www.idosr.org Alberta, 2026

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ISSN: 2579-0730

International Digital Organization for Scientific Research IDOSR JBCP/26/102.1700
IDOSR JOURNAL OF BIOLOGY, CHEMISTRY AND PHARMACY 11(1):42-46, 2026.
https://doi.org/10.59298/IDOSR/JBCP/26/102.4246

Environmental Toxicants, Oxidative Stress, and Hepatic Dysfunction: Can Natural Products Offer Dual Hepatoprotective and Antioxidant Shielding

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ABSTRACT

Environmental toxicants from industrial pollutants and agrochemicals to heavy metals and mycotoxins are pervasive contributors to liver injury worldwide. The liver's central role in xenobiotic metabolism renders it particularly vulnerable: biotransformation reactions produce reactive metabolites and reactive oxygen species (ROS), initiating oxidative stress, mitochondrial dysfunction, lipid peroxidation, endoplasmic reticulum (ER) stress, and maladaptive inflammatory signaling. Together these processes drive hepatocellular injury, cholestasis, fibrosis, and, in chronic exposure settings, cirrhosis or hepatic carcinogenesis. Natural products, plant-derived polyphenols, flavonoids, terpenoids, alkaloids, and certain marine-derived compounds exert pleiotropic activities that simultaneously scavenge free radicals, induce endogenous antioxidant defenses, stabilize mitochondria, and modulate detoxification enzymes and inflammatory pathways. This review synthesizes mechanistic links between environmental toxicants and hepatic oxidative injury, summarizes classes of natural compounds with dual antioxidant and hepatoprotective effects, examines translational evidence, discusses formulation and safety considerations, and outlines research priorities needed to translate natural-product strategies into preventive and therapeutic tools against environmental hepatotoxicity.

Keywords: Environmental toxicants, oxidative stress, hepatoprotection, natural products, liver injury

INTRODUCTION

The accelerating pace of industrialization, urbanization, and agricultural intensification has led to an unprecedented rise in environmental pollution and chemical exposure across ecosystems [1]. Industrial effluents, vehicle emissions, mining activities, and the widespread use of pesticides and fertilizers contribute significantly to the accumulation of toxicants in air, water, and food chains [2]. Humans, therefore, encounter these substances through inhalation, ingestion, and dermal contact on a daily basis. Among all internal organs, the liver remains the most critical in defending the body against such xenobiotic insults. It is responsible for the biotransformation and detoxification of harmful compounds via enzymatic systems such as cytochrome P450s, conjugating enzymes, and antioxidant defenses [3]. However, these same metabolic processes can inadvertently convert inert compounds into reactive intermediates that harm hepatocytes. Common environmental hepatotoxins include polycyclic aromatic hydrocarbons (PAHs) from combustion processes, polychlorinated biphenyls (PCBs) from industrial wastes, organophosphate and organochlorine pesticides, and heavy metals like arsenic, lead, and cadmium [4]. Mycotoxins such as aflatoxins, often contaminating grains and nuts, further aggravate liver injury in low-resource regions [5]. Despite their chemical diversity, many of these toxicants converge mechanistically by generating reactive oxygen species (ROS) and inducing oxidative stress—a pathological imbalance between oxidants and antioxidants that leads to cellular damage. Persistent oxidative stress not only impairs hepatocyte metabolism but also triggers inflammation, fibrosis, and carcinogenesis [6]. In the search for safer and sustainable protective interventions, natural products have gained growing scientific and clinical interest. Plant-derived polyphenols, flavonoids, terpenoids, and alkaloids exhibit strong antioxidant, anti-inflammatory, and detoxifying effects [7]. Well-known examples such as silymarin (from Silybum marianum) and curcumin (from Curcuma longa) have demonstrated significant hepatoprotective potential in preclinical and clinical settings [8]. These bioactive compounds not only

neutralize free radicals but also activate cellular defense systems, enhance glutathione synthesis, and modulate detoxification enzymes. As research advances, the potential for developing dual-function natural therapeutics—combining antioxidant and hepatoprotective actions-offers a promising strategy to mitigate the burden of environmentally induced liver diseases.

2. Environmental toxicants and their hepatic impacts: an overview

The liver's unique anatomical position and metabolic role make it a primary target for environmental toxicants. Upon absorption, most xenobiotics are delivered to the liver through the portal circulation, where they undergo phase I and phase II metabolism [9]. While these processes aim to render toxins water-soluble for excretion, they can also generate reactive intermediates that attack cellular macromolecules. Aflatoxin B1, for instance, is metabolically activated by cytochrome P450 enzymes into a reactive epoxide that binds DNA, promoting mutagenesis and predisposing to hepatocellular carcinoma [10]. Similarly, heavy metals such as cadmium and arsenic interfere with mitochondrial oxidative phosphorylation, leading to ATP depletion and excessive ROS formation [11].

Organic solvents and halogenated hydrocarbons, including carbon tetrachloride and trichloroethylene, initiate chain reactions of lipid peroxidation that damage membranes and organelles [12]. Persistent low-dose exposure to such toxicants can cause subtle yet progressive hepatic alterations, including steatosis, mild inflammation, and collagen deposition-hallmarks of early fibrosis. In contrast, acute or high-dose exposures may result in massive hepatocellular necrosis or acute liver failure. Moreover, toxicant effects are rarely isolated: synergistic interactions between multiple chemicals, alcohol consumption, malnutrition, or pre-existing conditions like nonalcoholic fatty liver disease (NAFLD) greatly exacerbate hepatic vulnerability [13].

Collectively, these findings underscore that environmental hepatotoxicity is multifactorial, involving oxidative injury, mitochondrial dysfunction, immune activation, and impaired bile secretion. Recognizing these interconnected pathways provides a rationale for using antioxidant and hepatoprotective natural products as integrative countermeasures against toxicant-induced liver dysfunction.

3. Oxidative stress as a central mechanistic node

Oxidative stress stands at the core of toxicant-induced hepatic dysfunction, serving as a key convergence point for diverse environmental insults. It reflects a physiological imbalance in which the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) overwhelms the cellular antioxidant defense network [14]. In hepatocytes, oxidative stress can arise from several overlapping sources. One major contributor is mitochondrial dysfunction—specifically, the leakage of electrons from the electron transport chain under the influence of toxicants such as heavy metals or halogenated hydrocarbons [15]. These leaked electrons reduce molecular oxygen to form superoxide anion, initiating a cascade of ROS production.

Additionally, environmental chemicals frequently induce cytochrome P450 enzymes during detoxification, particularly CYP2E1 and CYP1A2, which generate reactive intermediates as byproducts of metabolism [16]. These intermediates can undergo redox cycling, further amplifying oxidative burden. NADPH oxidases (NOX), another enzymatic source of ROS, are often activated by inflammatory stimuli and contribute to sustained oxidative signaling [17]. Kupffer cells and infiltrating neutrophils release superoxide, hydrogen peroxide, and peroxynitrite during inflammatory responses, thereby exacerbating tissue injury [18].

The biochemical consequences of excessive ROS and RNS are profound. Lipid peroxidation disrupts membrane fluidity and damages organelles such as mitochondria and endoplasmic reticulum [19]. Proteins undergo carbonylation and thiol oxidation, impairing enzymatic functions and signaling pathways [20]. Oxidative DNA lesions such as 8-hydroxy-2′-deoxyguanosine trigger mutagenic events, increasing the risk of hepatocellular carcinoma [21]. Redox-sensitive transcription factors like NF-κB and AP-1 are activated, leading to the expression of proinflammatory cytokines (TNF-α, IL-6, IL-1β) and adhesion molecules that perpetuate inflammation [22]. Likewise, mitogen-activated protein kinase (MAPK) cascades p38, ERK, and JNK mediate stress responses that can culminate in apoptotic or necroptotic cell death [23].

Another crucial downstream effect of oxidative stress is its role in hepatic fibrogenesis. ROS not only injure hepatocytes but also activate hepatic stellate cells, transforming them into myofibroblast-like cells that overproduce extracellular matrix proteins such as collagen [24]. This process, when chronic, leads to fibrosis and cirrhosis. Moreover, oxidative stress disrupts calcium homeostasis, destabilizing mitochondrial permeability and amplifying apoptotic signaling [25]. Thus, oxidative stress acts both as an initiator and a propagator of hepatocellular injury, bridging metabolic dysfunction, inflammation, and tissue remodeling into a self-reinforcing pathological loop.

4. Natural products: classes and mechanisms of dual antioxidant–hepatoprotective action

Natural products derived from plants, marine organisms, and microorganisms exhibit multifunctional actions that make them ideal candidates for protecting the liver against environmental toxicants [26]. These bioactive compounds act not only as direct antioxidants but also as modulators of cellular defense mechanisms, effectively targeting both oxidative and inflammatory components of hepatic injury.

Polyphenols and flavonoids, such as quercetin, resveratrol, and epigallocatechin gallate (EGCG), represent one of the most studied groups. They are potent free-radical scavengers that neutralize superoxide, hydroxyl, and peroxyl radicals, while also chelating transition metals like iron and copper that catalyze the Fenton reaction [27]. Beyond direct antioxidant activity, they activate the Nrf2–ARE (antioxidant response element) signaling pathway, leading to transcriptional upregulation of key cytoprotective enzymes such as heme oxygenase-1 (HO-1), glutathione S-transferase (GST), and NAD(P)H:quinone oxidoreductase-1 (NQO1) [28]. By simultaneously inhibiting NF-κB signaling, these compounds reduce the expression of proinflammatory mediators and cytokines, thus dampening hepatic inflammation.

Silymarin, a flavonolignan complex from Silybum marianum, is among the most clinically validated hepatoprotective agents. Its primary component, silybin, stabilizes hepatocyte membranes, prevents toxin penetration, and promotes protein and ribosomal RNA synthesis, facilitating regeneration [29]. It enhances glutathione concentration, improves superoxide dismutase (SOD) and catalase activity, and interrupts lipid peroxidation chains [30]. Clinically, silymarin has shown benefits in cases of drug-induced liver injury, viral hepatitis, and aflatoxin toxicity, making it a prototype of dual antioxidant–hepatoprotective intervention [31].

Curcuminoids and terpenoids, found in turmeric (Curcuma longa) and ginseng (Panax ginseng), respectively, further illustrate the multitargeted nature of natural hepatoprotectants. Curcumin mitigates oxidative and nitrosative stress by inhibiting inducible nitric oxide synthase (iNOS) and downregulating TNF-α and IL-1β production [32]. It stabilizes mitochondrial membranes and suppresses apoptotic pathways via modulation of Bcl-2 family proteins and caspases. Terpenoids like oleanolic acid and ginsenosides additionally support bile acid homeostasis and attenuate cholestasis, while enhancing mitochondrial respiration and ATP generation [33].

Marine-derived antioxidants such as carotenoids (astaxanthin, fucoxanthin) display remarkable ROS-quenching capacities and maintain mitochondrial integrity [34]. Astaxanthin, in particular, can cross lipid membranes, protecting against lipid peroxidation and improving lipid metabolism—an important consideration where steatosis coexists with toxicant-induced injury [35]. These compounds often regulate peroxisome proliferator-activated receptors (PPARs), thereby influencing lipid oxidation and energy balance.

Alkaloids and glycosides, including berberine and rutin, offer additional benefits by improving insulin sensitivity, modulating AMP-activated protein kinase (AMPK), and supporting hepatic lipid and glucose metabolism [36]. These systemic effects indirectly lower oxidative load by improving mitochondrial efficiency and reducing lipotoxicity.

Collectively, natural hepatoprotective compounds function through a network of interrelated mechanisms: direct radical scavenging, metal chelation, activation of Nrf2-driven antioxidant genes, inhibition of NF-κB-mediated inflammation, stabilization of mitochondria, and modulation of detoxification enzymes [37]. Their capacity to simultaneously protect against oxidative stress and support hepatocellular repair underscores their therapeutic promise as dual-action agents. By addressing the multifaceted pathology of environmental hepatotoxicity-oxidative damage, inflammation, and fibrogenesis-natural products offer a scientifically grounded and biologically integrative approach to liver health preservation.

5. Research gaps and future directions

Key priorities include: well-designed clinical trials in populations with documented environmental exposures; biomarker-driven studies linking mechanistic changes (oxidative stress markers, metallothionein expression, mitochondrial function) to clinical endpoints; standardized, bioavailable formulations and dose–response studies; investigation of combination strategies (antioxidant + chelator or anti-fibrotic agent); and population-level interventions integrating nutrition, remediation, and phytochemical prophylaxis. Mechanistic research should also address mixture toxicology and identify interactions between metabolic disease (e.g., NAFLD) and toxicant susceptibility.

CONCLUSION

Environmental toxicants exert substantial hepatic risk via oxidative stress, mitochondrial dysfunction, and inflammatory pathways. Natural products that simultaneously scavenging ROS, inducing endogenous antioxidant defenses, stabilizing mitochondria, modulating detoxification enzymes, and suppressing inflammation offer a plausible dual-function strategy for hepatoprotection and antioxidant shielding. Translating this promise into public health impact requires rigorous clinical evidence, optimized formulations, safety vigilance, and integrated approaches that combine exposure reduction with targeted nutritional or phytochemical interventions. With these steps, natural-product strategies could become valuable components of preventive and therapeutic toolkits against environmental hepatotoxicity.

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CITE AS: Alberta Jeanne N. (2026). Environmental Toxicants, Oxidative Stress, and Hepatic Dysfunction: Can Natural Products Offer Dual Hepatoprotective and Antioxidant Shielding. IDOSR JOURNAL OF BIOLOGY, CHEMISTRY AND PHARMACY 11(1):42-43. https://doi.org/10.59298/IDOSR/JBCP/26/102.4246