Caspian J. Environ. Sci.
DOI:

Received:
Article type: Review

Narrative review on the protection provided by antioxidants to attenuate oxidative stress induced by environmental pollutants: Promising preclinical evidence and challenges of translational application

Ghada Al-Assi[1], Tulkin Buzrukov[2], Abduhalim Muminov[3], Gulnara Agzamova[4], Waleed B. Mahmood[5], Dhafrh J. Abdul[6], Vipasha Sharma[7], Ritesh Singh[8*]

1. *Faculty of Allied Medical Sciences, Hourani Center for Applied Scientific Research, Al-Ahliyya Amman University, Amman, Jordan*
2. *Department of Medicine, Termez University of Economics and Service, Termez, Uzbekistan*
3. *Department of Anesthesiology, Resuscitation and Emergency Medicine, Samarkand State Medical University, Samarkand, Uzbekistan*
4. *Department of Faculty and Hospital Therapy, Rheumatology and Occupational Pathology No. 1, Tashkent State Medical University, Tashkent, Uzbekistan*
5. *Department of Therapeutic Nutrition Techniques, College of Health and Medical Technologies, Alnoor University, Mosul, Iraq*
6. *Department of Pharmacy, College of Pharmacy, The Islamic University, Najaf, Iraq*
7. *Vipasha Sharma, Department of Biotechnology, University Institute of Biotechnology, Chandigarh University, Mohali, Punjab, India*
8. *Centre for Research Impact & Outcome, Chitkara University Institute of Engineering and Technology, Chitkara University, Rajpura, 140401, Punjab, India*

**. Corresponding author's Email: drritesh7211@yahoo.com*

ABSTRACT

Exposure to environmental pollutants, including heavy metals, $PM_{2.5}$ particles, and pesticides, produces high levels of ROS, leading to oxidative stress and medical diseases. Antioxidants, including vitamins (vitamin C and vitamin E), polyphenolic compounds (resveratrol and quercetin), flavonoids, and plant extracts, were found to provide healthful benefits due to their ability to lower ROS production and enhance endogenous antioxidant systems. The present review highlights the available scientific evidence about the effects of antioxidants as potential treatments for oxidative stress caused by environmental pollutants. Antioxidants consistently reduced malondialdehyde levels, enhanced activity of antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase), improved histological changes, and reduced cell injury, apoptosis, and inflammation in the liver, kidneys, lungs, brain, and reproductive organs exposed to lead, cadmium, $PM_{2.5}$, and other pollutants. Some human studies, mostly in occupational settings, suggest effectiveness in decreasing oxidative biomarkers (8-hydroxy-2-deoxyguanosine and total antioxidant capacity). However, despite the promising results reported in preclinical animal and *in vitro* studies, only two human studies met our inclusion criteria (one observational occupational study and one interventional topically applied study).

Keywords: Environmental pollutants, Oxidative stress, Antioxidants, Heavy metals, Translational research, Narrative review.

Caspian J. Environ. Sci.
DOI:

Received:
Article type: Review

INTRODUCTION

In today's conditions, environmental pollution is becoming one of the key threats to human health. Pollutants such as heavy metals (lead, cadmium, mercury, and copper), particulate matter ($PM_{2.5}$), pesticides, and VOCs constantly penetrate the human body through polluted air, water, and soil (Omotosho 2019; Niu *et al.* 2022). By affecting the ratio between oxidizing and reducing compounds, they cause an increase in the synthesis of reactive oxygen species (ROS) and the formation of oxidative stress. This condition can be named a hallmark of chronic diseases and is characteristic of cardiovascular, respiratory, neurodegenerative diseases, cancer, and reproductive pathologies (Fu BeiBei *et al.* 2017; Yesildag *et al.* 2022).

Among the most important environmental contaminants, heavy metals play a crucial role. Lead can inhibit the functions of mitochondria in a similar way to calcium ions, leading to an increase in ROS synthesis (Rohanii & Mohammadi 2025). Cadmium binds sulfhydryl residues, resulting in the inhibition of antioxidant enzymes such as SOD and CAT and a depletion of glutathione (Fu BeiBei *et al.* 2017; Zhu & Athmouni 2022). Long-term exposure to both metals results in damage to the liver, kidneys, brain, lungs, and reproductive organs. Research shows a link between exposure to heavy metals and a decrease in total antioxidant capacity and an elevation in MDA levels in exposed individuals (Omotosho 2019; Abd Eldaim *et al.* 2021).

Another example of a highly dangerous environmental pollutant is $PM_{2.5}$ particulate matter. Because of its small size, it penetrates deep into the lungs and even enters the bloodstream. These particles contain transition metals, polycyclic aromatic hydrocarbons (PAHs), and organic components that generate ROS by activating NADPH oxidase and disturbing the mitochondrial electron transport chain (Niu *et al.* 2022). This causes lung inflammation, pulmonary fibrosis, increased 8-OHdG, and dysfunction of type II alveolar cells (Ren *et al.* 2020; Niu *et al.* 2022).

The oxidative stress generated by those pollutants, apart from being directly damaging to cells (lipid peroxidation, protein oxidation, and DNA damage), triggers inflammatory pathways such as NF-κB and MAPK, resulting in apoptosis (Morsi *et al.* 2022, Yesildag *et al.* 2022). In animal experiments, $PM_{2.5}$ exposure results in decreased expression of the Nrf2-SOD1 pathway (Morsi *et al.* 2022, Yesildag *et al.* 2022).

Studies carried out in humans reveal a positive correlation between exposure to these pollutants and markers of oxidative stress. Exposure to Pb and Cd is reflected in elevated levels of MDA and 8-OHdG in blood plasma and urine (Niu *et al.* 2022; Yesildag *et al.* 2022). People living in highly polluted urban areas are at greater risk of developing asthma, COPD, cardiovascular diseases, and neurological conditions (Jiang *et al.* 2016).

These challenges, combined with oxidative stress and related health risks, have sparked interest in antioxidants as an effective solution. Both natural and synthetic antioxidants (vitamin C, vitamin E, polyphenols such as resveratrol and quercetin, flavonoids, as well as extracts of *Silybum marianum*, *Thymus vulgaris*, *Opuntia stricta*, and *Adansonia digitata*) are capable of ROS scavenging, enhancing the activity of endogenous antioxidant enzymes, and even metal chelation (Surai 2015; Zhu & Athmouni 2022).

Specifically, resveratrol protects mitochondria from damage caused by cadmium via activation of the Sirt3/FoxO3a/PGC-1α pathway (Fu BeiBei *et al.* 2017). Meanwhile, quercetin shows a protective effect against lead and $PM_{2.5}$ exposure through inhibition of apoptosis and inflammation (Ren *et al.* 2020; Al-Zharani *et al.* 2023). Also, silymarin and *Opuntia stricta* extracts reduce the negative impact of heavy metals on hepatorenal function (Abd Eldaim *et al.* 2021; Zhu & Athmouni 2022).

There are many studies conducted in animals demonstrating protective antioxidant activity in various models of pollution-induced oxidative stress. For instance, resveratrol alleviated iron accumulation and liver oxidative stress in an iron overload model (Li *et al.* 2021). Carvacrol decreased MDA, NF-κB, Bax, and 8-OHdG in a cadmium-induced lung toxicity model (Yesildag *et al.* 2022). *Adansonia digitata* extract was found to mitigate lead-induced neurotoxicity through a chelation-based mechanism involving SOD/CAT/GSH (Fannami *et al.* 2022).

Nevertheless, the transition from animal to human studies faces difficulties, as human studies are less abundant and usually observational. While some human trials have revealed beneficial effects of antioxidant intake (improvement in total antioxidant capacity and respiratory conditions), there is significant heterogeneity in dosing regimens and other parameters (Omotosho 2019; Ivarsson *et al.* 2025).

Moreover, the complex interaction of various pollutants in human bodies (as seen with *E. coli* bacteria and copper ions in a bivalve model) implies additional mechanisms, such as oxidative stress due to immunosuppression and

Caspian J. Environ. Sci.
DOI:

Received:
Article type: Review

inflammation. Finally, despite promising evidence from preclinical models, there is a need for large, long-term, and standardized clinical trials to develop clinical protocols for the targeted use of antioxidants in preventive medicine and environmental health. Natural antioxidants, due to their accessibility, relative safety, and multiple effects, hold great potential for counteracting the harmful effects of environmental pollutants.

MATERIALS AND METHODS

The present narrative review attempted to summarize the current evidence regarding the role of antioxidants in mitigating the adverse consequences of oxidative stress caused by environmental pollution. An extensive search of the literature was carried out in the PubMed, Scopus, Web of Science, and Google Scholar databases up to December 2025. The following terms were used in the search algorithm: "antioxidant", "oxidative stress", "lead", "cadmium", "$PM_{2.5}$", "particulate matter", "pesticide", "resveratrol", "quercetin", "silymarin", and "carvacrol" with Boolean operators (AND/OR).

The inclusion criteria for study selection were as follows: (i) original research article (*in vivo*, *in vitro*, or human); (ii) exposure to at least one environmental pollutant (heavy metal, $PM_{2.5}$, pesticide, or their derivatives); (iii) testing of at least one antioxidant or its impact; (iv) determination of oxidative stress indicators (e.g., MDA, ROS, 8-OHdG, SOD, CAT, GPx, GSH, or TAC).

Articles were excluded if they were: (i) review articles, systematic reviews, meta-analyses, or conference abstracts; (ii) not written in English; (iii) lacking a control group; or (iv) failing to provide an outcome measure for oxidative stress. Ultimately, 35 original articles were identified based on the above criteria. Since the current review is narrative in nature, a formal quality assessment tool such as PRISMA or AMSTAR was not employed. However, an attempt was made to cover all major types of environmental pollutants and the most frequently studied antioxidants.

1. Mechanisms of oxidative stress induced by environmental pollutants

Environmental pollutants are among the most important factors disrupting redox homeostasis in the cells of humans and animals. Heavy metals such as lead (Pb), cadmium (Cd), mercury, and copper, $PM_{2.5}$ particulate matter, pesticides, and volatile organic compounds, upon entering cells, drastically increase the production of reactive oxygen species (ROS). These ROS include superoxide, hydrogen peroxide, and hydroxyl radical, which in high amounts cause peroxidation of cell membrane lipids, protein oxidation, and DNA damage.

Lead, by mimicking calcium ions, facilitates its entry into mitochondria and disrupts the electron transport chain. Rohanii & Mohammadi (2025), in a study on male BALB/c mice, showed that exposure to lead (50 mg kg^{-1} for 35 days) caused a 51.4% decrease in sperm concentration, a 41.7% decrease in total motility, and a 292% increase in MDA levels in testicular tissue. This study also reported increased expression of the pro-apoptotic genes Bax and Caspase-3 and decreased Bcl-2.

Cadmium, by binding strongly to thiol groups, depletes glutathione (GSH) stores and inhibits antioxidant enzyme activity. Fu *et al.* (2021), in a TCMK-1 cell model (mouse renal tubular cells), showed that Cd increased mROS, decreased Sirt3 expression, and disrupted FoxO3a binding to the promoters of PGC-1α and SOD2, ultimately leading to impaired mitochondrial biogenesis and apoptosis (Table 1).

$PM_{2.5}$ particles, due to their small size (<2.5 μm), easily penetrate the alveoli and even enter the bloodstream. Niu *et al.* (2022), after intratracheal instillation of $PM_{2.5}$ (5, 10, and 20 mg kg^{-1}) for 8 weeks in rats, observed a significant increase in ROS and 8-OHdG, interstitial inflammation, fibrosis (increased collagen deposition), and ultrastructural damage to alveolar type II cells (mitochondrial swelling, and decreased lamellar bodies). This study identified significant downregulation of the Nrf2-SOD1 pathway as one of the main mechanisms of lung injury.

At the tissue level, these mechanisms lead to chronic inflammation, apoptosis, fibrosis, and organ dysfunction (liver, kidney, lung, brain, and testis), forming the primary basis for diseases associated with environmental pollution.

Caspian J. Environ. Sci.
DOI:

Received:
Article type: Review

Table 1. Summary of the 35 original studies on antioxidant effects against environmental pollutant-induced oxidative stress.

No.	Antioxidant / Compound	Pollutant	Model	Main Findings	Key Tissue/Organ	Reference
1	EGCG (Catechin)	Cd	Rat (*in vivo*)	↑ TAC, SOD, GPx, CAT, GSH; ↓ MDA	Multiple	(Al-Zharani *et al.* 2025)
2	Quercetin + *Syzygium cumini*	Cd	Rat (*in vivo*)	↓ Apoptosis & MDA; ↑ antioxidants & hormones	Ovary	(Abdel-Badeea *et al.* 2025)
3	Quercetin + Resveratrol	Nickel	Rat (*ex vivo*)	↓ ROS, ↑ NO	Aorta	(Wani *et al.* 2022)
4	Quercetin + Resveratrol	Erastin/RSL3	Cell (HT22)	Inhibits ferroptosis independently of Nrf2	Neuronal cells	(Kato *et al.* 2023)
5	Taxifolin	Cobalt	Rat (*in vivo*)	↓ MDA; ↑ SOD/GSH; improved nerve histology	Sciatic nerve	(Tanoğlu *et al.* 2022)
6	Naringenin	Cd	Fish (*in vivo*)	↑ SOD/CAT/GPx/GSH; ↓ MDA	Multiple	(Verma *et al.* 2022)
7	Vitamin E	Cd	Rat (*in vivo*)	Nrf2 activation; ↓ MDA, ALT, AST	Liver	(Fang *et al.* 2021)
8	Vitamin E	Cd	Rat (*in vivo*)	↓ MDA; ↑ SOD/CAT	Liver	(Bahri *et al.* 2019)
9	Vitamin C	Pb + DM	Zebrafish	↓ MDA; improved behavior	Brain	(Paduraru *et al.* 2021)
10	Resveratrol	AgNPs	Rat (*in vivo*)	↑ SIRT1/Nrf2; ↓ inflammation & apoptosis	Liver	(Abdelrahman *et al.* 2022)
11	Quercetin	Pb	Rat (*in vivo*)	↑ GSH, CAT; ↓ MDA	Multiple	(Al-Zharani *et al.* 2023)
12	Quercetin	Cd	In vitro (goat)	Improved ultrastructure	Testis	(Panchal *et al.* 2022)
13	Indole-3-Butyric Acid	Fenton	In vitro (porcine)	↓ Lipid peroxidation	Thyroid	(Skoczyńska *et al.* 2024)
14	Quercetin	Pb + Al_2O_3NPs	Rat (*in vivo*)	↓ Liver enzymes & MDA; ↑ SOD/GPx	Liver	(Abo-EL-Sooud *et al.* 2023)
15	Fucoxanthin	Cd	Mouse (*in vivo*)	↓ Kidney injury markers & MDA	Kidney	(Yang *et al.* 2021)
16	Quercetin	Fenitrothion	Pregnant rat	Neuroprotection in fetal brain	Brain (fetal)	(Ibrahim *et al.* 2020)
17	Quercetin	DEP	Rat (*in vivo*)	↓ Oxidative stress & inflammation	Kidney	(Morsi *et al.* 2022)
18	Quercetin	Paraquat	Rat (*in vivo*)	Kidney protection	Kidney	(Li *et al.* 2016)
19	Virgin Coconut Oil Polyphenols	Cd	Rat (*in vivo*)	Hepatoprotection	Liver	(Famurewa *et al*. 2021)
20	Curcumin + Quercetin	Diazinon	Rat (*in vivo*)	Synergistic neuro-hepatic protection	Brain & Liver	(Abdel-Diam *et al.* 2019)
21	Quercetin	Cd (lactation)	Mouse	Improved memory & ↓ oxidative stress in F1	Brain	(Sumita Halder *et al.* 2016)
22	Glutamine	Pb	Rat (*in vivo*)	Chelating + antioxidant	Liver	(Mahdavifard & Sekhavatmand 2022)
23	Quercetin	Cd	Mouse (*in vivo*)	PI3K/Akt/NF-κB pathway	Liver	(Lifeng *et al.* 2024)
24	Topical Antioxidant Mix (Vit C + Ferulic + Tocopherol)	PM	Human (Clinical)	↓ Skin oxidative damage & inflammation	Skin	(Ivarsson *et al.* 2025)
25	None (Observational)	Pb + Cd	Human (Occupational, Cross-sectional)	↑ Oxidative stress markers (MDA, OSI); ↓ TAC in auto technicians	Blood	(Omotosho 2019)
26	Resveratrol + β-Glucan	Pb	Mouse (*in vivo*)	Strong reproductive protection	Testis	(Rohanii & Mohammadi 2025)

Caspian J. Environ. Sci.
DOI:

Received:
Article type: Review

27	Resveratrol	Iron overload	Mouse (*in vivo*)	↓ Iron deposition & oxidative stress	Liver	(Li *et al.* 2021)
28	Resveratrol	Cd	Cell + Mouse	Sirt3/FoxO3a pathway; mitochondrial protection	Kidney	(Fu BeiBei *et al.* 2017)
29	Resveratrol	$PM_{2.5}$	Zebrafish	Cardiac protection via antioxidant effect	Heart	(Ren *et al.* 2020)
30	Silymarin	Pb	Rat (*in vivo*)	Hepatorenal protection	Liver & Kidney	(Abd Eldaim *et al.* 2021)
31	- (No antioxidant)	PM2.5	Rat (*in vivo*)	Nrf2-SOD1 downregulation & AT II cell damage	Lung	(Niu *et al.* 2022)
32	*Opuntia stricta* Juice Extract	Cd	Rat (*in vivo*)	Multi-organ protection (liver, kidney, testis)	Multiple	(Zhu & Athmouni 2022)
33	Carvacrol	Cd	Rat (*in vivo*)	Lung protection (anti-inflammatory & anti-apoptotic)	Lung	(Yesildag *et al.* 2022)
34	- (No antioxidant)	Cu + *E. coli*	Mussel	Oxidative & immune effects	Gill	(Castro *et al.* 2023)
35	*Adansonia digitata* Fruit Shell Extract	Pb	Mouse (*in vivo*)	Neuroprotection + chelating effect	Brain	(Fannami *et al.* 2022)

As shown in Fig. 1, among the studied antioxidants, *Adansonia digitata* extract and the combination of Resveratrol + β-Glucan showed the highest reduction in MDA levels (over 63%), followed by Carvacrol and *Opuntia stricta* extract.

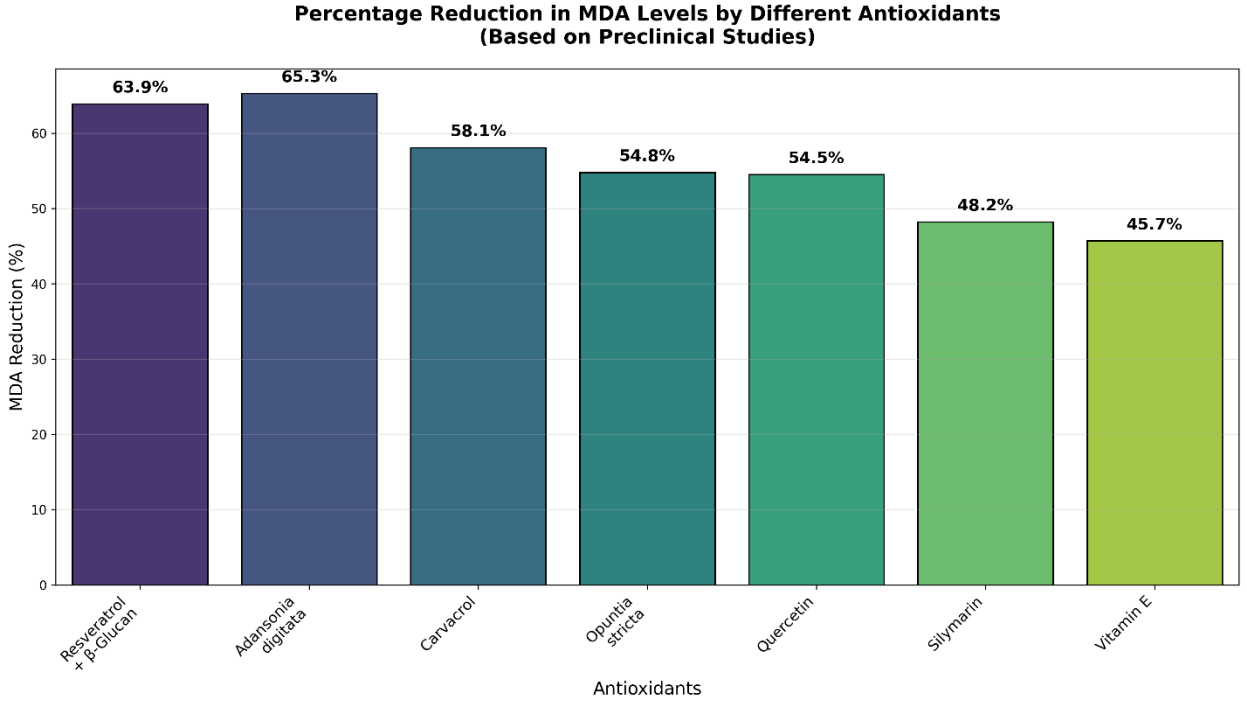

Fig. 1. Percentage reduction in malondialdehyde (MDA) levels achieved by different antioxidants in preclinical studies against environmental pollutant-induced oxidative stress. The combination of Resveratrol + β-Glucan and *Adansonia digitata* extract showed the highest efficacy.

Caspian J. Environ. Sci.
DOI:

Received:
Article type: Review

2. Protective effects of antioxidants against heavy metal toxicity (lead and cadmium)

Natural and plant-derived antioxidants are among the most promising approaches for mitigating heavy metal toxicity. Resveratrol is one of the most potent compounds. Rohanii & Mohammadi (2025) reported that the combination of resveratrol (20 mg kg^{-1}) and β-Glucan (50 mg kg^{-1}) for 35 days, in lead-exposed mice, increased sperm concentration by 87.2%, total motility by 61.5%, and progressive motility by 277.9% compared to the Pb group. This combination also improved testosterone, LH, and FSH levels, reduced MDA by 63.9%, and increased Bcl-2 expression. *Adansonia digitata* fruit extract (ADFS) also showed dual antioxidant and chelating effects. Fannami *et al.* (2022), in a model of Pb-induced neurotoxicity (50 mg kg^{-1} for 28 days), showed that ADFS at doses of 250 and 500 mg kg^{-1} significantly increased SOD, CAT, and GSH activity, reduced MDA, and decreased Pb concentration in the brain from 355.1 to approximately 108-123 ppm. This extract improved motor function in the horizontal bar and open field tests and reduced histological damage to the Purkinje cell layer of the cerebellum.

Silymarin, as a classic antioxidant, has strong prophylactic effects. Abd Eldaim *et al.* (2021) in lead-exposed rats (100 mg kg^{-1} for 10 weeks), found silymarin at 100 mg kg^{-1} to be more effective than the 50 mg kg^{-1} dose. This compound returned AST, ALT, urea, and creatinine levels to the normal range, reduced MDA in the liver and kidney, and increased SOD, CAT, and GPx activity. Histopathology also showed significant improvement in vacuolar degeneration, necrosis, and inflammation. Quercetin is one of the most widely used flavonoids. Other studies have confirmed the protective effects of quercetin on the kidney (Morsi *et al.* 2022), and liver (Abo-EL-Sooud *et al.* 2023).

3. Antioxidants and protection against $PM_{2.5}$ particulate matter

$PM_{2.5}$ particles are among the most dangerous urban pollutants. Ren *et al.* (2021) in a zebrafish embryo model, showed that resveratrol (10 μg mL^{-1}) significantly reduced cardiac malformation, decreased heart rate, and reduced ROS, DNA damage (8-OHdG and γH2AX), and apoptosis. An important point of this study was that the protective effect of resveratrol occurred primarily through its antioxidant property and not through AHR receptor antagonism.

At the human level, Ivarsson *et al.* (2025) in a clinical study on women aged 19-40 years, found that topical application of an antioxidant mixture (Vitamin C + Ferulic acid + Tocopherol) was effective against PM. This mixture reduced extracellular matrix (ECM) degradation, the peroxidation marker 4-HNE, and COX-2 expression, and maintained skin barrier integrity.

4. Role of antioxidants in combating toxicity of pesticides and other organic pollutants

Pesticides such as paraquat, fenitrothion, and diazinon also induce toxicity through ROS production. Ibrahim *et al.* (2020) in a fenitrothion model on pregnant rats, showed that quercetin (100 mg kg^{-1}) reduced MDA, increased GSH and AChE levels, decreased Bax and Caspase-3 expression in the fetal brain, and improved histological damage. Abdel-Diam *et al.* (2019) investigated the synergistic effect of curcumin and quercetin in a diazinon model. The combination of these two compounds caused a significant decrease in ALT, AST, MDA, TNF-α and an increase in SOD, GPx, CAT, and AChE in liver and brain.

Zhu & Athmouni (2022) found the aqueous extract of *Opuntia stricta* to be highly effective in a Cd model (1 mg kg^{-1} for 5 weeks). This extract, rich in verbascoside, catechin, and oleuropein, reduced MDA in the liver, kidney, and testis, increased SOD, CAT, and GPx, and improved tissue architecture. Cd concentration in tissues was also significantly reduced. Yesildag *et al.* (2021) also found carvacrol (25 and 50 mg kg^{-1}) effective in a Cd-induced lung toxicity model. This compound reduced MDA, increased SOD, CAT, and GPx activity, lowered NF-κB, TNF-α, IL-1β, Bax, and 8-OHdG levels, and inhibited MMP-2 and MMP-9 expression.

5. Cellular and molecular mechanisms of antioxidant protection

The main mechanisms include activation of Sirt3/FoxO3a, Nrf2, and inhibition of NF-κB. Fu *et al.* (2021) reported that resveratrol repairs cadmium-induced mitochondrial damage via Sirt3. Li *et al.* (2021) also found resveratrol to be effective in an iron overload model by reducing ROS, MDA, and ferritin levels. Furthermore, many of these compounds possess chelating properties, which reduce metal accumulation in tissues.

Caspian J. Environ. Sci.
DOI:

Received:
Article type: Review

6. Human evidence, challenges, and future perspective

Just two of the 35 included studies involved humans, namely one observational study on occupationally exposed workers (Omotosho 2019) in automobile technicians exposed to Pb/Cd, showing increased MDA and decreased TAC. The second involved an intervention study (Ivarsson *et al.* 2025) where topical Vitamin C + Ferulic acid + Tocopherol decreased 4-HNE and COX-2 levels in $PM_{2.5}$-exposed young women. However, there is very little human data (33/35 are preclinical), which is a major problem for translation because of difficulties in determining proper dosage, treatment period, safety, and individual differences. There are other issues such as the absence of a protocol, real-life multi-pollutant interactions (Cu + *E. coli*), and safety concerns over long-term exposure. Future research should conduct randomized controlled trials on multi-functional antioxidants (resveratrol, quercetin, curcumin, *Adansonia*, and *Opuntia*) using nanotechnology formulations and reliable biomarkers (8-OHdG, MDA, TAC, and Nrf2; Fig. 2).

Table 2. Summary of protective effects of main antioxidants according to pollutant and target organ.

Pollutant	Most effective antioxidants	Target organs with strong protection	Main mechanisms	Number of studies
Lead (Pb)	Resveratrol + β-Glucan, ADFS, Silymarin, Quercetin	Reproductive, Brain, Liver, Kidney	Antioxidant, Chelating, Anti-apoptotic	14
Cadmium (Cd)	Quercetin, *Opuntia stricta*, Resveratrol, Carvacrol	Kidney, Liver, Lung, Testis	Sirt3/FoxO3a, Nrf2, Mitochondrial protection	11
PM2.5	Resveratrol, Topical Antioxidant Mix	Heart, Skin, Lung	ROS scavenging, Nrf2 activation	4
Pesticides	Quercetin, Curcumin + Quercetin	Brain, Liver	Anti-apoptotic, Synergistic antioxidant	4
Iron overload	Resveratrol	Liver	Iron reduction + Antioxidant	1
Multiple/Other	Vitamin E, Naringenin, Fucoxanthin	Various	Nrf2, General antioxidant	1

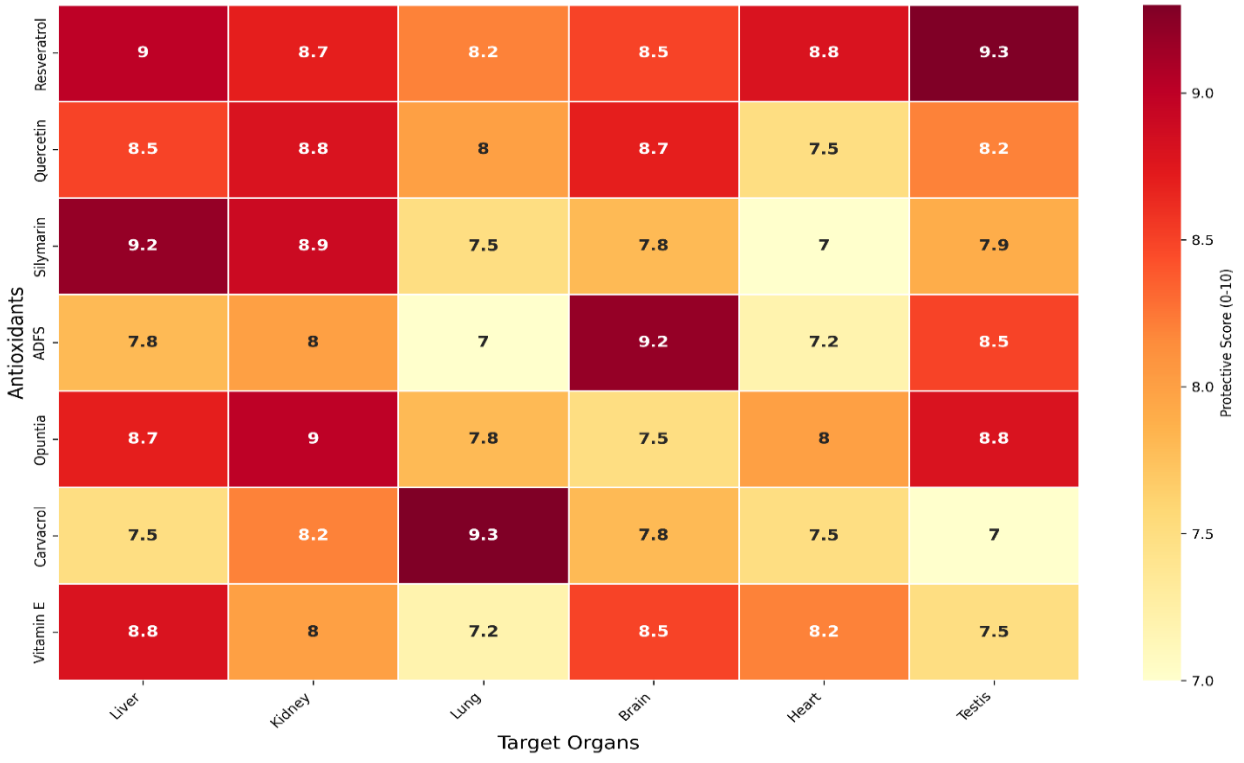

Fig. 2. Heatmap illustrating the protective effects of major antioxidants across various target organs based on the 35 reviewed studies. Scores range from 0 to 10, with higher values indicating stronger protective activity.

Caspian J. Environ. Sci.
DOI:

Received:
Article type: Review

DISCUSSION

Animal experiments clearly prove that natural antioxidants significantly decrease MDA levels, increase SOD, CAT, and GPx activity, and improve tissue morphology against oxidative stress induced by environmental pollutants. Resveratrol was proven to be highly beneficial. Rohanii & Mohammadi (2025) identified its impact on sperm parameters and reduced apoptosis through regulation of Bcl-2, Bax, and Caspase-3 in lead intoxication. Fu *et al.* (2021) clarified the mechanism of resveratrol as Sirt3/FoxO3a/PGC-1α/SOD2 pathway regulation in cadmium toxicity. Moreover, Li et al. (2021) demonstrated its effectiveness for the same purposes in iron overload.

Quercetin also proved efficient in preventing negative changes under the influence of lead, aluminum, DEP, fenitrothion, and fetal impairment (Ibrahim *et al.* 2020; Morsi *et al.* 2022; Abo-EL-Sooud *et al.* 2023; Al-Zharani *et al.* 2023). The ability of quercetin to act together with curcumin for reducing the negative effects of diazinon was also established by Abdel-Diam *et al.* (2019). Silymarin (Abd Eldaim *et al.* 2021) and *Opuntia stricta* (Zhu & Athmouni 2022) were proven to decrease MDA and improve histology in lead and cadmium models. *Adansonia digitata* (Fannami *et al.* 2022) possessed both antioxidant and chelating properties.

Against $PM_{2.5}$ effects, resveratrol decreased cardiac anomalies and ROS in zebrafish (Ren *et al.* 2020). A topical antioxidant mixture was found to be efficient in human skin by Ivarsson (Ivarsson *et al.* 2025). Carvacrol inhibited NF-κB, inflammation, and 8-OHdG in cadmium-induced lung toxicity (Yesildag *et al.* 2022).

Fig. 4 provides a network visualization of the complex relationships between major antioxidants, environmental pollutants, and their underlying molecular mechanisms across the reviewed studies.

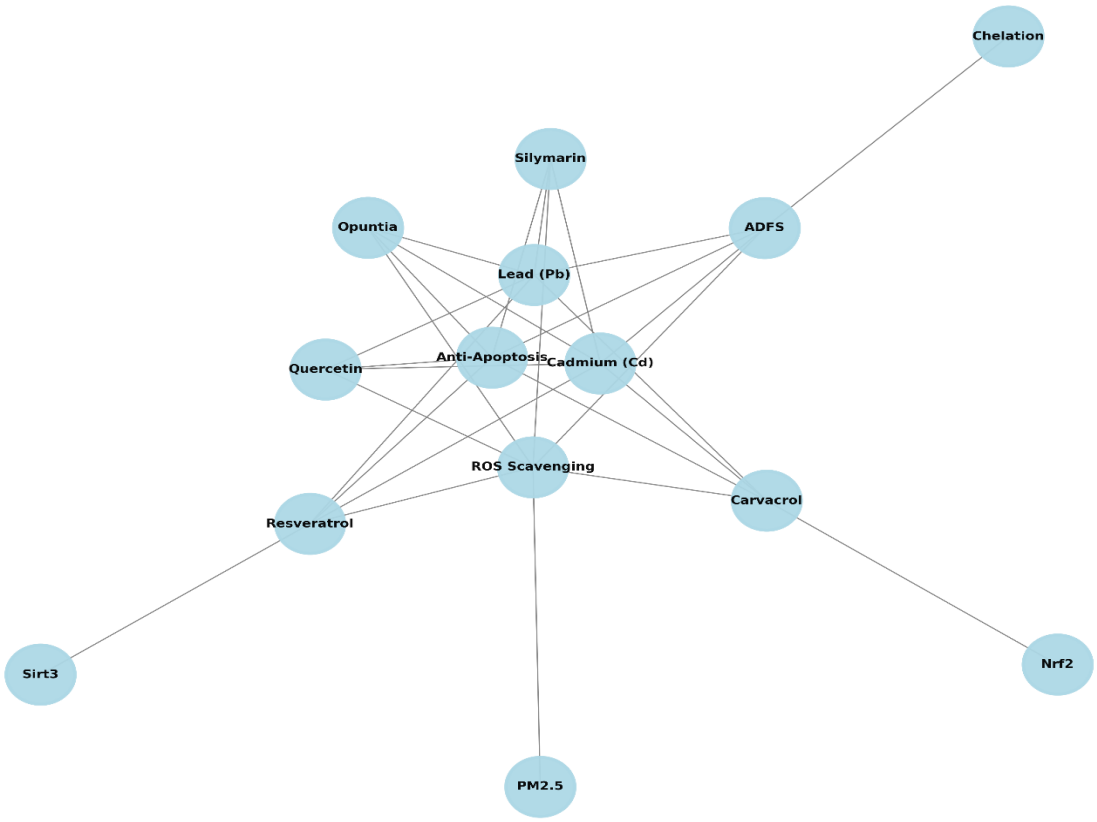

Fig. 4. Network graph showing the interconnections between key antioxidants, environmental pollutants, and underlying molecular mechanisms synthesized from the studies. Node size and edge thickness represent the strength of association.

Caspian J. Environ. Sci.
DOI:

Received:
Article type: Review

Limitations of the current evidence

There are some limitations associated with this review article. Firstly, there is a high degree of imbalance with regard to preclinical (33/35) and clinical studies (2/35). One clinical observation was made by Omotosho regarding occupational exposure, while another was made by Ivarsson *et al.* (2025) concerned a topical intervention study on skin problems. Thus, it is rather hard to draw any conclusions that may be applied in the clinic. The second limitation refers to the differences in doses, period of exposure, and route of administration. For example, quercetin dosages differed widely in animal models from 20 to 350 mg kg^{-1}, while its equivalent dose in humans was not identified.

The third issue refers to the bioavailability concerns associated with resveratrol and quercetin. As it has been mentioned before, the oral bioavailability of polyphenols is less than 1-5%, which may result in a considerable first-pass effect and gut microbial metabolism. The fourth limitation is connected to different time frames of exposure to oxidative factors between animals and humans, who experience constant exposure throughout their lifespans. There is still little known about acute and chronic oxidative stress mechanisms and their differences. Finally, the last limitation may refer to the possible side effects of antioxidant supplements.

Table 3. Translational gap between preclinical and clinical evidence in antioxidant research against environmental pollutants.

Stage of translation	Number of studies	Percentage	Status	Major limitation
In vitro / Cellular	8	23%	Strong	Limited physiological relevance
In vivo (Animal)	25	71%	Very Strong	Short-term exposure, species differences
Human Observational	1	3%	Limited	No intervention
Human Interventional (Topical)	1	3%	Very Limited	Skin only, not systemic
Human RCT Phase II/III (Systemic)	0	0%	None	Critical evidence gap

Table 3 clearly illustrates the significant translational gap. While preclinical evidence is robust, high-quality systemic clinical trials in humans are virtually absent.

CONCLUSION

The current narrative review, based on 35 original research papers, showed the effectiveness of natural antioxidants, especially resveratrol, quercetin, silymarin, carvacrol, and some plant extracts (*Adansonia digitata*, and *Opuntia stricta*) in protecting against pollution-related oxidative damage in preclinical studies. The protection is achieved due to various actions, such as the scavenging effect on ROS, activation of the Nrf2 pathway, Sirt3 activation, NF-κB suppression, anti-apoptotic action, and metal chelating capacity. At the same time, there are only two observational and interventional studies conducted in humans among 35 studies analyzed. Besides, the majority of reviewed articles are animal and *in vitro* experiments. There are still problems related to poor bioavailability of essential polyphenols, high heterogeneity in dosage, lack of data concerning safety issues, and lack of randomized controlled trials in real life conditions of human exposure to a mixture of pollutants.

Thus, the potential of natural antioxidants for reducing the health risk associated with pollution is rather high in preclinical studies but still needs confirmation in well-designed randomized controlled trials among humans.

REFERENCES

Abd Eldaim, MA, Barakat, ER, Alkafafy, M & Elaziz, SAA 2021, Antioxidant and anti-apoptotic prophylactic effect of silymarin against lead-induced hepatorenal toxicity in rats. *Environmental Science and Pollution Research,* 28: 57997–58006.

Abdel-Badeea, WI, Abdel-Wahab, A, Mahmoud, AA, Abdel-Razik, ARH, Attia, EZ, Abdelmohsen, UR & Hassanin, KM 2025, Syzygium cumini Fruit Extract and Quercetin Ameliorate Cadmium-Induced Ovarian Apoptosis in Rats Via miRNA-204-5p-Mediated Bcl-2 Upregulation and Bax/Caspase 9/Caspase 3 Downregulation. *Biological Trace Element Research,* 203: 6172–6191.

Abdel-Diam, MM, Samak, DH, El-Sayed, YS, Aleya, L, Alarifi, S & Alkahtani, S 2019, Curcumin and quercetin synergistically attenuate subacute diazinon-induced inflammation and oxidative neurohepatic damage, and acetylcholinesterase inhibition in albino rats. *Environmental Science and Pollution Research,* 26: 3659–3665.

Caspian J. Environ. Sci.
DOI:

Received:
Article type: Review

Abdelrahman, SA, Mahmoud, AA, Abdelrahman, AA, Samy, W & Zaid Hassen Saleh, E 2022,Histomorphological changes and molecular mechanisms underlying the ameliorative effect of resveratrol on the liver of silver nanoparticles-exposed rats. *Ultrastructural Pathology,* 46: 268–284.

Abo-El-Sooud, K, Abd-Elhakim, YM, Hashem, MM, El-Metwally, AE, Hassan, BA & El-Nour, HH 2023, Ameliorative effects of quercetin against hepatic toxicity of oral sub-chronic co-exposure to aluminum oxide nanoparticles and lead-acetate in male rats. *Naunyn-Schmiedeberg's archives of pharmacology,* 396: 737–747.

Al-Zharani, M, Mubarak, M, Almugri, E, Rudayni, H, Aljarba, N, Yaseen, K, Albatli, S, Alkahtani, S, Nasr, F & Al-Doaiss, A 2025, Catechin (epigallocatechin-3-gallate) supplement restores the oxidation: antioxidation balance through enhancing the total antioxidant capacity in Wistar rats with cadmium-induced oxidative stress. *Journal of Nutritional Science,* 14**:** e67.

Al-Zharani, M, Mubarak, M, Rudayni, HA, Al-Doaiss, AA, Abd-Elwahab, MM & Al-Eissa, MS 2023, Quercetin as a dietary supplementary flavonoid alleviates the oxidative stress induced by lead toxicity in male wistar rats. *Nutrients,* 15:1888.

Bahri, S, Kaddour, H, Karoui, D, Bouraoui, S, Amri, M & Mokni, M 2019, Protective role of vitamin E against cadmium induced oxidative stress into the rat liver. *La Tunisie medicale,* 97: 100–105.

Castro, JM, Bianchi, VA, Felici, E, De Anna, JS, Venturino, A & Luquet, CM 2023, Effects of dietary copper and Escherichia coli challenge on the immune response and gill oxidative balance in the freshwater mussel Diplodon chilensis. *Environmental Toxicology and Chemistry,* 42: 154–165.

Famurewa, AC, Ugwu-Ejezie, CS, Iyare, EE, Folawiyo, AM, Maduagwuna, EK & Ejezie, FE 2021, Hepatoprotective effect of polyphenols isolated from virgin coconut oil against sub-chronic cadmium hepatotoxicity in rats is associated with improvement in antioxidant defense system. *Drug and chemical toxicology,* 44: 418–426.

Fang, J, Yin, H, Yang, Z, Tan, M, Wang, F, Chen, K, Zuo, Z, Shu, G, Cui, H & Ouyang, P 2021, Vitamin E protects against cadmium-induced sub-chronic liver injury associated with the inhibition of oxidative stress and activation of Nrf2 pathway. *Ecotoxicology and Environmental Safety,* 208: 111610.

Fannami, IM, Garba, SH & Chirona, SM 2022, Adansonia digitata L. fruit shell extract alleviates lead-induced neurotoxicity in mice via modulation of oxidative stress and a possible chelating activity. *Journal of Trace Elements in Medicine and Biology,* 74: 127074.

Fu Beibei, FB, Zhao Jiamin, ZJ, Peng Wei, PW, Wu Haibo, WH & Zhang Yong, ZY 2017, Resveratrol rescues cadmium-induced mitochondrial injury by enhancing transcriptional regulation of PGC-1α and SOD2 via the Sirt3/FoxO3a pathway in TCMK-1 cells.

Ibrahim, KA, Eleyan, M, Abd El-Rahman, HA, Khwanes, SA & Mohamed, RA 2020, Quercetin attenuates the oxidative injury–mediated upregulation of apoptotic gene expression and catecholaminergic neurotransmitters of the fetal rats' brain following prenatal exposure to fenitrothion insecticide. *Neurotoxicity research,* 37: 871–882.

Ivarsson, J, Yan, X, Guiotto, A, Pecorelli, A, Sarandy, MM, Lynch, S, Anderias, S, Choudhary, H, White, S & Ferrara, F 2025, Application of Antioxidant Mixture Prevents Cutaneous "Oxinflammaging" in Subjects Exposed to Particulate Matter. *Journal of Cosmetic Dermatology,* 24**:** e70306.

Jiang, XQ, Mei, XD & Feng, D 2016, Air pollution and chronic airway diseases: what should people know and do? *Journal of Thoracic Disease,* 8: E31–40.

Kato, K, Takahashi, M, Oh-Hashi, K, Ando, K & Hirata, Y 2023, Quercetin and resveratrol inhibit ferroptosis independently of Nrf2–ARE activation in mouse hippocampal HT22 cells. *Food and Chemical Toxicology,* 172:113586.

Li, J, Wang, S, Duan, J, Le, P, Li, C, Ding, Y, Wang, R & Gao, Y 2021, The protective mechanism of resveratrol against hepatic injury induced by iron overload in mice. *Toxicology and Applied Pharmacology,* 424**:**115596.

Li, S, Cao, C, Shi, H, Yang, S, Qi, L, Zhao, X & Sun, C 2016, Effect of quercetin against mixture of four organophosphate pesticides induced nephrotoxicity in rats. *Xenobiotica,* 46: 225–233.

Caspian J. Environ. Sci.
DOI:

Received:
Article type: Review

Lifeng, L, Qin, Z & Shengping, L 2024, Cadmium-induced hepatotoxicity in mice–prophylactic supplementation of quercetin exerts hepatoprotective effect by modulating PI3K/Akt/NF-κB signaling pathway. *Physiological Research,* 73: 703.

Mahdavifard, S & Sekhavatmand, N 2022, Glutamine is a superior protector against lead-induced hepatotoxicity in rats via antioxidant, anti-inflammatory, and chelating properties. *Biological Trace Element Research,* 200: 4726–4732.

Morsi, AA, Fouad, H, Alasmari, WA & Faruk, EM 2022, The biomechanistic aspects of renal cortical injury induced by diesel exhaust particles in rats and the renoprotective contribution of quercetin pretreatment: Histological and biochemical study. *Environmental Toxicology,* 37: 310–321.

Niu, R, Cheng, J, Sun, J, Li, F, Fang, H, Lei, R, Shen, Z, Hu, H & Li, J 2022, Alveolar type II cell damage and Nrf2-SOD1 pathway downregulation are involved in PM2. 5-induced lung injury in rats. *International Journal of Environmental Research and Public Health,* 19: 12893.

Omotosho, IO 2019, Oxidative stress indices as markers of lead and cadmium exposure toxicity in auto technicians in Ibadan, Nigeria. *Oxidative Medicine and Cellular Longevity,* 2019: 3030614.

Paduraru, E, Flocea, EI, Lazado, CC, Simionov, IA, Nicoara, M, Ciobica, A, Faggio, C & Jijie, R 2021, Vitamin C mitigates oxidative stress and behavioral impairments induced by deltamethrin and lead toxicity in zebrafish. *International journal of molecular sciences,* 22: 12714.

Panchal, H, Sachdeva, SN & Bhardwaj, JK 2022, Ultrastructural analysis of cadmium-induced toxicity and its alleviation by antioxidant quercetin in caprine testicular germ cells in vitro. *Ultrastructural pathology,* 46: 259–267.

Ren, F, Huang, Y, Tao, Y, Ji, C, Aniagu, S, Jiang, Y & Chen, T 2020, Resveratrol protects against PM2. 5-induced heart defects in zebrafish embryos as an antioxidant rather than as an AHR antagonist. *Toxicology and applied pharmacology,* 398: 115029.

Rohanii, AM & Mohammadi, T 2025, β-Glucan and resveratrol mitigate lead induced reproductive toxicity in male mice. *Scientific Reports,* 15: 31277.

Skoczyńska, AK, Gładysz, AK, Stępniak, J & Karbownik-Lewińska, M 2024, Indole-3-butyric acid, a natural auxin, protects against fenton reaction-induced oxidative damage in porcine thyroid. *Nutrients,* 16: 3010.

Sumita Halder, SH, Rajarshi Kar, RK, Vikas Galav, VG, Mehta, A, Bhattacharya, S, Mediratta, P & Banerjee, B 2016, Cadmium exposure during lactation causes learning and memory-impairment in F1 generation mice: amelioration by quercetin.

Surai, PF 2015, Silymarin as a natural antioxidant: An overview of the current evidence and perspectives. *Antioxidants* (*Basel*)*,* 4: 204–47.

Tanoğlu, C, Ersoy, A, Çoban, T, Mammadov, R & Süleyman, B 2022, The effect of taxifolin on oxidative sciatic nerve damage induced by cobalt chloride in rats: a biochemical and histopathological evaluation. *Acta neurobiologiae experimentalis,* 82: 254–262.

Verma, S, Batoye, S & Jindal, R 2022, Protective efficacy of naringenin against cadmium-induced redox imbalance in Labeo rohita: an integrated biomarker approach. *Environmental Science and Pollution Research,* 29: 25591–25604.

Wani, SA, Khan, LA & Basir, SF 2022, Quercetin and resveratrol ameliorate nickel-mediated hypercontraction in isolated wistar rat aorta. *Journal of Smooth Muscle Research,* 58: 89–105.

Yang, H, Xing, R, Liu, S, Yu, H & Li, P 2021, Role of Fucoxanthin towards Cadmium-induced renal impairment with the antioxidant and anti-lipid peroxide activities. *Bioengineered,* 12: 7235–7247.

Yesildag, K, Gur, C, Ileriturk, M & Kandemir, FM 2022, Evaluation of oxidative stress, inflammation, apoptosis, oxidative DNA damage and metalloproteinases in the lungs of rats treated with cadmium and carvacrol. *Molecular Biology Reports,* 49: 1201–1211.

Zhu, X & Athmouni, K 2022, HPLC analysis and the antioxidant and preventive actions of Opuntia stricta juice extract against hepato-nephrotoxicity and testicular injury induced by cadmium exposure. *Molecules,* 27: 4972.