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REVIEW ARTICLE

Cardiotoxicity of some pesticides and their amelioration

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Abstract

Pesticides are used to control pests that harm plants, animals, and humans. Their application results in the contamination of the food and water systems. Pesticides may cause harm to the human body via occupational exposure or the ingestion of contaminated food and water. Once a pesticide enters the human body, it may create health consequences such as cardiotoxicity. There is not enough information about pesticides that cause cardiotoxicity in the literature. Currently, there are few reports that summarized the cardiotoxicity due to some pesticide groups. This necessitates reviewing the current literature regarding pesticides and cardiotoxicity and to summarize them in a concrete review. The objectives of this review article were to summarize the advances in research related to pesticides and cardiotoxicity, to classify pesticides into certain groups according to cardiotoxicity, to discuss the possible mechanisms of cardiotoxicity, and to present the agents that ameliorate cardiotoxicity. Approximately 60 pesticides were involved in cardiotoxicity: 30, 13, and 17 were insecticides, herbicides, and fungicides, respectively. The interesting outcome of this study is that 30 and 13 pesticides from toxicity classes II and III, respectively, are involved in cardiotoxicity. The use of standard antidotes for pesticide poisoning shows health consequences among users. Alternative safe medical management is the use of cardiotoxicity-ameliorating agents. This review identifies 24 ameliorating agents that were successfully used to manage 60 cases. The most effective agents were vitamin C, curcumin, vitamin E, quercetin, selenium, chrysin, and garlic extract. Vitamin C showed ameliorating effects in a wide range of toxicities.

Keywords Pesticides · Cardiotoxicity · Heart complication · Ameliorating agents

Introduction

Pesticides are chemical compounds that are widely used to control pests that harm plants, animals, humans, and the environment and negatively affect food production and public health. Their application resulted in the contamination of honey with concentrations above the acute reference dose of pesticides in many countries (El-Nahhal 2020).

So far, aerial application of pesticide may contaminate surface water with considerable concentration with various pesticide residues. Moreover, pest control in home, offices, school, and/or universities may lead to direct exposure to pesticide. Additionally, application of pesticide may contaminate, several types of food items such as water, honey, fruits, vegetables, milk, fish, and eggs. Consumption of contaminated food may lead to several types of health consequences. Furthermore, considerable concentrations of carbendazim, diuron, imidacloprid, metolachlor, chlorpyrifos, and simazine were detected in water resources, including drinking water (Pinasseau et al., 2020). Exposure to pesticides may occur via several routes; for instance, children may be exposed to pesticides through the ingestion of pesticide-contaminated food and water, contact with pesticide-treated animals and plants in domestic gardens and rural environments, playing with contaminated clothes and equipment, and the treatment for head lice in schools (Pascale and Laborde, 2020; Nahhal 2016). Occupational exposures to pesticides may occur in people working in greenhouses and open fields in agriculture (Nahhal 2016), workers in the pesticide industry, and exterminators for house pests (Damalas and Eleftherohorinos, 2011). The exposure of the general population to pesticides occurs primarily through eating food and drinking water contaminated with pesticide residues, of which substantial exposure occurs in or around the home and during work (Suratman et al., 2015; Roberts et al., 2012).

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Exposure to pesticides may cause health consequences in the short term, such as acute poisoning (El-Nahhal 2017), skin and eye irritation, headache, dizziness, and nausea (Kim et al., 2017). Long-term exposure may result in reproductive system disorders (El-Nahhal 2020), cancers (Safi et al., 1993; Safi 2002), asthma, diabetes (Kim et al., 2017), and other health consequences.

Cardiovascular toxicity may occur due to direct or indirect exposure to pesticides such as occupational exposure to pesticides or the consumption of pesticide-contaminated food and water. Cardiovascular toxicity may be denoted here as complications occurring in the cardiovascular system, including the lungs, and may result in morphological, physiological, biological, serological, histopathological, and biochemical changes.

Several authors elucidated the sensitivity of the cardiovascular system to external and internal environmental stressors during the stages of gestation, infancy, childhood, and adulthood. Exposure in the early stages (infancy, childhood) may have more severe cardiovascular complications than exposure in adulthood. For instance, damage to cardiomyocytes during the fetal or infant stage can cause long-lasting injury to the heart (Mone et al., 2004). To date, cardiovascular diseases have been correlated with nutritional and hormonal factors, diabetes, and cardiovascular failure in adult life stages (Trevenzoli et al., 2007). Cardiotoxicity was characterized as an outcome of environmental pollutants (Bhatnagar, 2004).

The current literature on the cardiotoxicity induced by pesticides has not been profoundly reviewed. The available information in the literature is not satisfactory to the interested readers. There are few experimental studies on pesticides and cardiotoxicity using different animal models. Furthermore, there is a pressing need to summarize the current knowledge on pesticides and cardiotoxicity and to present the therapeutic agents that ameliorate the cardiotoxicity caused by pesticides. This review summarizes the cardiotoxicity of some insecticides, herbicides, and fungicides; explores mechanisms of cardiotoxicity; and provides information on the therapeutic agents that ameliorate cardiotoxicity.

Methodology

Data collection

An extensive search of the scholarly databases such as Scopus, Web of Science, ScienceDirect, PubMed, BMC, Research Gate, and Google Scholar was conducted using the following specific keywords: “pesticide exposure and cardiotoxicity,” “insecticide/herbicide/fungicide and cardiotoxicity,” “specific pesticide name and cardiotoxicity,” “cardiovascular disease and pesticides,” and “arteriosclerosis and pesticides.”

Inclusion and exclusion criteria

The articles were downloaded and carefully reviewed. Articles that mentioned pesticides and cardiotoxicity were included in this review. Articles that investigated cardiotoxicity and pesticides in experimental animal models were also included in this review. Review articles on pesticide exposure and cardiotoxicity were considered relevant and included. Articles that explored cardiotoxicity with medical drugs or correlations between cardiovascular diseases and physiological conditions (e.g., obesity) were excluded from this review.

Data processing and calculations

Pesticides related to cardiotoxicity in these studies are listed in a table, classified into groups according to the WHO (2009) recommended toxicity classification, and subdivided into subgroups according to their chemical or functional activities. Furthermore, the ameliorating agents for cardiotoxicity are also summarized in a separate table.

The statistical parameters the percentage (%) of the total, the reference average (Ref Aver), and the relative average (Rel Aver) were calculated based on the statistical analysis recently described (El-Nahhal 2020).

Results and discussion

Pesticide residues in water

Pesticide residues in water samples from different countries are presented in Tables 1, 2, and 3. It can be seen that water samples from China, Mexico, India, Ghana, and Canada contained 14, 13, 11, 6, and one organochlorine (OC) insecticide residue, respectively, (Table 1). On the other hand, water samples from Canada, the USA, and Canada contained one neonicotinoid (N) residue, whereas water samples from Japan contained six organophosphorus (OP) insecticide residues and two carbamate residues (CT). The differences in pesticide residues in the above-mentioned countries may be explained by different regulations and restriction in each country. For instance, USEPA restricted the use of DDT and its analogs since 1970 but it may be still in use in some countries such as India. Additionally, historical application of OC insecticide and low biodegradation may result in persistence in soil for long periods of time and slow release to water systems.

Table 2 shows the occurrence of herbicide residues in water samples from many countries worldwide. It can be noticed that seven, five, four, three, three, two, and one herbicide residues were detected in water samples from Brazil, Lebanon, Spain, Slovenia, the USA Canada, and Korea, respectively. The explanation of these differences may be due to

Table 1 Detected insecticide residues in drinking water from several countries

Insecticide name	Wu et al. 2014 China	Díaz et al., 2009 Mexico	Kaushik et al., 2012 India	Fosu-Mensah et al., 2016 Ghana	Sultana et al., 2018 Canada	Klarich et al., 2017 USA	Tanabe et al., 2001 Japan
α-HCH	√	√	√	–	–	–	–
β-HCH	√	√	√	–	–	–	–
γ-HCH	√	√	√	√	–	–	–
δ-HCH	√	√	–	–	–	–	–
p,p′-DDE	√	√	√	–	–	–	–
o,p′-DDE	–	–	√	–	–	–	–
o,p′-DDD	–	–	√	–	–	–	–
p,p′-DDD	√	√	√	–	–	–	–
p,p′-DDT	√	√	√	√	–	–	–
o,p′-DDT	–	–	√	–	–	–	–
Heptachlor	√	√	–	√	–	–	–
Heptachlor-epo	√	√	–	–	–	–	–
HCB	√	–	–	–	–	–	–
Aldrin	√	√	–		–	–	–
Dieldrin	√	–	–	√	–	–	–
Endrin	√	√	–	–	–	–	–
Endrin aldehyde	√	√	–	–	–	–	–
α-Endosulfan	–	√	√	√	–	–	–
β-Endosulfan	–		√	–	–	–	–
Endosulfan sulfate	–	–	–	√	√	–	–
Thiacloprid	–	–	–	–		–	–
Imidacloprid	–	–	–	–	√	√	–
Malathion	–	–	–	–	–	–	√
Chlorpyrifos	–	–	–	–	–	–	√
Diazinon	–	–	–	–	–	–	√
Dichlorvos	–	–	–	–	–	–	√
Dimethoate	–	–	–	–	–	–	√
Fenitrothion	–	–	–	–	–	–	√
Carbaryl	–	–	–	–	–	–	√
Propoxur	–	–	–	–	–	–	√

Table 2 Detected herbicide residues in drinking water in several countries

Herbicide name	Albuquerque et al., 2016 Brazil	Chaza et al. 2018 Lebanon	Ccanccapa et al., 2016 Spain	Koroša et al. (2016) Slovenia	Postle et al. (2004) USA	Woudneh et al., 2009 Canada	Oh et al., 2014 Korea
2,4-D	√	–	–	–	–	–	–
Acetochlor	√	√	–	–	√	–	–
Metolachlor	√	√	√	√	√	–	–
Alachlor	√	√	–	–	√	√	–
Diuron	√	–	√	–	–	–	–
Atrazine	√	√	√	√	–	√	–
Simazine	√	–	√	√	–	–	–
Butachlor	–	√	–	–	–	–	–
Paraquat	–	–	–	–	–	–	√

Table 3 Detected fungicide residues in drinking water in several countries

Fungicide name	Ccanccapa et al., 2016 Spain	Albuquerque et al., 2016 Brazil	Tanabe et al., 2001 Japan
Imazalil	√	–	–
Prochloraz	√	–	–
Carbendazim	√	√	–
Thiabendazole	√	–	–
Chlorothalonil	–	√	–
Tebuconazole	–	√	–
Difenoconazole	–	√	–
Flutolanil	–	–	√
Iprobenfos	–	–	√
Isoprothiolane	–	–	√
Tricyclazole	–	–	√

different agricultural practices and regulation restrictions in the above-mentioned countries.

Table 3 shows the occurrence of fungicide residues in some countries. It appears that 11 fungicide residues were detected in water samples from Spain, Brazil, and Japan. It appears that detected fungicide residues are different from each other. This is probably due to different agricultural system. For instance, fungicides are applied as seed dressings to control soil-borne diseases in Spain, whereas in Brazil and Japan fungicides may be applied as aerial and/or foliar application as shown in the graphical abstract.

Pesticide residues in honey

Table 4 shows insecticide residues detected in honey samples from many countries worldwide. It can be seen that honey samples from Egypt, Italy, France, China, Portugal, and Ghana contained nine, seven, nine, one, zero, two, and one OC residues, respectively. On the other hand, honey samples from Egypt contained one pyrethroid (PY) residue, whereas honey samples from Italy contained two OP residues. Additionally, honey samples from France contained one OP residue, two CT residues, and one PY and one N residues. Furthermore, honey samples from China contained two N residues. On top of that, honey samples from Portugal contained two OP residues and three CT residues, and besides, honey samples from Ghana contained 3 OP residues and one CT residue (Table 4).

The occurrence of insecticide residues in honey may be attributed to direct and indirect application of pesticides to control pests in agricultural system during the flowering season, or due to historical application of OC to control agricultural pests and insects of public health importance.

Table 5 shows the occurrence of herbicide residues in many countries worldwide. It can be noticed that three herbicide residues were detected in honey samples from Canada, whereas two herbicide residues were detected in honey samples from Lebanon, Brazil, and Switzerland. Additionally, one herbicide residue was detected in honey samples from Estonia and the USA. In general, the total number of herbicide residues detected in honey samples is five.

Table 6 shows the occurrence of fungicide residues in honey samples worldwide. It can be seen that the total number of fungicide residues detected in honey samples is 5. So far, three fungicide residues were detected in honey samples from Poland and France, whereas only one fungicide residue was detected from honey samples from Estonia, Israel, Italy, and Lebanon. The difference in occurrence of fungicide residues in honey samples among countries worldwide may be attributed to the type of fungicide application, fungicide formulations, and agricultural system in the country.

Table 7 shows the insecticide residues in fruits and vegetables samples from many countries worldwide. It can be seen that five OP residues and one N residue were detected in fruits and vegetables samples from Mexico, whereas two N residues were detected in fruits and vegetables samples from the USA. Meanwhile, one OP residue was detected in samples from Poland. Additionally, three OP residues and one PY residue were detected in fruits and vegetables samples from Egypt. Two OP residues, one N residue, and two PY residues were detected in fruits and vegetables samples from Kuwait. On the other hand, three OC residues, two OP residues, and one PY and one CT residues were detected in fruits and vegetables samples from Palestine (Table 7). In general, 14 insecticide residues of different chemical structure were found in fruits and vegetables samples from many countries worldwide.

Table 8 shows fungicide residues in fruits and vegetables samples from many countries worldwide. It can be seen that fruits and vegetables samples from Mexico and Spain contained three fungicide residues of different chemical structure, whereas samples from Palestine contained two fungicide residues. Additionally, samples from China, India, and

Table 4 Detected insecticide residues in honey from several countries

Insecticide name	Malhat et al., 2015 Egypt	Saitta et al., 2017 Italy	Chauzat et al., 2009 France	Song et al., 2018 China	Blasco et al., 2003 Portugal	Darko et al., 2017 Ghana
2,4′-DDE	√	√	–	–	–	–
2,4′-DDD	√	√	–	–	–	–
4,4′-DDD	–	√	–	–	–	–
2,4′-DDT	–	√	–	–	–	–
4,4′-DDT	√	√	–	–	√	√
γ-HCH	√	√	√	–	√	–
Endosulfan	–	√	–	–	–	–
Aldrin	–	–	–	–	–	–
Endrin	√	–	–	–	–	–
Heptachlor	√	–	–	–	–	–
Hept. epoxide	√	–	–	–	–	–
γ-Chlordane	√	–	–	–	–	–
Methoxychlor	√	–	–	–	–	–
Chlorpyrifos	–	√	–	–	–	√
Parathion-ethyl	–	–	√	–	√	–
Malathion	–	–	–	–	–	√
Dimethoate	–	–	–	–	–	√
Diazinon	–	√	–	–	–	√
methidathion	–	–	–	–	√	–
Carbaryl	–	–	√	–	√	–
Carbofuran	–	–	√	–	√	–
Methiocarb	–	–	–	–	√	–
Permethrin	√	–	–	–	–	√
Deltamethrin	–	–	√		–	–
Thiacloprid	–	–	–	√	–	–
Imidacloprid	–	–	√	√	–	–

Kuwait contained only one fungicide each. The explanation of these results is that different pattern of agricultural system and different regulations and restrictions on pesticide use among countries.

Herbicide residues were not detected in fruits and vegetables samples, due to the fact that plants are sensitive to low concentrations of herbicide so that normal plant life cycle cannot be continued in the presence of herbicides.

Table 9 shows insecticide residues detected in fish samples from many countries worldwide. It can be seen that nine OC residues were detected in fish samples from China and from India, whereas eight and seven OC residues were detected in fish samples from Turkey and Uganda respectively. Additionally, three OC residues were detected in fish samples from Pakistan and Ghana. On the other hand, one CT residue, two OP residues, and one OP residue were detected in fish samples from Pakistan, Ghana, and Taiwan respectively.

Table 5 Detected herbicide residues in honey from several countries

Herbicide name	Thompson et al., 2019 Canada	Al-Alam et al., 2017 Lebanon	de Souza et al., 2021 Brazil	Zoller et al., 2018 Switzerland	Karise et al., 2017 Estonia	Berg et al., 2018 USA
Glyphosate	√	–	√	√	√	√
AMPA	√	–	√	√	–	–
Glufosinate	√	–	–	–	–	–
Diuron	–	√	–	–	–	–
Acetochlor	–	√	–	–	–	–

Table 6 Detected fungicide residues in honey from several countries

Fungicide name	Gaweł et al., 2019 Poland	Lambert et al., 2013 France	Karise et al., 2017 Estonia	Bommuraj et al., 2019 Israel	Saitta et al., 2017 Italy	Al-Alam et al., 2017 Lebanon
Carbendazim	√	√	–	√	–	–
Tebuconazole	√	√	√	–	√	–
Cyproconazole	√	–	–	–	–	–
Imazalil	–	√	–	–	–	–
Penconazole	–	–	–	–	–	√

The common sense among the above-mentioned countries is that the majority of detected insecticide residues are OC and the minority is CT. This is probably due to the physical properties of the compounds such as partitioning coefficient (log P) and dissociation constant (pKa).

Table 10 shows detected insecticide residues in eggs from many countries worldwide. It can be seen that 14, 10, 8, and 5 OC residues were detected in egg samples from Hong Kong, India, Spain, and Jordan respectively. On the other hand, a single OP residue was detected in egg samples from Jordan. In general, the number of OC residues detected is 16 and one OP.

Table 11 shows insecticide residues detected in milk samples from many countries worldwide.

It appears that 15, 10, 8, 6, 5, 4, 3, and 2 OC residues were detected in different milk samples from Mexico, India, Tanzania, Pakistan, Tunisia, the USA, China, India, and Romania, respectively. On the other hand, three PY residues and two OP residues were detected in milk samples from India and Romania (Table 11). In general, OC residues were most frequently detected in water samples (Table 1), honey samples (Table 4), fish samples (Table 9), egg samples (Table 10), and milk samples (Table 11) and less frequently detected in fruits and vegetables samples (Tables 7 and 8). This may be due to the historical application of OC insecticides in agricultural and public health sectors beside the fact that OC insecticide has long persistence in ecosystems. Additionally, OC compounds have high partitioning coefficient value (Kow) and low solubility in water (PPDB 2007). Accordingly, they tend to accumulate in lipid tissues.

Pesticide residues in Tables 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11 were summarized and classified to four toxicity classes as follows: toxicity class Ia (extremely toxic compounds, these compounds have LD50 values < 5 mg/kg b.w.); toxicity class Ib (highly toxic compounds, these compounds have LD50 values in the range of 5 to < 50 mg/kg b.w.); toxicity class II (moderately toxic compounds, these compounds have LD50 values in the range of 50 to < 500 mg/kg b.w.); toxicity class III (slightly toxic compounds, these compounds have LD50 values in the range of 500 to < 2000 mg/kg b.w.); and toxicity class IV (less toxic compound, these compounds have LD50

Table 7 Detected insecticide residues in fruits and vegetables from different countries

Pesticide name	Suárez-Jacobo et al., 2017 Mexico	Craddock et al., 2019 USA	Mojsak et al., 2018 Poland	Abbassy, 2001 Egypt	Jallow et al., 2017 Kiewit	Safi et al., 2002 Palestine
α-Endosulfan	–	–	–	–	–	√
β-Endosulfan	–	–	–	–	–	√
Endosulfan sulfate	–	–	–	–	–	√
Malathion	√	–	–	√	√	–
Chlorpyrifos	√	–	√	–	√	√
Methidathion	√	–	–	–	–	–
Dimethoate	√	–	–	√	–	–
Parathion	√	–	–	–	–	√
Fenitrothion	–	–	–	√	–	–
Imidacloprid	√	√	–	–	√	–
Thiacloprid	–	√	–	–		–
Cypermethrin	–	–	–	√	√	√
Deltamethrin	–	–	–	–	√	–
Carbofuran	–	–	–	–	–	√

Table 8 Detected fungicide residues in fruits and vegetables from different countries

Pesticide name	Suárez-Jacobo et al., 2017 Mexico	García-Reyes et al., 2008 Spain	Safi et al., 2002 Palestine	Li et al., 2016 China	Arora, et al., 2014 India	Jallow et al., 2017 Kuwait
Carbendazim	√	√	–	√	√	–
Pyraclostrobin	√	–	–	–	–	–
Thiabendazole	√	√	–	–	–	–
Difenoconazole	–	–	–	–	–	√
Iprodione	–	√	√	–	–	–
Penconazole	–	–	√	–	–	–

value > 2000 mg/kg b.w.). A summary of pesticide toxicity classes is presented in Table 12.

Table 12 left section shows 30 insecticides that were correlated with cardiotoxicity. These insecticides are 11 OC, 10 OP, 4 CT, 3 PY, and 2 N. The OC group included one, seven, one, and two insecticides from the toxicity classes Ib, II, III, and IV, respectively. The OP group included two, two, five, and one insecticides from the toxicity classes Ia, Ib, II, and III, respectively. The CT group included two and two insecticides from the toxicity classes Ib and II, respectively. The PY group included three insecticides from toxicity class II. The N group included one insecticide from toxicity class II and another one from toxicity class IV. Additionally, this section includes the partitioning coefficient (log P) and dissociation constants (pKa) of insecticides. It appears that OC insecticides have high log P values compared to that of OP. For instance, DDT, Aldrin, and Methoxychlor have log P values of 6.91, 6.5, and 5.83 respectively. Similarly, PY residues have high log P values (Table 12). These groups have also no dissociation constants. On the other hand, OP and CT insecticides have nearly lower log P (dichlorvos = 1.9, carbofuran = 2.78) than those of OC or PY insecticide, beside the fact that some of OP insecticides are strong acids (e.g., diazinon), a similar trend in CT insecticides which are weak acids (e.g., carbaryl).

Table 12 right upper section shows that the 13 herbicides from different chemical groups caused cardiotoxicities. These herbicides included five, seven, and one herbicides from the toxicity classes II, III, and IV, respectively. Additionally, the section includes the partitioning coefficient (log P) and dissociation constants (pKa) of herbicides. It appears that dinitroaniline and chloroacetanilide herbicides have higher

Table 9 Detected insecticide residues in fish from different countries

Insecticide name	Fang et al., 2015 China	Samidurai et al., 2019 India	Atmaca et al., 2019 Turkey	Kasozi et al., 2006 Uganda	Akhtar et al., 2014 Pakistan	Akoto et al., 2016 Ghana	Chang et al., 2020 Taiwan
α-HCH	√	√	√		–		–
β-HCH	√	√	√		–		–
γ-HCH	√	√	√	√	–		–
δ-HCH	√	√	√		–		–
Heptachlor epoxide	–	√	–	–	–	–	–
Aldrin			√	√	–	√	–
Dieldrin		√	–	√	–		–
Endosulfan	√	√	–	√	√		–
p,p′-DDE		–	–	√	√	√	–
Endosulfan II	√	–	–	–	–		–
p,p′-DDD		–	√	–	–	√	–
o,p″-DDT	√	√	√	–	–	–	–
p,p′-DDT	√	√	√	√	√	–	–
o,p′-DDD	√	–	–		–	–	–
Chlorpyrifos	–	–	–	–	–	√	√
Pirimiphos-methyl	–	–	–	–	–	√	–
Carbofuran	–	–	–	–	√		–

Table 10 Detected insecticide residues in eggs from different countries

Insecticide Residues	Wang et al., 2011 Hong Kong	Venugopal et al., 2020 India	Morales et al., 2012 Spain	Alaboudi et al., 2019 Jordan
α-HCH	√	√	–	√
β-HCH	√	√	–	√
γ-HCH	√	√	√	√
δ-HCH	√	√	√	√
Heptachlor	√		–	–
Heptachlor epoxide	√	√	–	–
Aldrin	√	–	–	√
Dieldrin	√	√	–	
Endosulfan	√	–		–
Endrin	–	–	√	–
Endosulfan II		–	√	–
Chlordane	√	–	√	–
p,p′-DDE	√	√	√	–
p,p′–DDD	√	√	√	–
o,p″-DDT	√	√		–
p,p′-DDT	√	√	√	–
Malathion	–	–	–	√

log P values compared to bipyridylium, triazine, and phosphonoglycine herbicides (Table 12). Moreover, some of these herbicides are strong acids and/or weak bases such as atrazine.

Meanwhile, Table 12, right lower section shows that the 17 fungicides from different chemical groups caused cardiotoxicities. This table includes 7, 4, and 6 fungicides from the toxicity classes II, III, and IV, respectively. Similarly, this section includes the partitioning coefficient (log P) and dissociation constants (pKa) of fungicides. It appears that triazole, triazolobenzothiazole, and oxazole fungicides have higher log P values compared to benzimidazole and carbamate fungicides. Moreover, some of these fungicides are strong acids (e.g., difenoconazole) and/or weak bases (e.g., carbendazim) and have values of pKa (Table 12, right lower section).

Furthermore, Fig. 1 shows the number of pesticides from the same toxicity class involved in cardiotoxicity. The highest number of pesticides that resulted in cardiotoxicity was from toxicity class II, and the lowest number was from toxicity class Ia. This suggests that moderately toxic pesticides (toxicity class II) are more potent cardiotoxic agents than the other classes. This result explains that highly toxic pesticides (toxicity class I) may lead to rapid death in poisoned individuals, whereas moderately toxic pesticides (toxicity class II) may not cause rapid death in poisoned individuals, and the reaction between pesticide and the target site may be slower than that of toxicity class I. This may enable the toxic substances from toxicity class II to reach the cardiovascular system and undergo certain reactions that may result in changes in morphology, physiology, and/or activity (cardiovascular parameters). This is in accord with a recent study (Pereira-Leite et al., 2020) that reported diclofenac, a medical drug previously considered safe, to be among the most cardiotoxic compounds, while naproxen, a medical drug, was associated with a low cardiovascular toxicity risk. In the same study, Pereira-Leite et al. revealed that anti-inflammatory drugs such as rofecoxib and valdecoxib, which were previously considered safe for human consumption, were associated with cardiovascular toxicity. Rofecoxib and valdecoxib were then removed from the market in 2004 and 2005, respectively (Marnett 2009). On the other hand, it can be suggested that pesticides of high log P values such as OC insecticides may be stored in the fat bodies in arteries and slowly released with the blood and reaching the hearts causing several complications. This is in agreement with Pines et al. (1986) who found considerable levels of OC residues (DDT isomers and their metabolites, and of lindane, dieldrin, heptachlor epoxide) in blood serum of 11 patients suffering from slight to moderate and 24 patients with moderate to severe arteriosclerotic lesions.

Cardiotoxicity due to occupational exposure to pesticides

Organochlorine insecticides and cardiotoxicity

There are limited cardiotoxicity studies on humans and pesticide residues found in honey, milk, and water. Some

Table 11 Insecticide residues in milk from different countries

Pesticide name	Gutierrez et al., 2013Mexico Cow milk	John et al., 2001 India Seasonally milk	Kampire et al., 2011 Tanzania Pasteurized and fresh	Muhammad Arif et al., 2021 Pakistan Raw milk	Ennaceur et al., 2008 Breast milk Tunisia	Xu, et al., 2016 USA Maternal colostrum	Zhou et al., 2012 Breast milk China	Gill et al., 2020 Bovine milk India	Dobrinas et al., 2016 Milk powder Romania
α-HCH	√	√	–	–	–	–	–	–	–
β-HCH	√	√	–	–	√	–	√	√	
γ-HCH	√	√	√	–	√	–	–	–	–
δ-HCH	√	√	–	–	–	–	–	–	–
Heptachlor	√	√	–	–	–	–	–	–	–
Heptachlor epoxide	√	√	–	–	–	–			√
Aldrin	√	√	√	–	–	–	–	–	–
Dieldrin	√	–	√	√	√	–	–	–	–
Endosulfan I	√	–	√	√	–	–		√	
Endosulfan II	√	–	√	√	–	–	–	–	–
Endosulfan sulfate	–	–		√	–	–			√
Endrin	√	–	–	–	–	–	√		
Endrin aldehyde	√	–	–	–	–	–	–	–	–
p,p′-DDE	√	√	√	√	√	√	√		
p,p′-DDD	√	√	–	–	√	√	–	–	–
o,p″-DDT	–		√			√			
p,p′-DDT	√	√	√	√	√	√	√	√	
o,p′-DDD	–	–	–	–		√			
Cypermethrin	–	–	–	–	–	–	–	√	
Permethrin	–	–	–	–	–	–	–	√	
Chlorpyrifos	–	–	–	–	–	–	–	√	√
Parathion-methyl	–	–	–	–	–	–	–		√

epidemiological surveys elucidated the cardiotoxicity among occupationally exposed workers. For instance, DDT and its analogs, most frequently detected in honey samples, caused cardiotoxicity in humans (Lamichhane et al., 2019).

The development of arteriosclerosis and arterial hypertension were correlated with occupational exposure to OC insecticides (Morgan et al., 1980), and patients with atherosclerosis had higher serum concentrations of DDT, DDE, DDD, lindane, dieldrin, heptachlor epoxide, and polychlorinated biphenyls than control groups (Pines et al., 1986).

Hypertension was positively associated with exposure to DDT or its analogs (Donat-Vargas et al. 2018; La Merrill et al. 2013; La Merrill et al. 2018; Vafeiadi et al. 2015; Teixeira et al. 2015). Chlorinated insecticides (*o,p′*-DDT, *p,p′*-DDT, *o,p′*-DDE, or *p,p′*-DDE) caused myocardial infarction in poisoned humans (Georgiadis et al., 2018), altered the function of the human heart, and induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs); these outcomes were studied by assessing the effect(s) of these compounds on hiPSC-CMs and Ca^{2+} dynamics (Truong et al., 2020).

Chlordane caused tachycardia in accidentally poisoned humans (EPA, 1980), whereas the cardiovascular impact was not reported in occupationally exposed populations (Alvarez and Hyman 1953), but equivocal evidence of increased risk was revealed among employees at a chlordane manufacturing industrial company (Wang and MacMahon 1979).

Occupational exposure to *p,p′*-DDE, trans-nonachlor, oxychlordane, dieldrin, and HCH caused severe peripheral arterial disease, leading to mortality among workers in the USA (Min et al., 2011), whereas occupational exposure to aldrin, DDT, and 2,4,5-T caused nonfatal myocardial infarction (Mills et al., 2009).

Hexachlorocyclohexane (HCH) and its isomers, especially γ-HCH (lindane), caused severe cardiac arrest, tachyarrhythmias, and death among humans (Solomon et al., 1977) and increased cardiac wall thickness and concentric left ventricular remodeling in humans (Sjöberg Lind et al., 2013). Endrin caused hypotension, bradycardia, and cardiac arrest (common

Table 12 Name (Na), toxicity class (ToxC), chemical group (ChemG), partitioning coefficient (log P), and dissociation constant (pKa) of pesticide residues found in water, honey, fruit and vegetable, fish, egg, and milk samples from many countries worldwide

Insecticides					Herbicides				
Na	ToxC	ChemG	Log P	pKa	Na	ToxC	ChemG	Log P	pKa
Parathion-methyl	Ia	OP	3	–	Alachlor	II	chloroacetanilide	3.09	0.62 SA
Parathion-ethyl	Ia	OP	3.8	–	2,4-D	II	Alkylchlorophenoxy	− 0.82	3.40 SA
Dichlorvos	Ib	OP	1.9	ND	Pendimethalin	II		5.4	2.8
Methamidophos	Ib	OP	− 0.79	–	Glufosinate	II	Dinitroaniline Organophosphate	− 3.96	2 SA
Methiocarb	Ib	CT	3.18	ND	**Paraquat**	II	bipyridylium	− 4.5	Not applicable
Carbofuran	Ib	CT	2.78	ND	Acetochlor	III	chloroacetanilide	4.14	ND
Dieldrin	Ib	OC	3.7	ND	Butachlor	III	chloroacetanilide	4.5	–
Chlorpyrifos	II	OP	2.78	ND	Atrazine	III	triazine	2.7	1.7 WB
Fenitrothion	II	OP	3.32	ND	Diuron	III	Phenylamide	2.87	ND
Dimethoate	II	OP	0.75	ND	Glyphosate	III	Phosphonoglycine	− 3.2	2.34 SA
Diazinon	II	OP	3.69	SA	Diclofop-methyl	III	Aryloxyphenoxypropionate	4.8	ND
Triadimefon	II	OP	3.18	–	**Metolachlor**	III	Chloroacetamide	3.4	ND
γ-Chlordane	II	OC	2.78	ND	Trifluralin	IV	Dinitroaniline	5.27	ND
γ-HCH	II	OC	3.50	–	Total 13	II = 5			
DDT	II	OC	6.91	–		III = 7			
Heptachlor	II	OC	5.44	–		IV = 1			
α-Endosulfan	II	OC	4.74	–	Fungicides				
β-Endosulfan	II	OC	3.83	–					
HCH	II	OC	–	–	Difenoconazole	II	Triazole	4.36	1.07 SA
Thiacloprid	II	N	1.26	–	Iprobenfos	II	Organophosphate	3.37	–
Deltamethrin	II	PY	4.6	ND	Tricyclazole	II	Triazolobenzothiazole	4.2	6.5 WA
Cypermethrin	II	PY	5.55	ND	Isoprothiolane	II	Phosphorothiolate	3.3	–
Permethrin	II	PY	6.1	–	Tebuconazole	II	Triazole	3.7	5.0
Carbaryl	II	CT	2.78	WA	Imazalil	II	Imidazole	2.56	6.49 WB
Propoxur	II	CT	0.14	–	Cyproconazole	II	Triazole	3.09	ND
Malathion	III	OP	2.75	ND	Thiabendazole	III	Benzimidazole	2.39	4.73
Methoxychlor	III	OC	5.83	–	Iprodione	III	Dicarboximide	3.0	ND
Aldrin	IV	OC	6.5	ND	Pyrimethanil	III	Anilinopyrimidine	2.84	3.52 WB
Endrin	IV	OC	3.2	–	Penconazole	III	Triazole	3.72	1.51 WB
Imidacloprid	IV	N	0.57	–	Carbendazim	IV	Benzimidazole	1.48	4.2 WB
					Chlorothalonil	IV	Chloronitrile	2.94	ND
OC = 11	IA = 2				Flutolanil	IV	Oxathiin	3.17	ND
OP = 10	1B = 5				Pyraclostrobin	IV	Strobilurin	3.99	ND
CT = 4	II = 18				Mancozeb	IV	Carbamate	2.3	10.3 WB
PY = 3	III = 3				Famoxadone-cymoxanil	IV	Oxazole	4.65	ND
N = 2	IV = 2								
Total = 30					Total fungicide	17	II = 7		
							III = 4		
							IV = 6		

OP organophosphorus, *CT* carbamate, *OC* organochlorine, *N* neonicotinoid, *PY* pyrethroid compounds, *ND* not found, no dissociation, *SA* strong acid, *WA* weak acid, *WB* weak base

symptoms of cardiotoxicity) in poisoning cases (Runhaar et al., 1985).

Endosulfan caused severe cerebral edema, cardiac failure, severe myocardial insufficiency, pulmonary edema (Eyer et al., 2004), hypotension, abnormalities in electrocardiograms, and rhabdomyolysis in humans (Moon and Chun, 2009).

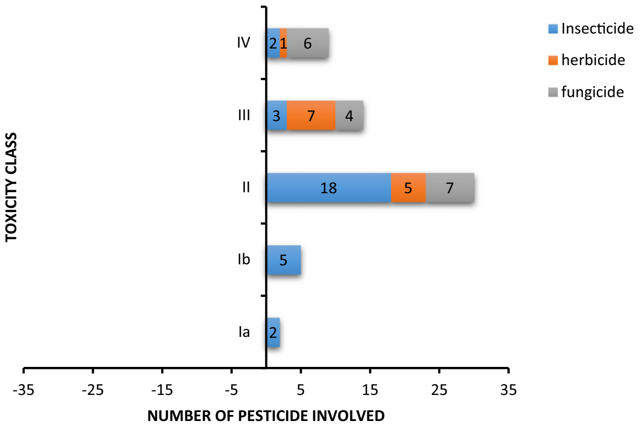

Fig. 1 Number of pesticides and their toxicity class that are involved in the cardiotoxicity

Organophosphorus residues and cardiotoxicity

OP insecticide residues found in honey samples (El-Nahhal 2020) are strong cholinesterase inhibitors and may cause heart complications due to direct or indirect exposure. For instance, occupational exposure to chlorpyrifos increased the risk factor above 1 for acute infarction, whereas exposure to fenitrothion and malathion residues increased blood pressure, leading to cardiovascular complications among male farmworkers (Zago et al., 2020) and female farmworkers (Dayton et al., 2010).

Additionally, occupational exposure to OP residues increased mortality from heart diseases among humans (Charles et al., 2010; Wahab et al., 2016; Hung et al., 2015); caused fatal myocardial infarction (Mills et al., 2009); increased heart rate and cardiac enzyme levels (Samsuddin et al., 2016); and caused inappropriate peripheral vasodilatation, hypotension, and distributive shock (Davies et al., 2008).

Further, acute organophosphate poisoning caused arrhythmias, hypertension, and sudden death in poisoned individuals (Luzhnikov et al., 1975; Kiss and Fazekas 1979; Roth et al., 1993; Bar-Meir et al., 2007) and caused severe hypotension in individuals poisoned with dimethoate (Eddleston et al., 2005).

OP residues caused ventricular tachycardia, ventricular fibrillation, and various degrees of bradycardia among self-poisoned adults (Ludomirsky et al. 1982; Kiss and Fazekas 1983) and children (Liang et al., 2020). Heart failure was caused by the elevated level of cardiac enzymes (Joshi et al., 2013; Ellidag et al., 2017). Additionally, non-OP residues caused myocardial necrosis and abnormalities in electrocardiograms among children poisoned with phosphine (Atiq and Shaikh, 2017).

Parathion caused myocardial infarction (Kidiyoor et al., 2009) and changes in electrocardiograms among self-poisoned farmers (Karasu-Minareci et al., 2012). Moreover, when exposed to parathion prenatally, children carrying the paraoxonase 1 192R allele had higher abdominal circumference, blood pressure, and serum concentrations of leptin and IGF-I at school age than unexposed children (Andersen et al., 2012), whereas parathion self-poisoning increased heart rate and led to arterial metabolic blood acidosis (Aardema et al., 2008). Chlorpyrifos caused various heart complications among humans exposed to the compound (Mirenga, 2018). Diethyltoluamide (DEET) caused cardiovascular toxicity in adults and children exposed to the compound (Clem et al. 1993). Additionally, non-OP insecticide such aluminum phosphide induced electrocardiographic changes and cardiogenic shock among 90 poisoned patients (Katira et al., 1990).

Carbamate residues and cardiotoxicity

Exposure to carbamate insecticides may result in cardiovascular complications in humans. For instance, carbaryl and bendiocarb induced electrocardiographic manifestations (i.e., atrial fibrillation and ventricular tachycardia) and other cardiac manifestations (sinus bradycardia, hypertension, and hypotension) in self-poisoned patients (Saadeh et al., 1997).

Carbofuran caused tachypnea, salivation, miosis, elevated blood pressure, and fasciculation among occupationally poisoned farmers (Satar et al., 2005); myocardial infarction among female farmworkers (Dayton et al., 2010); carbofuran intoxication in humans (Yen et al., 2015); and intoxication in pesticide formulators and spray men (Zago et al., 2020).

Carbofuran was found in nontarget mammalian tissues such as the maternal plasma, umbilical cord, and blood in African American women and newborn babies (Whyatt et al., 2003) and accumulated in heart tissue (Gupta 1994).

Methiocarb concentrations reached 4.0 μg/mL within the blood of the heart in a self-poisoned elderly woman (Thierauf et al., 2009).

Pyrethroid, neonicotinoid, and other residues and cardiotoxicity

Pyrethroid residues may cause cardiotoxicity and heart complications in humans. Previous studies reported cardiotoxic symptoms that were caused by occupational exposure to pyrethroids among spray men (Zhang et al., 1991) and female farmworkers (Chen et al., 1991). Delgado and Paumgartten (2004) observed cardiotoxicity due to the intensive use of pyrethroids among farmworkers. Recently, permethrin induced the formation of reactive oxygen species in heart tissues in exposed populations (Wang et al., 2016).

Potential cardiotoxicity was induced by pyrethroid poisoning among farmworkers (Bradberry et al., 2005). Mills et al. (2009) reported the association between fatal myocardial infarction and pendimethalin. Tripathi et al. (2006) reported bradycardia among 8 patients in Nepal who ingested pyrethroids with suicidal intents. Selvam and Srinivasan (2019) noticed that individuals poisoned with neonicotinoid showed symptoms of dizziness, hypertension, and tachycardia, which are the most common cardiovascular symptoms.

Herbicide residues and cardiotoxicity

Herbicide residues (Table 2) may cause cardiovascular complications in humans due to either occupational exposure or poisoning. For instance, 2,4-D caused severe tachycardia (150 beats/min), hypertension (170/110 torr), and disturbances in electrocardiograms such as QT interval prolongation, peaked T wave, and sinus tachycardia among humans (Osterloh et al., 1983). Glyphosate resulted in prolonged QT intervals, followed by intraventricular conduction delay and atrioventricular block, leading to mortality among poisoned humans (Kim et al., 2014) and caused rapid cardiotoxicity symptoms leading to death among human intoxication cases (Sorensen and Gregersen, 1999; Talbot et al., 1991). Alachlor and butachlor caused hypotension and coma among humans (Lo et al., 2008), whereas atrazine caused heart and lung complications at low concentrations in drinking water (EC 1998; Meghdad et al., 2013).

Moreover, pendimethalin and trifluralin caused cardiovascular complications among exposed workers and populations (Zimmermann and Green, 2001). Additionally, maternal exposure to herbicides caused cardiovascular malformations in infants (Loffredo et al. 2001) and congenital heart defects in newborns (Kimmel et al., 2013).

Fungicide residues and cardiotoxicity

Fungicides are less toxic than insecticides, acaricides, and herbicides. However, fungicides cause cardiovascular disease in exposed humans. For instance, difenoconazole produced free radicals in the human body and caused cell damage in cardiac tissues (Farrell and Roberts, 1994). Thiabendazole caused cardiac damage among patients treated for systemic toxocariasis (visceral larva migrans) (Rugiero et al., 1995). Occupational exposure to tricyclazole, isoprothiolane, iprobenfos, carbendazim, and chlorothalonil caused shortness of breath, leading to severe cardiac complications over time (Kesavachandran et al., 2009).

Cardiotoxicity with experimental animal models

Organochlorine insecticide residues

The cardiotoxicity of OC residues was tested using several experimental animal models. The most common experimental animal used is zebrafish, which is because zebrafish genes are highly similar to human genes (Postlethwait et al., 1998), and the cardiovascular development processes, cardiac function, and heart disease characteristics of zebrafish are similar to those in humans (Brown et al., 2016).

For instance, DDT and its analogs or metabolites caused cardiotoxicity in experimental animal models (La Merrill et al., 2016). Chlordane decreased the heart rate and blood flow in a dose-dependent manner in exposed zebrafish larvae (Xiong, 2017). Aldrin caused bradycardia, vasodepression, and miosis and potentiated the effect of vagal stimulation on the heart; increased the secretory and vasodilator effects of chorda tympani stimulation of the submaxillary salivary gland; and potentiated the effects of acetylcholine in acute experiments on cats, dogs, guinea pigs, rabbits, and frogs (Gowdey et al., 1952). Dieldrin caused similar cardiovascular complications in cats (Gowdey et al., 1952).

Endosulfan caused microscopic hemorrhages, single-cell necrosis, inflammatory reactions, and fibrotic changes in the myocardium in rabbits (Ozmen, 2013). Similar observations were reported in rats (Kalender et al., 2004; Wei et al., 2020).

Endrin caused large increases in total limb vascular resistance, hypertension followed by hypotension and death in dogs (Emerson Jr and Hinshaw, 1965; Reins et al., 1966).

γ-HCH caused hypertension and myocarditis in rabbits (Anand et al., 1990), caused severe cardiac arrest and tachyarrhythmias in rats (Anand et al., 1995), altered the electrocardiograms and sinus rhythms of the heart, and caused biochemical and histological changes in cardiac tissues in rats (Sauviat and Pages, 2002). Other OC residues caused abnormalities in electrocardiograms, along with moderate to severely edematous fetuses, in rats (Grabowski and Payne 1983).

Organophosphorus residues

OP residues may cause cardiotoxicity in experimental animal models. For instance, chlorpyrifos increased heart weight in chickens (El-Nahhal and Lubbad 2018), decreased heart weight in rabbits (El-Nahhal et al., 2020), and caused atherosclerosis in mice (Shih et al., 1998). Methamidophos attenuated the bradycardic component of chemoreceptors and the Bezold–Jarisch cardiovascular reflex in Wistar rats (Maretto et al., 2012) and caused cardiac arrhythmias along with myocardial damage in rats (Singer et al., 1987).

Chlorpyrifos and diazinon caused necrosis in cardiac tissues in rabbits (Zafiropoulos et al., 2014), whereas chlorpyrifos, parathion, and methyl parathion interacted with cardiac muscarinic receptors in neonatal and adult rats (Howard and Pope, 2002).

Dimethoate inhibited acetylcholinesterase activity and reduced heart rate in sand crabs (Lundebye et al., 1997), and it induced toxic cardiac failure in guinea pigs (Marosi et al., 1985).

Carbamate residues

Carbamate insecticides (Table 12) may cause cardiovascular complications in experimental animal models. For instance, methiocarb caused hypersalivation, tachycardia (heart rate, 240 beats per minute), tachypnea (respiratory rate, 36 breaths per minute), and pale mucous membranes with prolonged capillary refill time (2–3 seconds) in dogs (Corfield et al., 2008). Carbaryl induced bradycardia at 1–2 days postfertilization in zebrafish embryos (Lin et al., 2007) and caused defects in zebrafish heart formation (Schock et al., 2012). Carbofuran caused extensive hemorrhages and congestion located mainly within the respiratory and cardiovascular systems in dogs (Pivariu et al., 2020); decreased the activities of acetylcholinesterase and lactate dehydrogenase; elevated the levels of malondialdehyde, total thiols, and glutathione in rat heart tissues (Jaiswal et al., 2013); and created oxidative stress in erythrocytes in Wistar rats (Rai et al., 2009). Propoxur caused morphological changes in heart tissues in rabbits (Zafiropoulos et al., 2014).

Pyrethroid residues

Pyrethroid residues (Table 12) may cause cardiotoxicity and heart complications in experimental animal models. For instance, deltamethrin caused cardiovascular developmental toxicity in zebrafish larvae (Li et al., 2019a) and interfered with the normal expression of the cardiovascular development-related genes *vegfr2*, *shh*, *gata4*, and *nkx2.5*, causing functional defects in the cardiovascular system in zebrafish (Li et al. 2019b; Song et al., 2018); in addition, deltamethrin caused cardiotoxic actions in semi-isolated *Apis* bee hearts (Chrisovalantis and George, 2001).

Cypermethrin caused the impairment of myocardial tissue in male Wistar rats (Ghazouani et al., 2020) and frog hearts (Coşkun et al. 2004). Permethrin caused a heart rate of 200/min in cats (Haworth and Smart, 2012), induced oxidative damage to purine bases in the cardiac cells of rats (Vadhana et al., 2010), caused cardiac hypotrophy and increased calcium and Nrf2 gene expression levels in aged rats (Dhivya Vadhana et al., 2013), and induced biochemical changes in the heart (Vadhana et al., 2011).

Herbicide residues

The cardiotoxicity of herbicide residues in experimental animal models is summarized herein below (Table 12). Diuron increased heart weight in chickens (El-Nahhal and Lubbad 2018) and lowered heart weight in rabbits (El-Nahhal et al., 2020). Diclofop-methyl induced cardiac defects, such as pericardial edema, slow heart rate, and long sinus venosus (SV)–bulbus arteriosus (BA) distance in zebrafish larvae (Cao et al., 2020).

2,4-D caused cardiotoxicity in zebrafish embryos (Li et al., 2017) and affected the left ventricle in mice, manifesting as cardiomyocyte hypertrophy (Negrão et al., 2019).

Glyphosate caused developmental heart toxicity in zebrafish heart (Roy et al., 2016); cardiac cell damage in rats (Song et al. 2012); mitochondrial damage, apoptosis, and necrosis in rat heart (Kim et al. 2013); and developmental cardiotoxicity in rabbits (Kimmel et al., 2013). Glyphosate affected enzyme activity in pregnant rats and their fetuses (Daruich et al., 2001). Glufosinate caused cardiotoxicity in in vitro and in vivo tests in rats (Koyama et al., 1997), and glyphosate, glufosinate, and atrazine treatment inhibited normal twitch tensions in isolated rat hearts (Chan et al., 2007).

Acetochlor induced cardiovascular toxicity in zebrafish larvae (Liu et al., 2017a, b).

Atrazine induced cardiotoxicity in birds (Li et al., 2018) and dogs (Hauswirth and Wetzel, 1998) and altered electrocardiograms and caused cardiac lesions in dogs (Hazelette and Green, 1987).

Fungicide residues

Fungicide residues may cause cardiovascular diseases in experimental animal models. For instance (Table 12), tebuconazole induced morphological changes in the heart (pericardial edema, circulation abnormalities, and serious venous thrombosis) (Ben Othmène et al., 2020) and led to functional deficits (bradycardia and a significantly reduced cardiac output) in adult rats (Chaâbane et al., 2016).

Iprodione induced edema in the pericardium, decreased heart rate, and caused the failure of cardiac cyclization in zebrafish (Wei et al., 2021). Pyrimethanil at concentrations of 2, 4, and 6 mg/L decreased the hatching rate, heart rate, and survival rate of zebrafish embryos (Meng et al., 2020). Pyraclostrobin at a concentration of 36 μg/L or above had significant influences on the heart and brain of larvae, including pericardial edema, brain malformations, and histological and mitochondrial structural damage in the brain and heart (Li et al., 2019b). Famoxadone-cymoxanil induced morphological changes in the hearts of zebrafish exposed until 72 h postfertilization, including pericardial edema and cardiac linearization. In addition, famoxadone-cymoxanil reduced heart rate, and the cardiac output after exposure was positively correlated with the concentration of famoxadone-cymoxanil (Huang et al., 2020).

Cyproconazole caused a significant decrease in heart rates and malformations (i.e., pericardial edema, yolk sac edema, tail deformation, and spine deformation) in zebrafish embryos/larvae (Cao et al., 2019). Pyraclostrobin significantly influenced the larval heart and caused pericardial edema and mitochondrial structural damage in two organs of zebrafish larvae (Li et al., 2019b).

Difenoconazole increased total lipid and polyunsaturated fatty acid contents and decreased saturated fatty acid contents in fish hearts (Dong et al., 2016). Flutolanil induced slower heart rates and larger pericardial areas in treated zebrafish embryos (Teng et al., 2018). Imazalil concentrations of 10 mM and above negatively affected the survival and cardiac health of zebrafish embryos (*Danio rerio*) (Sişman and Türkez, 2010). Tebuconazole promoted reactive oxygen species production in cardiac cells and induced DNA damage and apoptosis in an H9c2 cardiomyoblast cell line derived from embryonic rat hearts (Othmène et al., 2020), led to histopathological alterations in adult rat hearts (Othmène et al., 2020) and elevated cardiac levels of malondialdehyde in adult rats (Chaâbane et al., 2016). Thiabendazole and its metabolites have been found in the hearts of laying hens treated with thiabendazole (Shang et al., 2011).

Proposed mechanisms of cardiotoxicity

Organochlorine residues

OC residues (Tables 1, 4, 9, 10, 11 and 12) include approximately 11 compounds with common features, such as very low water solubility (1–10,000 μg/L) and very high lipid solubility (log P of 4–7) (PPDB A to Z Index - University of Hertfordshire, 2007). DDT and its analogs had strong effects on the nervous system of insects (Welsh and Gordon 1947), the brains of rats (Dale et al., 1963), and the sensory nerves of insects as particularly active sites (Roeder and Weiant, 1946). Yamasaki and Narahashi (1957) indicated that DDT interfered with the electric potential of neuronal membranes, whereas O'Brien and Matsumura (1964) indicated that DDT or its analogs had a biological effect on the formation of a charge-transfer complex with a component of the axon of nerves. From a cardiotoxic point of view, DDT and its analogs may interfere with the sodium-potassium and chloride ion pumps in the nervous system supporting the heart, resulting in electrical imbalance in the sensory nerves or heart cell membrane. This electrical imbalance may affect the depolarization/repolarization process, resulting in the overstimulation of the heart-supporting nerves. This may lead to the hyperactivity of the heart, resulting in hypertension, and alterations in electrocardiograms in poisoned individuals. Positive associations between exposure to DDT and DDE and hypertension were reported (Donat-Vargas et al. 2018; La Merrill et al. 2013; La Merrill et al. 2018; Morgan et al., 1980; Reins et al., 1966; Vafeiadi et al. 2015). Alterations in electrocardiograms in endosulfan poisoning were observed (Moon and Chun, 2009; Sauviat and Pages, 2002).

Organophosphate and carbamate residues

Organophosphate and carbamate insecticide residues are strong acetylcholinesterase inhibitors. In acute organophosphate/carbamate poisoning cases, the inhibition of acetylcholinesterase in heart-supporting neurons may occur, leading to nerve convulsions, tremors, and paralysis and resulting in heart complications. In chronic organophosphate/carbamate poisoning cases, a marked elevation of acetylcholine may occur in synaptic gaps in the heart-supporting nervous system, leading to an overstimulation of both muscarinic and nicotinic acetylcholine receptors in accord with other case (Pereira et al., 2014).

Potential muscarinic and nicotinic effects in cardiotoxicities of organophosphate and carbamate insecticides

Overstimulation of muscarinic receptors due to inhibition of acetylcholinesterase and accumulation of acetylcholine in the synaptic gaps may lead to a muscarinic syndrome characterized by miosis in the eyes, profuse secretions, bradycardia, bronchoconstriction (tightness in the chest and wheezing), hypotension, vomiting, and increase in the gastrointestinal motility (abdominal tightness, cramps, and diarrhea). Additionally, overstimulation of nicotinic receptors may trigger tachycardia and skeletal muscle fasciculation and muscle weakness. Moreover, at an acute cardiotoxicity, the following symptoms may appear on the central nervous system: anxiety, restlessness, confusion, ataxia, tremors, seizures, and central cardiorespiratory paralysis. Similar nicotinic and muscarinic effects in cardiotoxicities of organophosphate and carbamate insecticides were previously reported (Hurst et al., 2012; Yokoyama et al., 1998).

This overstimulation may result in heart complications, hypotension, and myocardial infarction in organophosphate/carbamate poisoning cases. To date, heart complications in cases of organophosphate poisoning were observed with fenitrothion and malathion (Zago et al., 2020; Samsuddin et al., 2016; Aardema et al., 2008), parathion and phosphamidone (Ludomirsky et al. 1982), and chlorpyrifos (El-Nahhal and Lubbad 2018, El-Nahhal et al., 2020). A reduction in heart rate was observed with dimethoate (Lundebye et al., 1997) and diclofop-methyl (Cao et al., 2020) poisoning. Hypotension was observed in dimethoate poisoning (Davies et al., 2008; Eddleston et al., 2005). Myocardial infarction was observed in carbofuran, fenitrothion, and malathion poisoning (Zago et al., 2020; Wahab et al., 2016; Yen et al., 2015) and dimethoate poisoning (Marosi et al., 1985). In the case of carbamate poisoning, heart complications were noticed with methiocarb (Thierauf et al., 2009; Corfield et al., 2008), carbofuran (Gupta 1994; Pivariu et al., 2020; Jaiswal et al. 2013), and carbaryl (Schock et al., 2012) pesticides. Hypotension was observed in carbaryl and bendiocarb poisonings (Saadeh et al., 1997).

Pyrethroid residues

Pyrethroid insecticides are toxic to insects but relatively safe to mammals and birds, primarily due to poor gut uptake and rapid detoxification in endotherms (Coats 1990). The primary mode of pyrethroid toxicity is the interaction with voltagegated sodium channels in neuron cell membranes (Narahashi, 1962). This suggests that pyrethroid residues may generate toxic effects similar to the effects of DDT (Narahashi, 1969). Consequently, pyrethroids may interfere with the sodium-potassium and chloride pumps in the nervous system supporting the heart, resulting in electrical imbalance in sensory nerves or myocardial cell membranes. This may affect the heart cycle, resulting in hypertension and alterations in the electrocardiograms in pyrethroid poisoned cases. A positive association between exposure to permethrin and hypertension was previously reported (Donat-Vargas et al. 2018; La Merrill et al. 2013; La Merrill et al. 2018; Morgan et al., 1980; Reins et al., 1966; Vafeiadi et al. 2015). Alterations in electrocardiograms and heart defects were seen in deltamethrin poisoning (Li et al., 2019a, b).

Management of cardiotoxicity

Medical treatment

For decades and up to date, the standard medical treatments in poisoning cases (OP/CT poisoning) include a muscarinic antagonist, e.g., atropine; an oxime, mostly pralidoxime or obidoxime (Sidell 1974; Okumura et al. 1996; Newmark 2004; Eddleston et al. 2008; Pawar et al. 2006; El-Nahhal, 2017, 2018); and benzodiazepines as neuroprotectants and anticonvulsants (Marrs and Sellstom, 2007).

A recent review (Worek et al., 2020) emphasized the use of standard drug treatment, which includes atropine and an oxime as a reactivator of OP-inhibited acetylcholinesterase.

The current practice of carbamate poisoning management involves compounds such as atropine, which can have serious neurological side effects (Moulton and Fryer 2011).

To date, the use of atropine has been associated with an increased prevalence of myopia among populations using atropine (Schittkowski and Sturm, 2018), photophobia and slowing eye growth (Tran et al., 2018), and visual side effects (Chia et al., 2012). Furthermore, the use of pralidoxime potentiated the pressor effect of adrenaline and facilitated the restoration of spontaneous circulation after prolonged cardiac arrest. The potentiation of the pressor effect of adrenaline was not accompanied by the worsening of the adverse effects of adrenaline (Lee et al., 2020). The administration of obidoxime created the following side effects: pallor, nausea, pyrosis, headache, generalized weakness, sore throat, and paresthesia of the face muscles. Activities of blood cholinesterase, glutamic oxaloacetic transaminase, and glutamic pyruvic transaminase; hematocrit values; and heart rate were altered (Simon et al., 1976).

Table 13 Names, number of ameliorated cases (# Am case), % of total, reference average (Ref Aver), and relative average (Rel Aver)

Antioxidants	# Am case	% of total	Ref Aver	Rel Aver
Vitamin C	9	15	2.5	6
Curcumin	8	13.33	2.5	5.33
Vitamin E	4	6.67	2.5	2.67
Quercetin	4	6.67	2.5	2.67
Selenium	3	5.00	2.5	2.00
Chrysin	3	5.00	2.5	2.00
Garlic	3	5.00	2.5	2.00
Resveratrol	2	3.33	2.5	1.33
propolis	2	3.33	2.5	1.33
N-Acetyl cysteine	2	3.33	2.5	1.33
Melatonin	2	3.33	2.5	1.33
Lycopene	2	3.33	2.5	1.33
α-Lipoic acid	2	3.33	2.5	1.33
α-Tocopherol	2	3.33	2.5	1.33
Ajwain	2	3.33	2.5	1.33
Ginger	2	3.33	2.5	1.33
Thymoquinone	1	1.67	2.5	0.67
Selegiline	1	1.67	2.5	0.67
Quercetin	1	1.67	2.5	0.67
Atorvastatin	1	1.67	2.5	0.67
Ziziphora	1	1.67	2.5	0.67
Bee pollen	1	1.67	2.5	0.67
Zingiber	1	1.67	2.5	0.67
Sesame oil	1	1.67	2.5	0.67

Amelioration of cardiotoxicity

The use of standard medical treatment (section above) showed several complications among exposed populations. It is necessary to find suitable alternatives to standard medical drugs that act as reactivators of the inhibited acetylcholine esterase. This review identified 24 ameliorating agents that successfully managed the 60 cases of cardiotoxicity. The most effective agents were vitamin C, curcumin, vitamin E, quercetin, selenium, chrysin, and garlic extract. These agents are vitamins, antioxidants, and dietary materials. These materials are naturally found in the environment. Details of these materials are shown in Table 13.

The section below shows the use of ameliorating agents for the successful management of cases of cardiotoxicity.

Cardiotoxicity induced by OC residues

It has been shown that several agents ameliorated the toxicity of organochlorine insecticides. For instance, the daily consumption of sun-dried Pedro Ximénez and white grapes protected the liver of aged mice from the damages caused by *p,p′*-DDE exposure (Morales-Prieto et al., 2020). Propolis ameliorated the level of oxidative stress in ovaries, repaired histopathological damage, and improved ovarian weight in rats treated with methoxychlor (El-Sharkawy et al., 2014).

It has been shown that vitamin C ameliorated cardiotoxicity, spleen injury, lymphocyte depletion, necrosis, hemorrhage, and other oxidative stress parameters and reduced the accumulation of endosulfan in the organs of rabbits (Mor and Ozmen, 2010; Ozmen, 2016). Similar observations were previously made in mice (Khan and Sinha, 1996). Further, the antioxidant lycopene partially restored the levels of the antioxidant enzymes catalase, superoxide dismutase, glutathione peroxidase, and glutathione and the levels of the lipid peroxide malondialdehyde in cases of fish heart toxicity induced by endosulfan (Hussein et al., 2019).

Moreover, the administration of curcumin (Sharma and Singh 2010) and ginger juice (Sharma and Singh, 2012) ameliorated lindane-induced cardiotoxicity and reproductive toxicity in Wistar rats. Additionally, quercetin, a dietary flavonoid, significantly decreased the alterations in the histology and serum hepatic and renal markers induced by lindane toxicity in rats and improved the cellular antioxidant status (Padma et al., 2012).

The combination of vitamin E, vitamin C, α-lipoic acid, and the stilbene resveratrol ameliorated the histopathological and neurological damage caused by lindane toxicity in mice (Bano and Bhatt, 2010).

Green tea, *Camellia sinensis* (Prasad et al., 2016), a dietary ajwain extract (Anilakumar et al., 2009), and dehydrated amaranth leaves (Anilakumar et al., 2006) ameliorated the cardiotoxicity and tissue damage; decreased the elevated serum levels of creatinine; and significantly increased the lower levels of the renal antioxidative enzymes catalase, superoxide dismutase, and glutathione peroxidase caused by γ-HCH in male Wistar rats. Additionally, pre-feeding of these materials reversed the activities of superoxide dismutase and glutathione transferase in rat liver and heart tissues.

Amelioration of organophosphate toxicity

It has been shown that melatonin treatment was very effective in controlling the activities of mitochondrial complexes and oxidative stress biomarkers caused by non-OP insecticide (aluminum phosphide, (AlP)) in heart tissue (Asghari et al., 2017). The administration of chrysin (an antioxidant agent) against cardiotoxicity induced by AlP in isolated cardiomyocytes and mitochondria obtained from rat hearts decreased cytotoxicity and oxidative, lysosomal, and mitochondrial damage. To date, chrysin has been shown to ameliorate the cardiotoxicity induced by AlP in isolated cardiomyocytes and mitochondria. Chrysin could be a promising agent in the treatment of AlP poisoning in humans (Khezri et al., 2020). The administration of triiodothyronine at a dose of 3 μg/kg to treat phosphine-induced cardiotoxicity in a rat model significantly improved electrocardiogram and oxidative stress parameters and increased the mitochondrial function and ATP levels within cardiac cells. Furthermore, triiodothyronine reduced apoptosis by diminishing caspase activities and improving cell viability (Abdolghaffari et al., 2015).

The administration of N-acetyl cysteine to treat the cardiovascular toxicity induced by AlP poisoning prevented the sharp heart rate fluctuations in AlP-exposed patients in the case group (Taghaddosinejad et al., 2016).

The administration of selegiline in rats exposed to AlP reduced the oxidative stress (decreased reactive oxygen species and malondialdehyde) and increased glutathione in cardiac tissues, improved the altered electrocardiogram parameters, enhanced the slowed heart rate, and eliminated the inflammation and injuries caused by AlP in cardiac tissues. Compared to other clinical treatments, the use of selegiline may better improve the quality of the treatment process in AlP toxicity (Maleki et al., 2019).

Iron sucrose at a dose of 10 mg/kg ameliorated all electrocardiogram changes (QRS, QT, P-R, ST, BP, and HR) induced by aluminum phosphide in rats (Solgi et al., 2015).

Additionally, Mehrpour et al. (2019) suggested an intra-aortic balloon pump for the treatment of cardiogenic shock induced by aluminum phosphide poisoning.

A mixture of ginger and zinc chloride ameliorated histopathological changes in the liver (congestion, edema, and leucocytic infiltrations) and kidney (swelling and hydropic degeneration of renal tubules) induced by malathion toxicity in rats. Malathion is toxic to the liver and kidney and must be avoided, and malathion toxicity can be ameliorated by the administration of a ginger and zinc chloride mixture (Baiomy et al., 2015). Ziziphora extract administration, as an antioxidant, reduced the oxidative stress markers in the liver and lung tissues in rats exposed to chlorpyrifos (Yazdinezhad et al., 2017). Propolis administration significantly ameliorated the hyperglycemia, hypoinsulinemia, hyperlipidemia, and antioxidant defense system disorder in rats with diabetes induced by chlorpyrifos. These outcomes revealed that the immunomodulatory, antidiabetic, and antioxidant properties of propolis were beneficial for the treatment of cardiovascular dysfunction, especially in cases of diabetes and/or pesticides exposure (Ibrahim et al., 2019). Curcumin administration significantly reduced the levels of malondialdehyde in heart tissues in a group of *Cyprinus carpio* exposed to chlorpyrifos, whereas a group exposed to chlorpyrifos without curcumin administration showed elevated levels of malondialdehyde. Additionally, curcumin reversed the activities of superoxide dismutase, catalase, glutathione peroxidase, and glutathione-S-transferase. In conclusion, simultaneous administration of curcumin neutralized cardiotoxicity in fish (Yonar, 2018).

Hydrogen-rich water intake ameliorated the cardiotoxicity, hepatic dysfunction, and histopathological damage induced by chlorpyrifos in rats (Xun et al., 2020).

Crocin (an antioxidant) treatment at 25 and 50 mg/kg improved the histopathological damage, decreased malondialdehyde and lipid peroxidation levels, and increased glutathione-S-transferase content in cases of diazinon toxicity. This result indicates the protective effect of crocin against cardiotoxicity (Razavi et al., 2013). The administration of thymoquinone, a natural antioxidant, decreased the diazinon cardiotoxicity and improved cholinesterase activity in rats through the mechanism of free radical scavenging (Danaei et al., 2019).

Vitamin C administration in both prophylactic and therapeutic groups reduced the levels of superoxide dismutase, glutathione-S-transferase, and malondialdehyde; decreased the catalase activity in the liver, kidney and heart; and increased cholinesterase and lactate dehydrogenase activities, indicating the amelioration of cardiotoxicity induced by diazinon in male Wistar rats (Khazaie et al., 2019). Glycyrrhizin administration protected the liver, kidney, and heart in male rats from the toxic effects of diazinon, with significant decreases in serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and lactate dehydrogenase activities, and improved hepatic and renal function indices (Karimani et al., 2019).

Sesame oil and/or α-lipoic acid supplementation ameliorated the toxicity induced by diazinon in male Wistar albino rats. Sesame oil and/or α-lipoic acid supplementation improved hematology and serum parameters, enhanced endogenous antioxidant status, and reduced lipid peroxidation. Sesame oil and/or α-lipoic acid supplementation exerted synergistic hepatoprotective, nephroprotective, and cardioprotective effects (Abdel-Daim et al., 2016).

Abdelhamid et al. (2020) showed that treatment with *Chlorella vulgaris*- and β-glucan-supplemented diets in diazinon-exposed fish (Nile tilapia, *Oreochromis niloticus*) ameliorated hepatic damage and enhanced antioxidant activity and innate immune responses.

Vitamins E and C in combination significantly decreased the level of malondialdehyde and increased the level of cholinesterase activity in the test group compared to a control group in experiments of the effect of this combination against the cardiotoxicity induced by methidathion in rats (Yavuz et al., 2004).

Chan et al. (2011) demonstrated the protective ability of tropomyosin receptor kinase B (TrkB) against the cardiotoxicity induced by mevinphos in Sprague-Dawley rats.

The administration of ginger juice and garlic extract ameliorated the neurotoxicity and tissue damage induced by dichlorvos in Wistar rats (Ramadan et al., 2017). Additionally, garlic extract was effective in modulating most adverse effects induced by malathion in male Wistar rats; hence, garlic extract may be useful as a dietary adjunct for alleviating the toxicity in highly vulnerable people with insecticide intoxication (Ramadan et al., 2017).

Selenium and/or vitamin E alleviated the cardiotoxicity induced by dimethoate in female Wistar rats. The coadministration of selenium or vitamin E in the diet in dimethoate-treated rats decreased glutathione peroxidase, superoxide dismutase, and catalase activities; decreased plasma levels of cholesterol and triglycerides; and increased acetylcholinesterase and Na^+ K^+-ATPase activities (Amara et al., 2013).

N-Acetylcysteine supplementation ameliorated the immunotoxic, neurotoxic, and oxidative DNA damage induced by fenitrothion in exposed male rats (Alam et al., 2019).

Selenium (0.5 mg/kg b.w.) and vitamin C (100 mg/kg b.w.) in combination improved the activity of antioxidants, reduced the oxidative stress and lipid peroxidation, and maintained the levels of antioxidants at optimal levels against cardiotoxicity induced by fenitrothion in rats (Milošević et al., 2017). In mice, vitamin C at a dose of 20 and/or 40 mg/kg b.w./day effectively protected against reproductive toxicity and heart impairment induced by phosphamidon (Khan and Sinha, 1996).

Vitamin E and C administration provided heart protection against toxicity induced by methidathion in rats by reducing lipid peroxidation and ameliorating tissue damage in female rats (Güney et al., 2007).

Amelioration of carbamate toxicity

Curcumin administration in Wistar rats intoxicated with carbofuran restored the activities of acetylcholinesterase, creatinine kinase, lactate dehydrogenase, and gamma-glutamyl transferase in tissues and serum. Curcumin treatment significantly improved carbofuran-induced neurobehavioral difficulties, indicating its ameliorating activity (Purushothaman and Kuttan, 2017). A recent report (Sindhu et al., 2020) showed that native and formulated curcumin ameliorated the oxidative stress and mitochondrial dysfunction induced by carbofuran in the myocardial cells of rats.

Bee pollen administration alleviated the oxidative stress and damage caused by carbaryl in the heart and other organs of female Wistar albino rats (Eraslan et al., 2009). Garlic extract administration was effective in modulating the most adverse effects induced by carbaryl in male Wistar rats. Hence, garlic extract may be useful as a dietary adjunct for alleviating toxicity in human intoxication (Ramadan et al., 2017).

Pretreatment with vitamin E and taurine in Wistar rats exposed to methiocarb resulted in a significant decrease in lipid peroxidation and alleviated the effects on the antioxidant defense systems in both liver and kidney tissues, while the protective effects on histological changes were shown only in the kidney when compared with the liver (Ozden et al., 2013).

Pyrethroids and others

Quercetin at a dose of 140 mg/L ameliorated deltamethrin-induced cardiotoxicity in aquatic organisms. The amelioration process included oxidative stress reduction, increased AchE activity, the recovery of deltamethrin-induced nucleic acid damage, and alterations in blood parameters (Bhattacharjee et al., 2020). Additionally, in fish, quercetin supplementation ameliorated the oxidative stress biomarkers induced by deltamethrin (Bhattacharjee and Das 2017).

Ascorbic acid (AA/vitamin C) and α-tocopherol (E307/vitamin E) gavage at 100 mg/kg/day for 3 weeks restored the liver, kidney, brain, and heart tissue damage in mice experimentally intoxicated by pyrethroid. In addition, α-tocopherol was effective in ameliorating the damage in kidney and lung tissues compared with control treatment (Al-Omar et al., 2020). In rats, naringenin administration to treat the reproductive toxicity induced by permethrin improved the testicular weight and biochemical alterations (Mostafa et al., 2016).

Melatonin administration restored the activities of brain enzymes, reduced the malondialdehyde and xanthine oxidase levels, and modulated the heat shock proteins in fish toxicity induced by permethrin. Moreover, melatonin increased the expression of nuclear factor-kappa-binding and melatonin receptors. Exogenous melatonin improved the oxidative status in permethrin-stressed fish brains (Moniruzzaman et al., 2020).

α-Tocopherol administration to treat deltamethrin-induced immunotoxicity in male BALB/C mice resulted in the reduction of oxidative stress markers of cell death and the restoration of glutathione-SH. These data show the immunoprotective effects of α-tocopherol against the toxicity induced by deltamethrin (Kumar et al., 2019).

N-Acetyl cysteine (NAC) ameliorated the cardiotoxicity caused by α-cypermethrin in male rat lung tissues. The ameliorating effect included a reduction in the adverse effects of α-cypermethrin on lung tissues and an improvement of the histological architecture of lung tissues (Arafa et al., 2015).

Flaxseed oil coadministration partially counteracted the changes in biochemical parameters related to hepatic injury, glutathione-S-transferase, and lipid peroxidation induced by thiacloprid in rats (Hendawi et al., 2016).

Herbicides

Administration of quercetin to treat the oxidative stress induced by atrazine in male albino rats succeeded in reversing the negative toxic effects of atrazine on serum oxidative stress indicators, serum testosterone levels, and testicular IgA levels and improved testicular CYP17A1 mRNA expression (Abdel Aziz et al., 2018).

Atorvastatin administration to treat paraquat-induced cardiotoxicity in male Wistar rats lowered the lipid peroxidation rate, nitric oxide concentration, activity of myeloperoxidase, and CK/MB levels in the heart and reduced histopathological injuries (Malekinejad et al., 2019).

The administration of resveratrol, a natural antioxidant, and tetracycline, an antibiotic with antimicrobial and anti-inflammatory properties, offered significant protection from severe oxidative stress and inflammation and improved the general well-being of mice with toxic outcomes resulting from paraquat exposure (Satpute et al., 2017).

Aspirin administration as an adjuvant treatment for paraquat poisoning in rats alleviated lung injury and improved mitochondrial dynamics (Marashi et al., 2019.)

A thymoquinone dose of 10 mg/kg to mice intoxicated with paraquat inhibited the elevations in liver function parameter and lipid peroxidation levels, restored the activity of superoxide dismutase, and ameliorated the histopathological alterations (Zeinvand-Lorestani et al., 2018).

Montelukast administration to treat the toxicity induced by paraquat in rats significantly reduced the lipid peroxidation, protein carbonyl content and DNA fragmentation in lung tissues, and normalized glutathione and myeloperoxidase activities. Moreover, after paraquat exposure, compared with no treatment, the lung paraquat concentration was significantly reduced after montelukast treatment (Ahmed, 2009).

Administration of N-acetyl cysteine has been shown to protect against severe, unremitting oxidative stress in a glutathione-dependent manner (Unnithan et al., 2014), alleviated mitochondrial fragmentation and autophagy in primary murine neural progenitor cells (Xiong et al., 2019), rescued toxicity in rat polymorphonuclear leukocytes (Kumar et al., 2015), and provided hepatoprotective effect on liver function in paraquat-induced acute poisoning in male rats (Firouzian et al., 2019; Ahmad et al., 2013).

Moreover, administration of N-acetyl cysteine as single ameliorating agent reduced the destruction of human lung epithelial cells caused by paraquat (Yeh et al., 2006), whereas its combination with ascorbic acid cured the pulmonary fibrosis induced by paraquat (Spangenberg et al., 2012). Moreover, it has been shown that N-acetylcysteine is an effective and safe ameliorating agent for treatment of acute lung disease such as idiopathic pulmonary fibrosis (Feng et al., 2019).

Fungicides

Vitamin C administration at two doses (20 and 40 mg/kg b.w./day) to treat the reproductive toxicity in mice induced by mancozeb successfully ameliorated biochemical and histological damage, but not to the levels of control mice, which were not exposed to mancozeb (Khan and Sinha, 1996).

The administration of *Zingiber officinale* extract on carbendazim-induced reproductive toxicity in rats significantly restored histological, serological, and hormonal damage; prevented the adverse effects on testis weight; and restored the quantity and quality of sperm in treated rats to near-control levels (Salihu et al., 2017).

Selenium administration ameliorated the cardiotoxicity induced by penconazole in adult rats (ChaâbaneDıaz et al., 2009 et al., 2016).

Mechanism of amelioration

Here, we suggest the following mechanisms of the amelioration of cardiotoxicity.

Cardiotoxicity induced by any pesticide may occur according to Eq. (1), where *P* and *E* represent free pesticide and free enzyme, respectively. At a certain level of pesticide exposure, free enzyme € becomes bound to free pesticide (P), forming a pesticide–enzyme complex that later results in cardiotoxic symptoms, as demonstrated above.

$$P+E\rightarrow[PE] \tag{1}$$

Using an ameliorating agent (A) in poisoning cases as in Eq. (2) may lead to the release of the bound enzyme, resulting in an elevation of free enzyme, as shown in the case of acetylcholine esterase.

$$[PE]+A\rightarrow[PA]+E \tag{2}$$

On the other hand, an ameliorating agent may protect from poisoning as shown in Eq. (3). In this case, the ameliorating agent may directly react with the pesticide molecules, forming a complex (PA) that does not allow the pesticide molecules to react with active sites in the cardiovascular system. In this case, no toxic symptoms may appear.

$$P+E+A\rightarrow[PA]+E \tag{3}$$

These mechanisms are quite similar to pesticide poisoning recovery using atropine, 2PAM, and/or obidoxime. More elaborations are given above.

Conclusions

This review highlights the pesticides that caused cardiotoxicity either in occupational exposure or in experimental animal models. The review shows 30 insecticides from four chemical groups (11 OC, 10 OP, 4 CT, 3 PY, and 2 N), 13 herbicides, and 17 fungicides from different chemical groups and toxicity classes causing cardiotoxicity among occupationally exposed workers and experimental animal models. There were 30, 14, 9, 5, and 2 cardiotoxic pesticides from toxicity classes II, III, IV, Ib, and Ia, respectively. The interesting outcome of this review is that toxicity class II contained the highest number of pesticides causing cardiotoxicity among all classes. The review identifies 24 ameliorating agents that successfully managed 60 cases. The most effective agents were vitamin C, curcumin, vitamin E, quercetin, selenium, chrysin, and garlic extract.

The limitation of this study is that cardiotoxicity and ameliorating agents are not reported for each pesticide.

The strength of this review is that it provides concrete information on the cardiotoxic mode of action and ameliorating agents for pesticides. In conclusion, the information in this review fills the research gap regarding cardiotoxic pesticides and their ameliorating agents.

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Author contribution Yasser El-Nahhal designed the study, wrote the manuscript, and classified the topics and statistical analysis and evaluation of data flow.

Ibrahim El-Nahhal conducted data collection, data analysis, chart drawing, and fruitful discussion, and editing the manuscript.

The authors read and approved the final manuscript.

Data availability The data of this study are shown in the body of the manuscript. Inquiries may be addressed to the corresponding author.

Declarations

Ethical approval The works in this study conform to code of ethics for scientific research and publishing.

Consent to participate Not applicable

Consent for publication The authors agree to publish this final manuscript. Consents from third party are not required.

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