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Cardiotoxicity of Organophosphate Pesticides: A Systematic Review of Recent Epidemiological and Experimental Evidence

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Abstract

Introduction: Organophosphate pesticides (OPs) are widely used globally, raising concerns about their long-term cardiovascular effects. While neurotoxicity is well established, OP-induced cardiotoxicity remains underexplored. This systematic review evaluated current evidence on cardiovascular outcomes, mechanisms, and potential protective interventions related to OP exposure.

Methods: A systematic search of PubMed, Scopus, Web of Science, Embase, and Google Scholar was conducted to identify eligible studies published between January 2014 and October 2024. Following PRISMA 2020 guidelines, randomized trials, observational human studies, animal experiments, and in vitro models examining OP exposure and cardiovascular outcomes were included. Data on exposure type, study design, cardiovascular endpoints, mechanisms of toxicity, protective agents, and study quality were extracted. Risk of bias was assessed using the Newcastle-Ottawa Scale, Cochrane RoB, and SYRCLE tools.

Results: Thirty-eight studies met inclusion criteria, comprising 23 animal studies, 15 human observational studies, and 3 in vitro/in silico studies. OP exposure was associated with various cardiovascular effects, including hypertension, arrhythmias, myocardial infarction, cardiac hypertrophy, QT prolongation, and heart failure. Key mechanisms identified included oxidative stress, mitochondrial dysfunction, calcium signaling disruption, inflammatory activation, and electrophysiological alterations. Several animal studies reported partial cardioprotection from antioxidants and phytochemicals, though human evidence remains limited. Selection bias and inconsistent exposure assessment were common across studies, restricting causal inference.

Conclusion: Available data suggest that OP exposure increases cardiovascular risk via oxidative and inflammatory mechanisms, with experimental evidence for potential protective interventions. More robust longitudinal human studies and intervention trials are needed to clarify causality and guide prevention strategies.

Keywords: Organophosphate pesticides, Cardiotoxicity, Oxidative stress, Mitochondrial dysfunction, Cardiovascular disease

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Introduction

Organophosphate (OP) pesticides are widely used environmental contaminants, particularly in agriculture, pest control, and public health applications, with growing concern about their potential long-term effects on human health, including the cardiovascular system (1-3). While OPs are traditionally studied for their neurotoxic effects via acetylcholinesterase inhibition, emerging evidence indicates that OP exposure may also contribute to significant cardiovascular risks, including myocardial infarction, arrhythmias, stroke, heart failure, hypertension, and vascular dysfunction (4-6). These adverse effects have been reported in both occupationally exposed populations and environmentally exposed communities, highlighting a broader public health concern.

Mechanistic studies suggest multiple pathways through which OPs exert cardiotoxic effects, including oxidative stress, mitochondrial dysfunction, calcium signaling disturbances, autonomic nervous system dysregulation, endothelial injury, chronic inflammation, and electrophysiological alterations leading to arrhythmogenic events (7-9). These mechanisms are supported by

experimental findings in various animal models and emerging epidemiological evidence, though inconsistencies in exposure assessment, study design, and outcome reporting limit definitive conclusions.

Despite the growing body of literature, systematic assessments of OP-induced cardiotoxicity remain limited, and existing studies often vary in methodological quality and focus predominantly on acute neurotoxic outcomes. Therefore, a focused review of cardiovascular effects is warranted to better understand the breadth of potential health risks associated with OP exposure. This systematic review, conducted in line with PRISMA 2020 guidelines, aimedto synthesize recent epidemiological and experimental evidence (2014–2024) on the cardiovascular effects of organophosphate (OP) pesticides. Specifically, this review aimed to: (i) summarize cardiovascular outcomes reported in human and animal studies, (ii) explore underlying biological mechanisms of toxicity, (iii) identify potential protective compounds, including phytochemicals and antioxidants that may mitigate OP-induced cardiac injury, and (iv) highlight methodological limitations and research gaps such as selection bias to guide future investigations and inform public health interventions.

Materials and Methods

Literature Search

This systematic review was conducted in accordance with PRISMA 2020 guidelines (10) to ensure transparency, replicability, and methodological rigor. Studies published between January 2014 and October 31, 2024, were included. A comprehensive search was performed across five electronic databases: PubMed, Scopus, Web of Science, Embase, and Google Scholar.

Separate search strategies were employed for human and animal studies as recommended by reviewers. For human studies, search terms focused on occupational or environmental OP exposure, epidemiological design (cohort, case-control, cross-sectional), and cardiovascular endpoints. For animal and in vitro studies, search terms emphasized experimental models, exposure routes, cardiac biomarkers, and mechanistic pathways.

The search combined relevant keywords and Medical Subject Headings (MeSH), including "organophosphate pesticides," "cardiotoxicity," "heart disease," "myocardial infarction," "arrhythmias," "oxidative stress," "mechanisms," "protective agents," as well as specific pesticide names (chlorpyrifos, dichlorvos, fenitrothion). Boolean operators were used to ensure comprehensive retrieval. Full search strings for each database are provided in the supplementary materials for replicability, and reference lists of included articles were manually screened for additional studies.

Study Selection

Inclusion Criteria

- *Study Design:* Randomized controlled trials (RCTs), cohort studies, case-control studies, and animal studies (in vivo and in vitro).
- *Exposure:* Organophosphate pesticide exposure assessed through biological, environmental monitoring, or validated self-reports.
- *Outcomes:* Studies reporting cardiotoxicity or cardiovascular endpoints (arrhythmias, cardiac hypertrophy, QT prolongation, fibrosis), underlying mechanisms (oxidative stress, mitochondrial dysfunction, inflammation), or protective interventions.
- *Population:* Animal models (rats, rabbits, zebrafish) and human populations exposed to OPs in occupational or environmental settings.

Exclusion Criteria

- Studies not focused on OPs or relevant cardiovascular effects.
- Reviews, meta-analyses, case reports without original data.
- Studies with insufficient details on exposure or outcomes.

Screening and Selection Process

Screening was performed in two stages by two independent reviewers:

- Title and abstract screening for relevance.
- Full-text assessment using eligibility criteria.

Disagreements were resolved by consensus or third-party adjudication. A PRISMA flow diagram (Figure 1) was used to document the process, including records identified, screened, excluded (with reasons), and included.

Data Extraction

Data extraction was performed independently by two reviewers using a standardized form. Extracted data included:

- *Study Details:* Author(s), year, country.
- *Pesticides:* Specific OP compounds studied.
- *Exposure Type and Model:* Routes of exposure (oral, inhalation, dermal, gestational), study population or animal model.
- *Cardiotoxic Outcomes:* Arrhythmias, myocardial infarction, cardiac hypertrophy, QT prolongation, fibrosis.
- *Mechanisms:* Oxidative stress biomarkers (MDA, GSH), mitochondrial damage, calcium dysregulation, endothelial dysfunction, inflammation.
- *Protective Interventions:* Phytochemicals, antioxidants (e.g., propolis, saffron, moringa oil), or pharmacological agents mitigating cardiotoxicity.
- *Epidemiological Evidence:* Chronic occupational or environmental exposure and cardiovascular risk estimates.

Discrepancies were resolved by discussion.

Quality Assessment

Methodological quality was evaluated using validated tools:

- Newcastle-Ottawa Scale (NOS) for observational studies.

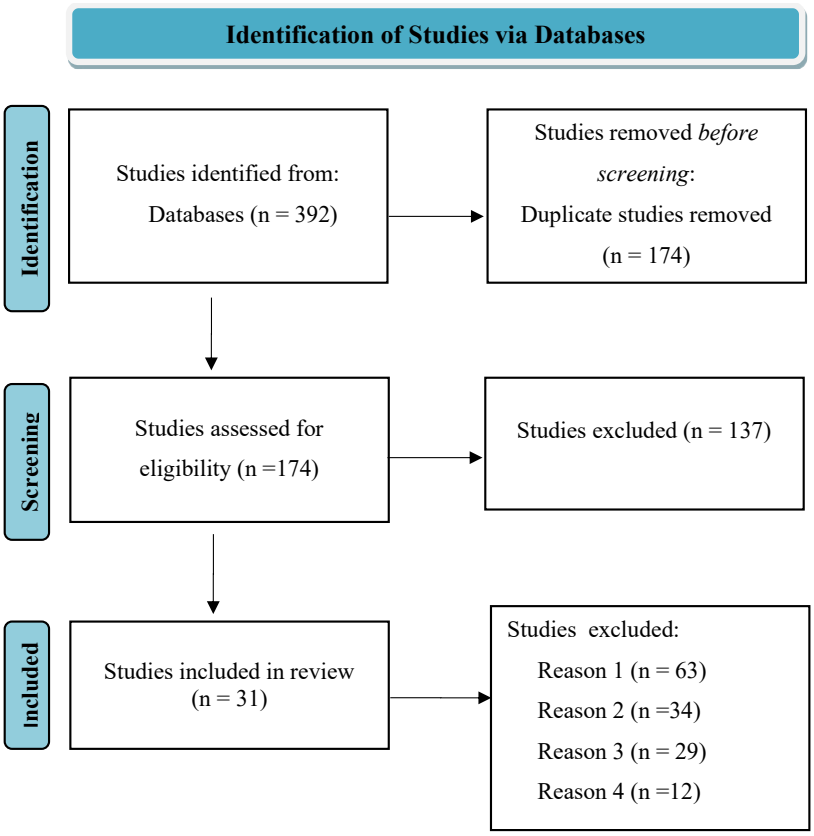

Figure 1. PRISMA flow Diagram for the Identification and Screening of Eligible Studies

- Cochrane Risk of Bias Tool for RCTs.
- SYRCLE Risk of Bias Tool for animal experiments.

Risk of bias was independently assessed by two reviewers, with disagreements resolved by a third reviewer. Studies with high risk of bias were flagged, and their findings interpreted cautiously.

Data Synthesis and Analysis

Due to heterogeneity in study designs, exposure levels, and outcome measurements, a meta-analysis was not feasible. Instead, a structured narrative synthesis was conducted using five thematic domains:

1. Pesticide Exposure and Models
2. Cardiotoxic Outcomes
3. Mechanisms of Cardiotoxicity
4. Protective Interventions
5. Epidemiological Evidence

Subgroup analyses were performed where appropriate, examining pesticide type, exposure level, and population (animal vs. human).

Statistical Analysis

Due to variability in study design, exposure routes, populations, and outcome measurements, quantitative pooling of results was not possible. Instead, a descriptive synthesis was performed for each thematic domain. Key trends and patterns were identified to summarize the weight of evidence for specific OP compounds, cardiovascular outcomes, mechanistic pathways, and protective interventions.

Limitations and Risk of Bias

Potential biases such as publication bias, selection bias, and selective outcome reporting were considered during screening and synthesis. Risk of bias assessments using NOS, Cochrane RoB, and SYRCLE tools informed interpretation of findings. Studies rated high risk were interpreted cautiously. Sensitivity analyses were performed, where feasible, to evaluate how study quality and methodological differences between human and animal studies influenced the overall conclusions

Ethical Considerations

As this study used published data, no ethical approval or informed consent was required, consistent with standard guidelines for systematic reviews.

Results

A total of 38 studies met the inclusion criteria for this systematic review, comprising 23 experimental investigations (animal, in vitro, and in silico studies) and 15 human observational or clinical studies**,** all published between 2014 and 2024. These studies explored a range of cardiovascular endpoints, including cardiac hypertrophy, arrhythmias, myocardial infarction, heart failure, QT prolongation, vascular dysfunction, and stroke, along with underlying mechanisms such as oxidative stress, mitochondrial damage, autonomic dysregulation, endothelial injury, and inflammation. Studies unrelated to OP exposure or lacking cardiovascular outcome data were excluded during screening.

Cardiotoxicity of Organophosphate Pesticides

To enhance clarity and follow reviewer recommendations, the findings are now presented in two separate tables:

Table 1a Experimental studies (animal, in vitro, and in silico), summarizing species/model, OP compound, exposure route and dose, cardiovascular endpoints, underlying mechanisms, and evaluated protective agents.

Table 1b Human epidemiological and clinical studies, specifying study population, type and level of exposure, cardiovascular outcomes, and associated risk estimates.

Across experimental studies, OP exposure was consistently linked to adverse cardiac effects, including oxidative stress-induced damage, mitochondrial dysfunction, arrhythmias, impaired contractility, and structural remodeling such as fibrosis and hypertrophy. Several animal experiments investigated potential protective agents (e.g., resveratrol, moringa oil, propolis, betulinic acid, vitamins C and E), which were shown to reduce lipid peroxidation, improve antioxidant enzyme activity, and ameliorate OP-induced myocardial injury. Human evidence, though fewer in number, indicated elevated risks of hypertension, ischemic heart disease, QT interval prolongation, systemic inflammation, and other cardiovascular disturbances in exposed populations, supporting experimental findings.

Risk of Selection Bias

The methodological quality of the 38 included studies varied considerably across experimental, in vitro, and human research designs (Table 2).

Among the 23 animal and in vitro studies, 13 were judged as low risk of bias, largely due to clear randomization procedures, well-defined exposure protocols, and comprehensive outcome reporting. However, 7 studies were rated moderate risk owing to unclear allocation methods, incomplete blinding of outcome assessments, or uncertain exposure quantification. Three studies (5,13,24) were rated high risk, primarily due to mixed pesticide exposures, non-randomized experimental designs, and incomplete mechanistic data.

In the 15 human epidemiological studies, 6 were considered low risk, benefiting from biomarker-based exposure assessment, robust confounder control, and validated cardiovascular endpoints. Six studies were judged as having moderate risk, typically due to reliance on self-reported exposure data, lack of standardized dose measurements, or incomplete adjustment for diet, lifestyle, and other environmental factors. Three studies (36,38,39) were rated high risk due to small sample sizes, non-standardized exposure ascertainment, and substantial residual confounding.

Across both groups, the most frequent sources of bias were exposure misclassification, non-randomized or convenience sampling, small sample sizes, and limited confounder adjustment in observational studies. These limitations highlight the need for longitudinal designs, biomarker-based exposure assessment, and improved methodological rigor in both animal and human research to strengthen causal inference regarding OP-induced cardiotoxicity.

Thematic Synthesis of Findings

Table 3 provides a thematic synthesis of evidence across key domains: exposure models, cardiotoxic outcomes, mechanistic pathways, protective interventions, and human epidemiological findings. This synthesis highlights consistent mechanistic evidence linking OP exposure to cardiovascular dysfunction, identifies protective agents with potential therapeutic value, and underscores major research gaps, such as the need for standardized exposure assessment methods, long-term prospective studies, and clinical trials evaluating cardioprotective interventions (Table 3).

Discussion

This systematic review provided an updated structured synthesis of the cardiotoxic effects of organophosphate (OP) pesticides, integrating evidence from both experimental and epidemiological studies published between 2014 and 2024. The findings highlight growing evidence that OP exposure can adversely affect cardiovascular health through multiple biological mechanisms. To facilitate understanding, the discussion is organized into five thematic domains: (1) Pesticide Exposure and Models, (2) Cardiotoxic Outcomes, (3) Mechanisms of Cardiotoxicity, (4) Protective Interventions, and (5) Epidemiological Evidence.

Pesticide Exposure and Models

OP exposure occurs through multiple pathways, including ingestion, inhalation, dermal absorption, and maternal transfer during pregnancy, affecting both occupationally exposed populations and nearby communities. Experimental models, primarily involving rodents and zebrafish, have been extensively used to investigate cardiotoxic effects under controlled exposure conditions (4,5,48). These models have provided critical insights into dose-response relationships and mechanistic pathways. However, extrapolation to human risk remains challenging due to differences in exposure levels, metabolic processes, and co-exposures. Harmonized approaches to exposure measurement are needed to improve comparability between animal and human studies.

Cardiotoxic Outcomes

Animal studies consistently report adverse cardiovascular outcomes following OP exposure, including cardiac hypertrophy, arrhythmias, myocardial infarction, heart failure, fibrosis, and QT prolongation (11,44,49-52). These findings are supported by emerging human epidemiological data, particularly in occupational settings, where long-term OP exposure has been linked to increased risks of hypertension, ischemic heart disease, and cerebrovascular events (2,24,34,53). However, human studies are limited in number, often cross-sectional, and vary widely in exposure quantification and outcome definitions. This heterogeneity

Table 1a. Experimental Studies (Animal and In Vitro) on the Cardiotoxicity of Organophosphate Pesticides (n = 23)

N/S	Study Title	Authors (Year)	Model	Pesticide(s) Exposure	Cardiovascular Outcome(s)	Mechanisms	Protective Agents
1	Intermittent Chlorpyrifos Exposure	Minassa et al. (2022) (11)	Rats	Intermittent chlorpyrifos	Cardiac hypertrophy, oxidative stress	↑MDA, ↓GSH	None
2	Propolis Ameliorates Chlorpyrifos Cardiotoxicity	Ibrahim et al. (2019) (12)	Diabetic rats	Chlorpyrifos	Altered PON-1 and XO gene expression	Antioxidant, anti-inflammatory	Propolis
3	Soil Extract and Target Organ Toxicity	Boamah et al. (2023) (13)	Rats	Soil extract with OP/carbamates	QTc prolongation, ↑brain lipid peroxidation	Mixed pesticide toxicity	None
4	Intermittent Chlorpyrifos and Cardiorespiratory Function	Batista et al. (2019) (14)	Rats	Intermittent chlorpyrifos	Reduced baroreflex gain, chemoreflex bradycardia	Autonomic dysregulation	None
5	Resveratrol and Fenitrothion Cardiotoxicity	Ibrahim et al. (2022) (15)	In vivo/in silico	Fenitrothion	Cardiac apoptosis	SIRT1/JNK/p53 modulation	Resveratrol
6	Ricinus Communis Extract and Dichlorvos Cardiotoxicity	Adeoye et al. (2023) (16)	Rats	Dichlorvos	Reduced cardiac dysfunction markers	Antioxidant, anti-inflammatory	Ricinus extract
7	Flaxseed and Gestational Exposure	Ibrahim et al. (2020) (17)	Rats	Fenitrothion + diesel exhaust (gestational)	Reduced apoptosis in the heart	PON-1 and apoptotic gene modulation	Flaxseed
8	Moringa Oil and Dichlorvos Cardiotoxicity	Saka et al. (2020) (18)	Rats	Dichlorvos inhalation	Reduced oxidative stress, improved function	Antioxidant effect	Moringa oil
9	Cardiotoxicity in Rabbits	Zafiropoulos et al. (2014) (5)	Rabbits	Diazinon, Propoxur, Chlorpyrifos	Increased heart rate	Not reported	None
10	Mitochondrial Impact of OPs	Karakuş et al. (2024) (19)	In vitro	Chlorpyrifos, Diazinon, Malathion	Mitochondrial dysfunction, oxidative stress	Mitochondrial injury	None
11	QT Prolongation After Dichlorvos Poisoning	Shiyovich et al. (2018) (20)	Rats	Dichlorvos	Long-term QT prolongation	Electrophysiological changes	None
12	Betulinic Acid vs. Chlorpyrifos Toxicity	Alruhaimi (2023) (21)	Rats	Chlorpyrifos	↓oxidative stress, ↓apoptosis	Antioxidant, anti-inflammatory	Betulinic acid
13	Saffron Against Chlorpyrifos Toxicity	Khalaf & El-Mansy (2019) (22)	Rats	Chlorpyrifos	Improved cardiac function	Unknown	Saffron
14	Morphological Abnormalities and Activity Reduction	Watson et al. (2014) (23)	Zebrafish, *Xenopus laevis*	Chlorpyrifos	↓Heart rate, ↓blood flow	Not reported	None
15	Daily Chlordecone Exposure and Cardiac Fibrosis*	Fundere et al. (2024) (24)	Rats	Chlordecone (organochlorine)*	Cardiac fibrosis, atrial fibrillation	Unknown	None
16	Reproductive/ Developmental Toxicity from OP Flame Retardants	Witchey et al. (2023) (25)	Toxicology study with Rats	Triphenyl phosphate (TPhP), IPP	Developmental toxicity with potential cardiac effects	Oxidative stress, endocrine disruption	None
17	Thymoquinone Against Diazinon Toxicity	Danaei et al. (2019) (26)	Rats	Diazinon	↓oxidative stress, improved function	Anti-inflammatory, antioxidant	Thymoquinone
18	Effects of OPs on Mitochondria	Samarghandian & Farkhondeh (2023) (27)	In vitro	Organophosphate exposure	Mitochondrial dysfunction, impaired calcium handling	Oxidative stress, calcium dysregulation	None
19	Methidathion Toxicity in Zebrafish	Wu et al. (2023) (28)	Zebrafish embryos	Methidathion	Developmental and cardiac toxicity	Oxidative stress, disrupted signaling	None
20	Tebuconazole-Induced Cardiotoxicity	Ben Othmène et al. (2020) (29)	Rats	Tebuconazole	↑CPK, ↑LDH (cardiac damage)	Oxidative stress, inflammation	None
21	Isoflavones Against Chlorpyrifos Toxicity	Abdulretha et al. (2022) (30)	Rats	Chlorpyrifos	Reduced cardiovascular toxicity	Anti-inflammatory, mitochondrial protection	Isoflavones
22	Cardiotoxicity in Human-Derived Cardiomyocytes (ToxCast Chemicals)	Burnett et al. (2021) (31)	Human iPSC-derived cardiomyocytes (in vitro)	OP-related chemicals	Cytotoxicity, disrupted cardiac function	Oxidative stress, calcium dysregulation	None
23	Melatonin in Aluminum Phosphide Cardiotoxicity	Asghari et al. (2017) (32)	Rats	Aluminum phosphide	Reduced cardiac injury	Antioxidant, anti-inflammatory	Melatonin
24	L-Arginine vs. Dichlorvos Toxicity	Saka et al. (2024) (33)	Rats	Dichlorvos	Reduced oxidative stress, improved heart function	Nitric oxide pathway activation	L-Arginine

Table 1b. Human Epidemiological and Clinical Studies on OP Exposure and Cardiovascular Effects (n = 15)

N/S	Study Title	Authors (Year)	Design/Population	Pesticide Exposure	Cardiovascular Outcome(s)	Mechanisms	Protective Agents
1	Long-Term Effects of OP Poisoning	Hung et al. (2015) (34)	Nationwide cohort, Taiwan	Various OPs	Increased CVD risk in survivors	Unknown	None
2	CRP Levels and QT Interval in Workers	Thandar et al. (2021) (35)	Cohort, Myanmar workers	Occupational OP exposure	Elevated CRP, QT abnormalities	Oxidative stress, inflammation	None
3	Myocardial Injury in OP Poisoning	Padma Prasad et al. (2019) (36)	Cross-sectional study, India	Acute OP poisoning	Myocardial injury, ECG changes	Oxidative stress, mitochondrial dysfunction	None
4	OP Ester Exposure and CVD (NHANES)	Guo et al. (2022) (37)	Cross-sectional, US adults	OP esters	Positive association with CVD	Oxidative stress, inflammation	None
5	Complications of OP Poisoning	Akhtar et al. (2020) (38)	Clinical case series, Pakistan	Acute OP poisoning	Arrhythmias, conduction defects	Oxidative stress, inflammation	None
6	ECG Changes in OP Poisoning	Badiger & Harish (2017) (39)	Clinical observational, India	OP poisoning cases	ECG abnormalities	Oxidative stress, mitochondrial dysfunction	None
7	ECG Changes (Prospective Study)	Sanket et al. (2017) (40)	Prospective, 50 patients	OP poisoning	Conduction abnormalities, arrhythmias	Oxidative stress, inflammation	None
8	AChE Inhibition in Dogs (Translational Study)	Ola-Davies et al. (2016) (41)	Experimental/clinical, dogs	OP poisoning	AChE inhibition, ECG changes	Neurocardiac disruption	None
9	OP Flame Retardants and Lipid Metabolism	Cheng et al. (2024) (42)	Human cohort study	OP flame retardants	Dyslipidemia, altered lipid metabolism	Inflammation, oxidative stress	None
10	OP Esters and BMI in Children	Li et al. (2023) (43)	Cohort study, children	OP esters	↑BMI, altered sex hormones	Endocrine disruption, oxidative stress	None
11	OP Esters and Metabolic Syndrome in Adults	Luo et al. (2020) (44)	Cohort study, adults	OP esters	Metabolic syndrome, CVD risk	Mitochondrial dysfunction, oxidative stress	None
12	Zebrafish OP Flame Retardant Study (Translational)	Ramesh et al. (2020) (45)	Zebrafish model linked to human health	OP flame retardants	Cardiotoxicity, AChE inhibition	Oxidative stress, enzyme inhibition	None
13	Children's Residential OP Exposure	Phillips et al. (2018) (46)	Observational, children in residential setting	OP flame retardants/ plasticizers	Possible cardiovascular impacts	Oxidative stress, endocrine disruption	None
14	Urinary OP Ester Metabolites and Liver/CVD Outcomes	Aimuzi et al. (2023) (47)	Adult cohort study	OP ester metabolites	Liver disease, potential cardiovascular outcomes	Oxidative stress, metabolic disruption	None

weakens causal inference and emphasizes the need for large-scale longitudinal studies incorporating biomarker-based exposure assessments.

Mechanisms of Cardiotoxicity

Experimental evidence highlights several interconnected pathways underlying OP-induced cardiotoxicity. Key mechanisms include oxidative stress, mitochondrial dysfunction, inflammation, calcium signaling disturbances, and electrophysiological alterations affecting ion channels (7,11,51,52). Activation of signaling pathways such as PI3K/Akt and MAPK contributes to structural remodeling, while mitochondrial injury triggers apoptotic pathways leading to cardiac cell death (44,45). These toxicodynamic mechanisms align with known processes in cardiovascular pathology induced by pesticide toxicants (27-29).

Animal vs. Human Evidence

While animal studies offer strong mechanistic evidence, translation to human populations is limited by methodological constraints in epidemiological research. Many human studies rely on self-reported pesticide use or proximity to treated fields, resulting in potential exposure misclassification (24). Differences in timing, duration, co-exposure to other chemicals, and lack of standardized cardiovascular endpoints further complicate interpretation. Prospective cohort studies using objective biomarkers and advanced cardiovascular imaging are needed to better understand long-term risks.

Protective Interventions

Numerous experimental studies have explored protective strategies against OP-induced cardiotoxicity. Antioxidants and phytochemicals such as vitamins C and E, resveratrol, moringa oil, saffron, flaxseed, and propolis have shown potential in mitigating oxidative damage and restoring antioxidant enzyme balance in animal models (3,15,18,21,22,26) (Table 3). Pharmacological agents targeting oxidative stress pathways or modulating cholinergic signaling (e.g., Nrf2 activators, cholinesterase inhibitors) also show promise (2). However, evidence from human trials remains sparse, with only limited occupational studies demonstrating reduced oxidative stress biomarkers following antioxidant supplementation (46). Well-designed randomized trials are needed to establish effective preventive and therapeutic interventions.

Table 2. Risk of Bias Assessment for Included Studies on Cardiotoxicity of Organophosphate Pesticides

Study ID	Study Type	Randomization / Allocation	Exposure Assessment Quality	Blinding of Outcome Assessment	Confounder Control	Outcome Reporting Completeness	Overall RoB Judgment	Key Factors Contributing to Bias
Animal / In Vitro Studies (n = 23)								
1. Minassa et al. (2022) (11)	Animal (rats)	Yes, randomized groups	High: precise dosing regimen	Not reported	NA (animal)	Complete	Low	Randomized groups, precise dose regimen, complete outcome reporting.
2. Ibrahim et al. (2019) (12)	Animal (diabetic rats)	Random allocation unclear	High: controlled exposure	Not reported	NA	Complete	Moderate	Randomization unclear, small sample, gene expression endpoints only.
3. Boamah et al. (2023) (13)	Animal (rats, soil extract)	Not randomized	Low: mixed contaminants, no OP quantification	Not blinded	NA	Partial (cardiac outcomes not fully described)	High	Mixed pesticide contaminants, unclear quantification of OP dose, partial cardiac data.
4. Batista et al. (2019) (14)	Animal (rats)	Randomized	High: intermittent dosing	Not reported	NA	Complete	Low	Randomized, controlled exposure, adequate outcome reporting.
5. Ibrahim et al. (2022) (15)	Animal/in silico	Randomized	High, fenitrothion dose-defined	Not reported	NA	Complete	Low	Randomized, clear exposure protocol, robust mechanistic analysis.
6. Adeoye et al. (2023) (16)	Animal (rats)	Random allocation	High	Not reported	NA	Complete	Low	Random allocation, clear intervention, outcome measures well defined.
7. Ibrahim et al. (2020) (17)	Animal (rats, gestational)	Randomized	High	Not reported	NA	Complete	Low	Randomized, exposure-dose-controlled, good data quality.
8. Saka et al. (2020) (18)	Animal (rats, inhalation)	Random allocation not stated	Moderate: inhalation exposure not quantified	Not blinded	NA	Complete	Moderate	Exposure quantification unclear, non-blinded outcome assessment.
9. Zafiropoulos et al. (2014) (5)	Animal (rabbits)	Not randomized	Low: multiple pesticides, unclear doses	Not reported	NA	Partial (no mechanism data)	High	Non-randomized, multiple pesticide types confound effects, missing mechanistic data.
10. Karakuş et al. (2024) (19)	In vitro	NA	High: controlled OP concentrations	NA	NA	Complete	Low	Controlled conditions, reproducible data, minimal bias risk.
11. Shiyovich et al. (2018) (20)	Animal (rats)	Randomized	High	Not blinded	NA	Complete	Low	Randomized, long-term outcomes measured, exposure protocol robust.
12. Alruhaimi (2023) (21)	Animal (rats)	Randomized	High	Not reported	NA	Complete	Low	Randomized, protective agent tested under clear protocols.
13. Khalaf & El-Mansy (2019) (22)	Animal (rats)	Randomization unclear	High	Not blinded	NA	Complete	Moderate	Randomization not stated, histological endpoints subjective.
14. Watson et al. (2014) (23)	Zebrafish, Xenopus	NA	Moderate: exposure control reported but variability possible	NA	NA	Partial	Moderate	Environmental exposure simulated, variable dosing, partial outcome data.
15. Fundere et al. (2024) (24)	Animal (rats, organochlorine)	Not randomized	Low: not primary OP, mixed exposure	Not blinded	NA	Partial	High	Non-OP exposure mix, unclear dose-response, non-randomized.
16. Witchey et al. (2023)	Toxicology (Rats)	NA	Moderate: extrapolated exposure	NA	NA	Partial	Moderate	Extrapolated exposure, no real-world dose data, partial reporting.
17. Danaei et al. (2019) (26)	Animal (rats)	Randomized	High	Not reported	NA	Complete	Low	Clear allocation, antioxidant effect well measured.
18. Samarghandian & Farkhondeh (2023) (27)	In vitro	NA	High	NA	NA	Complete	Low	Controlled OP exposure, no blinding but minimal bias risk.
19. Wu et al. (2023) (28)	Zebrafish embryos	NA	High	NA	NA	Complete	Low	Standardized developmental exposure, validated outcomes.

Table 2. Continued.

Study ID	Study Type	Randomization / Allocation	Exposure Assessment Quality	Blinding of Outcome Assessment	Confounder Control	Outcome Reporting Completeness	Overall RoB Judgment	Key Factors Contributing to Bias
20. Ben Othmène et al. (2020) (29)	Animal (rats)	Randomization unclear	High	Not blinded	NA	Complete	**Moderate**	Non-OP chemical, unclear randomization, moderate data completeness.
21. Abdulretha et al. (2022) (30)	Animal (rats)	Randomized	High	Not reported	NA	Complete	**Low**	Randomized, controlled exposure, protective agent well characterized.
22. Burnett et al. (2021) (31)	In vitro (human cells)	NA	High	NA	NA	Complete	**Low**	Automated screening, minimal selection bias, clear endpoints.
23. Asghari et al. (2017) (32)	Animal (rats)	Random allocation	High	Not reported	NA	Complete	**Low**	Randomized, protective effect evaluated, complete outcomes.
24. Saka et al. (2024) (33)	Animal (rats)	Randomized	High	Not reported	NA	Complete	**Low**	Randomized, antioxidant tested with good endpoint reporting.
Human Epidemiological Studies (n = 15)								
1. Hung et al. (2015) (34)	Cohort study (nationwide)	NA	High: registry data validated	NA	Adjusted for age, sex, comorbidities	Complete	**Low**	Large sample, registry-based exposure/outcomes, adjusted for confounders.
2. Thandar et al. (2021) (35)	Cohort (workers)	NA	Moderate: occupational exposure self-reported	NA	Adjusted for age, BMI, smoking	Complete	**Moderate**	Occupational exposure self-reported, adjusted for age/BMI only.
3. Padma Prasad et al. (2019) (36)	Cross-sectional	NA	Moderate: acute poisoning cases only	NA	Minimal confounder control	Partial (short-term follow-up only)	**High**	Small sample, acute exposure only, minimal confounder control.
4. Guo et al. (2022) (37)	Cross-sectional (NHANES)	NA	High: urinary metabolites measured	NA	Adjusted for demographics, lifestyle	Complete	**Low**	Biomarkers used, adjusted for demographics/lifestyle, robust data.
5. Akhtar et al. (2020) (38)	Clinical case series	NA	Low: diagnosis-based, no quantified exposure	NA	None reported	Partial	**High**	Non-standardized exposure data, lack of confounder adjustment, partial follow-up.
6. Badiger & Harish (2017) (39)	Observational	NA	Low: hospital records only	NA	None	Partial	**High**	Hospital-based, no quantified exposure, uncontrolled confounding.
7. Sanket et al. (2017) (40)	Prospective (50 patients)	NA	Moderate: OP type identified but dose not quantified	NA	Limited control for confounders	Complete	**Moderate**	OP exposure type identified but dose unmeasured, limited adjustment.
8. Ola-Davies et al. (2016) (41)	Translational (dogs/humans)	NA	Moderate: poisoning cases, no standardized dose	NA	Minimal confounder control	Partial	**Moderate**	Experimental design lacks human dose quantification, minimal confounder control.
9. Cheng et al. (2024) (42)	Human cohort	NA	High: exposure biomarkers analyzed	NA	Adjusted for lifestyle and BMI	Complete	**Low**	Biomarkers analyzed, adjusted for multiple confounders, high data quality.
10. Li et al. (2023) (43)	Children cohort	NA	High: urinary metabolites used	NA	Adjusted for age, sex, puberty status	Complete	**Low**	Urinary biomarkers, adjusted for sex/puberty, low misclassification risk.
11. Luo et al. (2020) (44)	Adult cohort	NA	High: metabolites measured	NA	Adjusted for multiple covariates	Complete	**Low**	Exposure measured via biomarkers, multivariate adjustment robust.
12. Ramesh et al. (2020) (45)	Translational zebrafish/human relevance	NA	Moderate: environmental OP exposure simulated	NA	NA	Partial	**Moderate**	Experimental translation uncertain, partial confounder data.
13. Phillips et al. (2018) (46)	Observational (children, home exposure)	NA	Moderate: environmental sampling only	NA	No dietary or lifestyle control	Partial	**Moderate**	Environmental sampling only, no biomarker confirmation, unadjusted for diet/lifestyle.
14. Aimuzi et al. (2023) (47)	Adult cohort	NA	High: urinary metabolites quantified	NA	Adjusted for diet, metabolic confounders	Complete	**Low**	Urinary metabolites measured, adjusted for metabolic confounders, complete data.

Table 3. Thematic Framework Table on Cardiotoxicity of Pesticides

Theme	Subtheme	Studies/ Authors	Pesticide(s)	Outcome	Mechanisms	Protective Agents	Study Design/ Limitations	Exposure Details
1. Pesticide Exposure and Models	Exposure Types	Minassa et al. (2022) (11), Georgiadis et al. (2018) (4), Boamah et al. (2023) (13)	Chlorpyrifos, Diazinon, Dichlorvos, OPs, etc.	Cardiotoxicity in rats, rabbits, zebrafish, and humans.	Animal and human exposure routes (oral, inhalation, gestational)	-	Animal study limitations (e.g., extrapolation to humans)	Duration of exposure, dosing concentrations
2. Cardiotoxic Outcomes	Heart Function Impairment	Minassa et al. (2022) (11), Ibrahim et al. (2022) (15), Shiyovich et al. (2018) (16)	Chlorpyrifos, Dichlorvos, Fenitrothion, etc.	Cardiac hypertrophy, arrhythmias, QT prolongation, cardiac fibrosis.	Heart enlargement, arrhythmias, altered heart rate	-	Potential bias in animal models	Dose-dependent effects
3. Mechanisms of Cardiotoxicity	Oxidative Stress	Minassa et al. (2022) (11), Georgiadis et al. (2018) (4), Karakuş et al. (2024) (19)	Chlorpyrifos, Diazinon, Dichlorvos, etc.	Increased MDA levels, decreased GSH, lipid peroxidation, oxidative damage.	Mitochondrial damage, impaired antioxidant system	-	Limited mechanistic details in human studies	Mitochondrial dysfunction
4. Protective Interventions	Phytochemicals & Natural Compounds	Ibrahim et al. (2019) (12), Khalaf & El-Mansy (2019) (22), Saka et al. (2020) (37), Alruhaimi (2023) (21)	Chlorpyrifos, Dichlorvos, Fenitrothion	Propolis, saffron, betulinic acid, moringa oil, flaxseed mitigate oxidative stress, inflammation, improve heart function.	Antioxidants, anti-inflammatory pathways	Propolis, Saffron, Betulinic Acid, Moringa Oil, Flaxseed	Lack of human clinical trials in some cases	Optimal doses needed for protection
5. Epidemiological Evidence	Chronic Occupational Exposure	Thandar et al. (2021) (35), Guo et al. (2022) (37), Hung et al. (2015) (34)	OPs, OP Esters	Increased cardiovascular disease, endothelial dysfunction, oxidative stress in workers exposed to OPs.	Chronic exposure to OPs linked to cardiovascular risk	-	Limited cohort size in some studies	Chronic exposure, exposure levels

Public Health and Regulatory Implications

The association between OP exposure and cardiovascular diseases carries significant public health implications. Regulatory frameworks currently emphasize neurotoxicity endpoints but often neglect potential cardiovascular risks. Stronger pesticide regulations, improved occupational safety protocols, and the adoption of sustainable agricultural practices such as integrated pest management (IPM) could reduce exposure risks for workers and surrounding populations (2,25,53). Public health campaigns should focus on raising awareness, promoting protective measures, and supporting biomonitoring programs to identify and manage high-risk groups.

Several limitations must be acknowledged when interpreting the findings of this review. First, most included studies relied on self-reported pesticide use or urinary metabolites, which may not accurately capture chronic, low-level, or cumulative OP exposure over time; the development of validated biomarkers would enhance exposure assessment accuracy (2). Many observational studies lacked sufficient control for confounding factors such as diet, lifestyle, and socioeconomic status, complicating the attribution of cardiovascular outcomes solely to OP exposure (34). Additionally, the predominance of cross-sectional or short-term studies limits the ability to establish causal relationships between OP exposure and cardiovascular disease risk, highlighting the need for robust longitudinal designs (47). Much of the current research focuses on occupationally exposed populations, which may not fully represent risks faced by the general population experiencing low-level environmental exposure (25). Furthermore, several studies demonstrated potential selection bias and variability in study quality, as identified in the risk of bias assessment, reducing the overall strength of the evidence base.

Conclusion

This systematic review consolidates growing evidence that organophosphate pesticides (OPs) are implicated in cardiovascular dysfunction in both animal models and human populations. Reported outcomes include cardiac hypertrophy, arrhythmias, myocardial infarction, heart failure, and QT prolongation, with underlying mechanisms primarily involving oxidative stress, mitochondrial dysfunction, inflammation, and electrophysiological disturbances. Protective interventions, particularly antioxidants and phytochemicals, have shown promise in animal studies but lack strong evidence from human trials. The heterogeneity of included studies, combined with limitations such as exposure misclassification, confounding, and selection bias, underscores the need for more rigorous and standardized research. These findings have important public health implications, calling for improved preventive measures and stricter regulatory oversight to reduce cardiovascular risks associated with OP exposure.

Future research should prioritize well-designed longitudinal epidemiological studies with validated biomarker-based exposure assessments to strengthen causal inference between OP exposure and cardiovascular disease,

especially in populations with chronic, low-level exposure. Mechanistic investigations should further explore oxidative stress, mitochondrial dysfunction, inflammatory pathways, and electrophysiological alterations to clarify toxicological pathways using both in vivo and in vitro models. Clinical trials are warranted to evaluate the efficacy and safety of antioxidants, phytochemicals, and pharmacological agents targeting oxidative stress and mitochondrial protection in mitigating OP-induced cardiac injury. Additionally, harmonizing study designs, exposure measurement techniques, and cardiovascular outcome definitions will improve comparability across studies. Stronger regulatory measures are needed to limit unnecessary OP use in occupational and residential settings, coupled with public health campaigns to raise awareness about potential cardiovascular risks. Addressing these research and policy gaps will improve the reliability of future studies and guide effective interventions to reduce OP-related cardiovascular burden.

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Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this study.

Ethical Approval

There is no ethical issue. The authors declare that all data collected during the study are as stated in the manuscript and that no data from the study have been or will be published separately elsewhere.

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