al., 2017)
9	Phenoxy herbicides	2,4-D, MCPA	Plants	Mimics plant growth hormones (auxins)	Non-Hodgkin lymphoma, Soft-tissue sarcoma	(*IARC Monographs Evaluate DDT, Lindane, and 2,4-D*, 2015)

Note. AChE = Acetylcholinesterase; nAChRs = Nicotinic acetylcholine receptors; EPA = Environmental Protection Agency; EFSA = European Food Safety Authority; IARC = International

Agency for Research on Cancer. This table summarizes pesticide classes, representative compounds, targets, biological mechanisms, and reported cancer associations. References support each entry.

2.2 Routes of Human Exposure

Human exposure to pesticides can occur through multiple pathways: occupational, environmental, dietary, and accidental. The most vulnerable populations include farmers, agricultural labourers, pesticide applicators, and rural residents in proximity to farmlands (Curl et al., 2020; Dereumeaux et al., 2020). Rural populations, particularly in developing countries like India, often face compounded risks due to inadequate protective measures, poor regulatory oversight, and widespread use of highly hazardous pesticides.

Humans are exposed to pesticides through various environmental and occupational pathways:

- **Dermal exposure** during handling or spraying (especially among agricultural workers). Dermal absorption occurs due to contact with contaminated soil, plants, or inadequately washed produce.
- **Inhalational exposure** from aerosolized or volatile compounds. Inhalation is a major route during spraying and aerial application.
- **Oral ingestion** arises through the consumption of pesticide-contaminated food and water.
- **Transplacental exposure** in pregnant women, affecting foetal development (Mnif et al., 2011).

Bioaccumulation and biomagnification further exacerbate risk, particularly for lipophilic pesticides such as DDT and endrin, which accumulate in fatty tissues and breast milk (Jurewicz & Hanke, 2008). Children, pregnant women, and immunocompromised individuals face disproportionately higher risks due to their physiological vulnerability and underdeveloped detoxification systems.

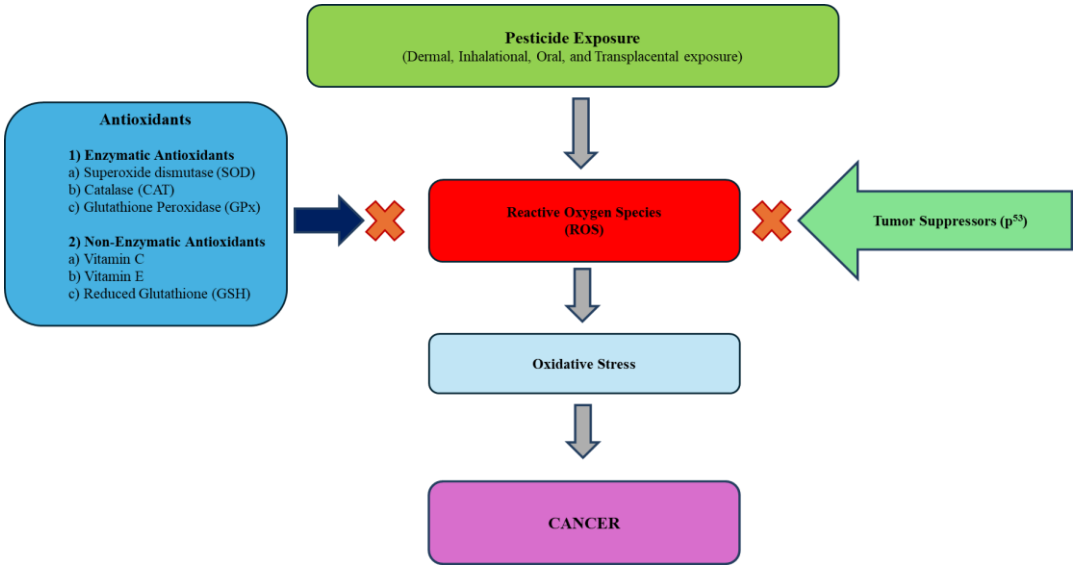

Figure: Pesticide exposure generates reactive oxygen species (ROS), leading to oxidative stress. Impaired antioxidant defences and suppression of p53 function enhance ROS activity, ultimately promoting cancer development.

2.3 Mechanisms of Toxicity

The toxic effects of pesticides on biological systems are diverse but share common mechanistic pathways:

a) **Oxidative Stress Induction**
Pesticides can trigger the overproduction of reactive oxygen species (ROS), such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH). These ROS attack lipids, proteins, and DNA, overwhelming cellular antioxidant defences like glutathione (GSH), catalase, superoxide dismutase (SOD), and glutathione peroxidase (GPx) (Sule et al., 2022).

b) **Inhibition of Cholinesterase**
Organophosphates and carbamates inhibit acetylcholinesterase (AChE), resulting in the accumulation of acetylcholine in synaptic clefts and causing neurotoxicity. Chronic inhibition of AChE has been linked with cognitive decline and neurodegeneration (Abou-Donia, 2003).

c) **Endocrine Disruption**
Many pesticides act as endocrine-disrupting chemicals (EDCs), mimicking or antagonizing hormones, particularly estrogen and androgen. This mechanism is significant in hormone-dependent cancers such as breast and prostate cancers (Liu et al., 2025; Mnif et al., 2011).

d) **Genotoxicity**
Pesticides may induce DNA strand breaks, chromosomal aberrations, and micronuclei formation. Organochlorines and some organophosphates are known to form DNA adducts or interfere with DNA repair enzymes, leading to mutations and genomic instability (Usman et al., 2021).

e) **Neurotoxicity**
Organophosphates and carbamates inhibit acetylcholinesterase, leading to the accumulation of acetylcholine at nerve synapses, causing overstimulation, paralysis, or death (Costa, 2006). Chronic inhibition is linked to neurodegeneration and CNS cancers.

f) **Mitochondrial Dysfunction**
Pesticides like rotenone and paraquat impair mitochondrial electron transport chain (ETC), increasing superoxide production and reducing ATP synthesis, contributing to neuronal and hepatic toxicity (Tanner et al., 2011).

g) **Epigenetic Modifications**
Chronic pesticide exposure alters DNA methylation, histone modification, and miRNA expression, ultimately contributing to oncogene activation or tumor suppressor gene silencing, paving the way for carcinogenesis (Zhang et al., 2012).

2.4 Persistence and Bioaccumulation

Organochlorine pesticides like DDT are highly persistent in the environment and accumulate in adipose tissue due to their lipophilic nature. Long-term exposure, even at low levels, leads to chronic health outcomes, including immunotoxicity, endocrine dysfunction, and carcinogenesis (*Toxicological Profile for DDT, DDE, and DDD*, 2022).

2.5 Indian Context of Pesticide Use

India ranks among the top consumers of pesticides in Asia, with a majority used in agriculture. The Indo-Gangetic Plain, including eastern Uttar Pradesh, shows significant usage of organophosphates, synthetic pyrethroids, and herbicides. Unfortunately, regulatory enforcement is often weak, and banned or restricted pesticides continue to be used (Dhananjayan et al., 2012; Yadav, 2024).

3 Role of Oxidative Stress in Pesticide-Induced Carcinogenesis

Oxidative stress plays a pivotal role in the cellular and molecular pathways that connect pesticide exposure to cancer development. Oxidative stress arises when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify these reactive intermediates or repair the resulting damage.

3.1 Mechanisms of ROS Generation by Pesticides

Many pesticides, especially organophosphates, organochlorines, carbamates, and triazines, can directly or indirectly stimulate ROS generation within cells. Oxidative stress arises when ROS levels exceed the antioxidant capacity of cells. Common ROS include:

- Superoxide anion ($O_2^{\bullet -}$)
- Hydroxyl radical (•OH)
- Hydrogen peroxide (H_2O_2)

ROS are by-products of cellular metabolism, particularly from mitochondria, peroxisomes, and cytochrome P450 systems. While they play roles in signaling, excessive ROS can:

- **Oxidize lipids (Lipid peroxidation):** ROS attacks membrane lipids, resulting in the formation of toxic aldehydes like malondialdehyde (MDA), which further damages proteins and DNA (Sule et al., 2022).
- **Damage proteins (carbonylation)/ Protein oxidation:** ROS oxidizes thiol groups in proteins, altering their function and leading to mitochondrial dysfunction (Khan et al., 2008).
- **DNA Damage and Mutagenesis:** Oxidative stress leads to strand breaks, formation of 8-hydroxydeoxyguanosine (8-OHdG), and base modifications, initiating mutagenesis and carcinogenesis (Valko et al., 2006).

These changes promote oncogene activation and tumor suppressor gene inactivation (Loft & Poulsen, 1996).

The body defends against ROS using:

- **Enzymatic antioxidants:** Superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx)
- **Non-enzymatic antioxidants:** Vitamin C, vitamin E, glutathione (GSH), flavonoids

3.2 Signaling Pathways Activated by Oxidative Stress

Persistent oxidative stress activates several oncogenic and inflammatory signaling pathways:

- **NF-κB pathway:** Enhances transcription of inflammatory cytokines, anti-apoptotic proteins, and cell proliferation genes (Morgan & Liu, 2011).
- **MAPK/ERK pathway:** Stimulates uncontrolled cell division and survival signaling under stress conditions.
- **p53 suppression:** Oxidative DNA damage impairs tumor suppressor p53 function, weakening apoptosis and cell cycle arrest mechanisms.

3.3 Oxidative Stress Biomarkers in Pesticide-Exposed Individuals

Biomarkers are measurable indicators of biological processes or conditions. In the context of pesticide-induced carcinogenesis, biomarkers reflecting oxidative stress, DNA damage, pesticide exposure, and antioxidant defense mechanisms serve as critical tools for understanding pathophysiology, risk assessment, and therapeutic monitoring.

Table 2 Key biomarkers of pesticide exposure, oxidative stress, and their clinical significance in cancer patients

S. No.	Biomarker	Category	Clinical Relevance	Direction in Cancer Patients	References
1	MDA (Malondialdehyde)	Oxidative Stress	Lipid peroxidation, membrane damage	↑ Elevated	(Noshy et al., 2017)
2	8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG)	DNA Oxidation	DNA strand breaks, mutagenesis	↑ Elevated	(Kasai, 1997; Loft & Poulsen, 1996)
3	GSH (Glutathione)	Antioxidant	ROS neutralization, redox homeostasis	↓ Depleted	(Flora et al., 2008; Valko et al., 2006)
4	CAT, SOD, GPx	Enzymatic Antioxidants	Defense against H_2O_2 and superoxide radicals	↓ Reduced activity	(Klaunig & Kamendulis, 2004)
5	AChE, BChE	Pesticides Exposure Biomarkers	Pesticide bioactivity, neuromodulation	↓ Significantly inhibited	(Costa, 2006; Reigart &

					Roberts, 1999)
6	Urinary bisphenol A (BPA), DAPs	Pesticides Exposure Biomarkers	Pesticide intake estimation	↑ High levels	(Barr et al., 2004; Ye et al., 2008)

4 Experimental Evidence and Case Studies Linking Oxidative Stress, Pesticide Exposure, and Cancer

This compiles both experimental (in vitro, in vivo) and epidemiological case studies that illustrate the relationship between pesticide-induced oxidative stress and the development or progression of cancer. It includes data from human samples, animal models, and cell cultures, particularly relevant to rural regions such as Eastern Uttar Pradesh, where pesticide exposure is a growing concern.

4.1 Evidence from In Vitro and In Vivo Studies

- In rat models, pesticide (Chlorpyrifos) exposure has been shown to elevate thiobarbituric acid reactive substances (TBARS) while suppressing the activity of key enzymes, including acetylcholinesterase (AChE), superoxide dismutase (SOD), catalase (CAT), and glucose-6-phosphate dehydrogenase (G6PDH), across multiple organs such as the liver, kidney, spleen, and brain (Verma et al., 2007).
- Endosulfan has been shown to induce oxidative stress in testicular tissues and, as reported by Priya et al. (2024), exerts reproductive and genotoxic effects in both male and female Swiss albino mice.
- Glyphosate exposure led to elevated ROS (including •OH) levels, resulting in DNA single- and double-strand breaks in human peripheral blood mononuclear cells (PBMCs) (Woźniak et al., 2018).

4.2 Epidemiological Studies Linking Pesticides, Oxidative Stress, and Cancer

- **Agricultural Health Study (USA):** Positive correlation between organophosphate exposure and prostate cancer risk (Alavanja et al., 2004).
- **Indian Studies:** Rastogi et al. (2009) reported elevated MDA, reduced AChE/BChE activity, and altered GSH levels in pesticide sprayers from Lucknow, indicating oxidative stress due to chronic exposure.
- **Case-Control Studies:** Pesticide-exposed farmers with leukemia, lymphoma, or breast cancer exhibited significantly elevated serum 8-OHdG levels, indicating increased oxidative DNA damage, compared to unexposed cancer patients and healthy controls (Pandiyan et al., 2024).

5 Therapeutic Interventions Targeting Oxidative Stress in Pesticide-Induced Cancer

Oxidative stress is a central mechanism by which pesticide exposure contributes to cancer development. Targeting this redox imbalance presents a therapeutic opportunity, particularly in malignancies associated with pesticide exposure. Interventions involve both pharmacological antioxidants and dietary phytochemicals, as well as strategies modulating redox-sensitive signaling pathways.

5.1 Pharmacological Antioxidants

Synthetic or natural antioxidant compounds can restore redox balance by scavenging ROS, enhancing endogenous antioxidant enzyme activity, or blocking pro-oxidant signaling.

- **N-acetylcysteine (NAC):** A precursor of glutathione, NAC replenishes intracellular GSH levels and reduces lipid peroxidation. It has shown protective effects against chlorpyrifos- and endosulfan-induced cytotoxicity (Singh et al., 2007)
- **Vitamin E (α-tocopherol):** Acts as a chain-breaking antioxidant, preventing lipid membrane damage caused by pesticides such as malathion and DDT (Jiang et al., 2001).
- **Melatonin:** Functions as a powerful free radical scavenger and enhances SOD, CAT, and GPx activity. It has been reported to counteract oxidative DNA damage and apoptosis in pesticide-exposed rodents (Reiter et al., 2014).

5.2 Dietary Antioxidants and Phytochemicals

Many plant-derived compounds exhibit antioxidant and chemopreventive properties by modulating oxidative pathways and epigenetic mechanisms.

- **Curcumin:** Inhibits lipid peroxidation and increases Nrf2-mediated antioxidant enzyme expression. It also modulates histone acetylation and DNA methylation (Aggarwal & Harikumar, 2009).
- **Resveratrol:** Suppresses ROS generation, inhibits COX-2 and NF-κB, and enhances apoptosis in pesticide-stimulated carcinogenic cells (Baur & Sinclair, 2006).
- **Quercetin:** A flavonoid that increases GSH levels, reduces MDA, and prevents DNA strand breaks induced by organophosphates (Boots et al., 2008).
- **Sulforaphane (from cruciferous vegetables):** Activates Nrf2-Keap1 pathway, restoring oxidative balance and suppressing tumor growth in pesticide-induced cancer models (Nandini et al., 2020).

Table 3 Natural and synthetic compounds with antioxidant and chemopreventive potential against pesticide-induced toxicity and cancer

S. No.	Compound	Source/Type	Mechanism	Targeted Effect	Reference
1.	N-acetylcysteine (NAC)	Synthetic	↑ GSH, ↓ LPO, DNA protection	Prevents oxidative DNA damage	(Kwon, 2021)

2.	Vitamin E (α-Tocopherol)	Dietary antioxidant (nuts, seeds, oils)	Free radical scavenging and stabilizes membranes	Protects lipids and DNA from oxidative stress, ↓ cancer risk	(Jiang et al., 2001)
3.	Melatonin	Endogenous hormone	↑ SOD, GPx, ↓ ROS	Reverses neurotoxicity, hepatotoxicity	(Reiter et al., 2014)
4.	Curcumin	Turmeric	Nrf2 activation, HDAC inhibition	Epigenetic restoration, ↓ inflammation	(Aggarwal & Harikumar, 2009)
5.	Resveratrol	Grapes, red wine	NF-κB inhibition, ↑ apoptotic pathways	Chemoprevention in breast and lung cancer	(Baur & Sinclair, 2006)
6.	Quercetin	Flavonoid (onion, apple, tea)	Inhibits ROS, modulates PI3K/Akt, NF-κB pathways	Anti-inflammatory, induces apoptosis, ↓ tumor progression	(Boots et al., 2008)
7.	Sulforaphane	Broccoli, cabbage	Nrf2 activation, ↓ DNA adducts	Tumor growth suppression	(Nandini et al., 2020)

6 Combination Therapies and Future Directions

A combination of chemotherapeutic drugs with antioxidant phytochemicals shows promise in overcoming resistance and minimizing toxicity. For example:

- **Curcumin + Cisplatin:** Synergistically reduces oxidative DNA damage and tumor volume in mice exposed to malathion.
- **NAC + 5-FU:** Enhances 5-FU efficacy by protecting normal cells from oxidative injury while sensitizing cancer cells.

Emerging strategies like nanoparticle-based antioxidant delivery, gene therapy targeting redox enzymes, and CRISPR-mediated DNMT silencing represent future therapeutic frontiers. Antioxidant therapy, both pharmacological and nutraceutical, offers significant potential in mitigating oxidative damage induced by pesticide exposure. By restoring redox homeostasis and modulating key signaling pathways, these agents help prevent, manage, and reverse the carcinogenic effects of environmental toxins.

7 Challenges in Targeting Oxidative Stress in Cancer

Despite the promise of antioxidant and oxidative stress-targeted therapies in cancer management, multiple challenges limit their clinical application:

Table 4 Key challenges in the therapeutic application of antioxidants for cancer prevention and treatment

S. No.	Challenge	Explanation	References
1.	Dose Optimization	Determining the right therapeutic window for antioxidants is critical, as overdosing may impair ROS-mediated apoptosis of cancer cells.	(Cairns et al., 2011; Sayin et al., 2014)
2.	Dual Role of ROS	Reactive oxygen species have both tumor-promoting and tumor-suppressing roles depending on concentration and cancer type.	(Trachootham et al., 2009; Valko et al., 2007)
3.	Bioavailability	Many natural antioxidants, like curcumin and resveratrol, have poor absorption and rapid metabolism.	(Anand et al., 2007; Walle, 2011)
4.	Tumor Heterogeneity	Different cancer types and even subtypes vary in their oxidative profiles and response to interventions.	(Hanahan & Weinberg, 2011; Ward & Thompson, 2012)
5.	Resistance Mechanisms	Cancer cells may adapt to antioxidant treatments via upregulation of endogenous detoxification systems.	(Gorrini et al., 2013; Hayes & Dinkova-Kostova, 2014)

Targeting oxidative stress in cancer therapy presents a promising but complex frontier. While significant advances have been made in understanding redox biology, translating these insights into safe and effective treatments remains a challenge. A deeper understanding of redox signaling, tumor heterogeneity, and the role of the tumor microenvironment is essential. Future therapeutic approaches must integrate advanced delivery systems, patient-specific redox profiling, and synergistic combination therapies to harness the full potential of oxidative stress modulation in oncology.

8 Future Perspectives and Public Health Implications

- Measuring the pesticide residues in food and water content: Continuous surveillance of residues in consumables is essential to facilitate prevention techniques for chronic exposure. Advanced detection technologies can strengthen early warning systems and safeguard public health-related issues.

- Pesticide usage regulations by regulatory policies: To implement evidence-based regulatory policies that will reduce hazardous exposures. Global harmonization of safety standards is crucial to minimize environmental and health risks.
- Promotion of organic farming and integrated pest management (IPM): Shifting toward sustainable agricultural practices reduces reliance on chemical pesticides. IPM and organic farming balance crop protection with ecosystem preservation.
- Antioxidant-rich diet in high-risk populations: Nutritional interventions emphasizing antioxidant-rich foods may mitigate oxidative stress from pesticide exposure. Public health programs should integrate dietary guidelines for vulnerable groups.
- Personal protective equipment for workers: Mandatory use of PPE can significantly reduce occupational pesticide exposure. Training and enforcement are critical to ensuring compliance among agricultural workers.
- Molecular epidemiology studies to identify genetic susceptibility: Genomic and biomarker-based approaches can help identify populations at higher risk. Such insights enable precision prevention strategies and targeted interventions.

9 Conclusion

Now these days, oxidative stress is emerging as a central mechanistic pathway, and evidence reviewed underscores the significant role of pesticide exposure in the development of cancer. Pesticide concentration not only generates free radicals but major cause of excessive reactive oxygen species with compromise antioxidant defence capabilities that's resulting in cumulative damage to DNA strands, proteins, and lipid content. This will create a biological environment conducive to malignant transformation due to these molecular alterations, disruptions in hormonal signalling, and epigenetic modifications (modifications in base pairs through phosphorylation, methylation, etc). Experimental studies, clinical data, with epidemiological findings consistently highlight the association between chronic pesticide exposure that has ultimately elevated the risks of haematological, reproductive, and hormone-dependent cancers

Several challenges remain in translating these strategies into routine clinical practice, while antioxidant therapies and dietary interventions show promise in mitigating pesticide-induced oxidative damage. Their prevention and treatment slowly depend on the variability in pesticide formulations, bioaccumulation patterns, individual genetic susceptibility, and tumor heterogeneity that addressing the cancer risk posed by pesticides requires a multifaceted approach that integrates stricter regulatory frameworks, sustained monitoring of residues in food and water content, worldwide adoption of safer agricultural practices, and community-level education on protective measures.

In India, several regions such as rural areas often see that unregulated pesticide use and its exposure risks are heightened, and we have to needed to urgent interventions for the safeguard of vulnerable populations. These improvement in agricultural practices ultimately leads to reducing the carcinogenic burden of pesticides and will depend on bridging scientific advances with public health policies, ensuring that agricultural productivity does not come at the cost of human health.

Conflict of interest: The authors declare that there is no conflict of interest.

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