Research Article

Metabolism and Toxic Effects of Xenobiotics on Humans: An Overview

Sadia Altaf[1]*, Nawaira Fatima[1], Narmeen Shahzad[1], Syrut Nasir[2], Neha Ilyas[1] and Laiba Shakeel[1]

[1]Department of Chemistry, University of Sialkot, Sialkot, Pakistan; [2]Department of Biotechnology, University of Sialkot, Sialkot, Pakistan.

Abstract | In today's chemically intensified world, humans are continuously exposed to a wide range of xenobiotics, foreign compounds originating from food, air, water, pharmaceuticals, and industrial sources. Although many of these substances are present at trace levels, their long-term biological impact raises significant concerns for human health. This review comprehensively examines the effects of xenobiotics in the human body, from exposure and absorption to their systemic distribution and eventual elimination. Once inside the body, xenobiotics interact with complex metabolic networks that determine their biological disposition. Central to this process is hepatic biotransformation, in which Phase I reactions introduce or unmask functional groups via oxidation, reduction, or hydrolysis, often altering biological activity. Phase II reactions subsequently enhance water solubility through conjugation, thereby facilitating detoxification and excretion. Together, these metabolic pathways serve as a critical defense system, yet they may also generate reactive intermediates that can induce cellular and molecular damage. The review further highlights renal and biliary excretion as essential routes for xenobiotic clearance, emphasizing how inefficiencies in these systems can lead to accumulation and toxicity. Emerging evidence links prolonged xenobiotic exposure to oxidative stress, endocrine disruption, and organ dysfunction, underscoring their relevance in modern public health challenges. By integrating sources, metabolic mechanisms, and physiological outcomes, this article emphasizes the delicate balance between detoxification and toxicity. Understanding xenobiotic behavior is crucial not only for toxicological assessment but also for developing strategies that minimize exposure and safeguard long-term human health in an increasingly chemical-dependent environment.

Received | May 15, 2026; **Accepted** | June 18, 2026; **Published** | June 26, 2026
***Correspondence** | Sadia Altaf, Department of Chemistry, University of Sialkot, Sialkot, Pakistan; **Email:** sadia.altaf@uskt.edu.pk
Citation | Altaf, S., N. Fatima, N. Shahzad, S. Nasir, N. Ilyas and L. Shakeel. 2026. Metabolism and toxic effects of xenobiotics on humans: An overview. *Biologia (Lahore)*, 72(1): 29-42.
DOI | https://dx.doi.org/10.17582/journal.biologia/2026/72.1.29.42
Keywords | Xenobiotics, Metabolism, Cytochrome P450 (CYP450), Reactive oxygen species (ROS), Toxicity, Detoxification, Excretion

Introduction

Xenobiotics are externally derived chemical substances that enter biological systems and possess the potential to alter normal physiological activities (Egwu *et al.*, 2026). These substances, including potentially toxic elements (PTEs) and organic pollutants, pose a serious risk due to their long-lasting presence and poisonous nature in the environment (Xu *et al.*, 2022).

To highlight the diversity and biological relevance of xenobiotics, Table 1 summarizes representative xenobiotics along with their chemical structures

and associated toxicological impacts. This overview provides a structural basis for understanding how different classes of xenobiotics influence metabolic behavior and toxicity in biological systems.

These chemicals possess various routes of entry into the living system based on their sources and environmental occurrence. The most common exposure routes include inhalation, ingestion, and dermal absorption (Xu *et al.*, 2022). Foreign harmful substances from human-made emissions, which are easily inhaled and directly affect the respiratory system. Intake risks occur when pollutants are present in food or drinking water. While dermal absorption happens through polluted soil, water, or household commodities.

After entering the body, these substances are taken up into the bloodstream and carried to different body tissues and organs. Their transportation depends on factors like their chemical nature and blood circulation in the body. For example, fat-soluble xenobiotics can easily pass-through cell barriers and disperse rapidly across various tissues.

Xenobiotic metabolism occurs through two sequential phases, Phase I and Phase II (Esteves *et al.*, 2021; Rathore *et al.*, 2022). The initial stage of biochemical transformation, known as Phase I, involves enzymes like CYP450 in the liver to perform oxidation, reduction, and hydrolysis processes (Esteves *et al.*, 2021). Second-phase reactions include conjugation processes with compounds like glucuronic acid or antioxidant compounds, which further increase their ability to dissolve (Rathore *et al.*, 2022; Xu *et al.*, 2022).

This study examines the specific biochemical pathways involved in the metabolism of foreign compounds and assesses the resulting effects of these substances on human health.

Types and sources of xenobiotics

Xenobiotics arise from numerous environmental and human-made sources, including pharmaceuticals, pesticides, industrial compounds, and food contaminants (Miglani *et al.*, 2022). Due to their diverse chemical characteristics and biological interactions, they are classified into different categories. To provide a broader perspective on exposure, Table 2 outlines the main types of xenobiotics along with their primary sources, highlighting the diverse environmental, industrial, and dietary origins through which humans are commonly exposed.

Table 1: *Xenobiotics, their structures, and impact.*

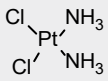
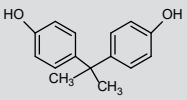
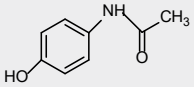
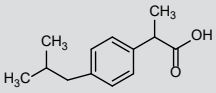
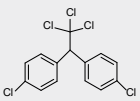
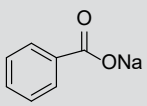
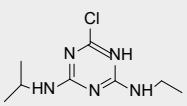
Chemicals	Chemical formula	Structure	Impact	Reference
cisplatin	$Pt(NH_3)_2Cl_2$		Kills cancer cells, causes nephrotoxicity and hepatotoxicity due to oxidative stress.	(Cecati, M *et al.*, 2026)
Bisphenol A (BPA)	$C_{15}H_{16}O_2$		Linked to reproductive, metabolic and cardiovascular disorders, especially with impaired renal excretion.	(Sebastian Mas *et al.*, 2021)
Paracetamol	$C_8H_9NO_2$		May cause liver and kidney toxicity in humans.	(Żur, J *et al.*, 2018)
Ibuprofen	$C_{13}H_{18}O_2$		Gastrointestinal, Cardiovascular, and Renal health risks in humans.	(Żur, J *et al.*, 2018)
DDT	$C_{14}H_9Cl_5$		Can disrupt systemic metabolic pathways and hepatic metabolism.	(Kodai Motohira, *et al.*, 2023)
Sodium benzoate	C_6H_5COONa		Cause dose-dependent hepatic toxicity leading to biochemical and histopathological alterations at higher concentrations.	(Khan, I. S *et al.*, 2022)
Atrazine	$C_8H_{14}ClN_5$		organic pollutant that can disturb ecological balance by disrupting endocrine functions.	(Nikita, Dhiman a *et al.*, 2022)

Table 2: *Main Types and sources of xenobiotics.*

Types	Effects on humans	Sources of exposure	References
Pharmaceuticals	Triggers microbial resistance, hormonal imbalance and marine life poisoning	Hospitals, human excretion, pharmaceutical industries	aus der Beek *et al.*, 2016; Anetor *et al.*, 2022)
Pesticides	Release brain damaging agents that remain stable in biosphere and intensify through food chain accumulation.	Agricultural spraying, soil contamination	Rathore *et al.*, 2022
Industrial chemicals	Initiate hormonal obstruction, widespread poisoning, and durability.	Industrial effluents, petroleum refining, chemical plants	Brack *et al.*, 2023; Ali *et al.*, 2024
Environmental pollutants	Exhibit cancer causing properties, cause bio-accumulation, and lead to nature destruction.	Combustion processes, waste burning, industrial emissions	Anetor *et al.*, 2022; Suzuki *et al.*, 2022
Food additives	Disrupt biological processes and alter digestive system microbial balance if ingested excessively.	Processed foods	Aentor *et al.*, 2022

Biological fate of xenobiotics: Absorption, distribution, metabolism, and excretion (ADME)

The biological effects of xenobiotics depend on their movement and interaction within the human body. After entering the body, these foreign compounds undergo a series of processes, including absorption, distribution, metabolism, and excretion, which collectively determine their toxicity and physiological impact (Lang *et al.*, 2025; Esteves *et al.*, 2021).

Absorption and distribution

The systemic entry of exogenous substances is fundamentally a trans-barrier process, where the final concentration reaching the blood is governed by intestinal permeability and preliminary hepatic degradation. The overall bioavailability of a xenobiotic is fundamentally dictated by its intrinsic molecular properties, specifically its fat solubility, ionization, and water-based diffusion, which collectively regulate its movement across biological barriers. Once systemic absorption is achieved, xenobiotics undergo bloodstream transport to various body compartments, enabling interaction with specific target tissues to produce beneficial or harmful effects. The spatial allocation or distribution of these substances is modulated by a complex interplay of hemodynamic variables, protein-binding affinities, and carrier-mediated transport, all of which dictate the localized concentration and overall kinetic disposition within specific tissues. Moreover, phenomena such as bile-intestinal recycling can substantially alter the retention time and systemic behavior of foreign compounds by enabling the continual re-entry of compounds, increasing the apparent distribution volume, and prolonging the elimination half-life. The gut microbiota represents an extra-genetic metabolic pool capable of altering foreign compound kinetics (Garcia-Santamarina *et al.*, 2024) and biological activity, thereby contributing significantly to the observed individual variability in overall exposure (Rzeczycki *et al.*, 2025). Concisely, the interplay between absorption and distribution serves as the primary architect of foreign compound toxicokinetics, as these processes collectively dictate the overall burden, tissue-specific localization, and the eventual metabolic or toxic effects within the human body.

Metabolism of xenobiotics

Metabolism of xenobiotics refers to the enzymatic biotransformation of foreign compounds into more polar metabolites that facilitate their elimination from the body. This process primarily occurs in the liver and involves a coordinated sequence of enzymatic reactions that determine whether a compound is detoxified or converted into more reactive species. (Mahanayak, 2024). This overall process is illustrated in Figure 1, which summarizes the sequential biotransformation of xenobiotics through Phase I and Phase II metabolic pathways leading to either detoxification or metabolic activation.

Xenobiotic metabolism is broadly responsible for regulating biological exposure by modifying the lipophilicity, chemical reactivity, and excretability of compounds. The outcome of metabolism is not uniform, as it may lead to either detoxification or metabolic activation depending on the chemical structure of the xenobiotic and the enzymatic pathways involved.

Phase I reactions (Functionalisation reactions)

Phase I reactions introduce or expose functional groups through oxidation, reduction, and hydrolysis,

thereby increasing polarity and facilitating subsequent conjugation reactions. CYP450 enzymes, particularly CYP3A4, CYP2E1, and CYP1A2, dominate this phase and exhibit remarkable substrate diversity. However, this broad specificity makes them highly vulnerable to induction and inhibition by drugs, pollutants, and dietary components, leading to significant inter-individual variability in metabolic responses (Mahanayak, 2024).

Oxidation is the predominant Phase I pathway and generally enhances xenobiotic elimination, yet it simultaneously generates ROS and electrophilic metabolites. These reactive species can damage DNA, proteins, and lipids, directly linking Phase I metabolism to oxidative stress, mutagenesis, and carcinogenesis.

Reduction and hydrolysis reactions cannot be considered purely detoxifying processes, as they may also produce metabolites with enhanced biological activity or toxicity depending on physiological conditions (Esteves *et al*., 2021).

The toxicological significance of Phase I metabolism therefore lies in its dual role: it facilitates elimination but also drives metabolic activation. Excess enzyme induction or impaired downstream detoxification can shift metabolism toward accumulation of harmful intermediates (Araújo *et al*., 2024).

Although Phase I metabolism primarily facilitates xenobiotic elimination through functionalization reactions, it also represents a critical stage in the generation of reactive intermediates. The induction or inhibition of CYP450 enzymes by drugs, environmental pollutants, and dietary constituents can substantially alter metabolic outcomes and contribute to inter-individual variability in toxic responses. Consequently, Phase I metabolism serves not only as a detoxification mechanism but also as a potential source of metabolic activation and toxicity.

Phase II reactions (Conjugation reactions)

Phase II reactions are generally considered protective because they convert xenobiotics into highly water-soluble metabolites for excretion. However, this protective capacity is not absolute (vanVugt-Lussenburg *et al*., 2022).

Glucuronidation, sulfation, glutathione conjugation, acetylation, and methylation collectively maintain chemical detoxification. Yet each pathway has inherent limitations. Glucuronidation is a major detoxification route, but sulfation is easily saturated due to limited sulfate availability during high exposure conditions. Glutathione conjugation protects against electrophiles and ROS, but depletion of glutathione weakens cellular defense and enhances oxidative injury. Acetylation and methylation show genetic variability among individuals, contributing to differences in susceptibility to xenobiotic toxicity. Therefore, Phase II efficiency depends on enzyme capacity, cofactor availability, and cellular redox status. When Phase I activation exceeds Phase II detoxification capacity, reactive metabolites accumulate, leading to oxidative stress, lipid peroxidation, DNA damage, and cellular dysfunction (Pietrzak *et al*., 2026).

Although Phase II conjugation reactions are primarily detoxifying, their capacity can be limited by enzyme activity, cofactor availability, and genetic variation, allowing reactive metabolites to accumulate. Consequently, the balance between metabolic activation and detoxification determines xenobiotic toxicity and is fundamental to toxicity prediction and safer chemical design.

Detoxification and excretion

Detoxification refers to metabolic processes that convert xenobiotics and their intermediates into less toxic, more water-soluble compounds that can be efficiently eliminated from the body (Hassan *et al*., 2024). This is achieved through conjugation reactions involving endogenous molecules such as glutathione, sulfate, and glucuronic acid, which increase hydrophilicity and reduce biological reactivity. (Surendradoss *et al*., 2023).

Following detoxification, xenobiotics are eliminated through excretory pathways, including renal excretion (urine), hepatobiliary excretion (bile and faeces), pulmonary exhalation, and minor routes such as sweat and breast milk. Figure 2 illustrates the integrated detoxification and excretion pathways of xenobiotics in the human body, showing how biotransformed metabolites are processed and eliminated through renal, hepatic, pulmonary, and secondary excretory routes.

Factors affecting xenobiotic metabolism

Xenobiotic metabolism is influenced by multiple biological and environmental factors that alter enzyme

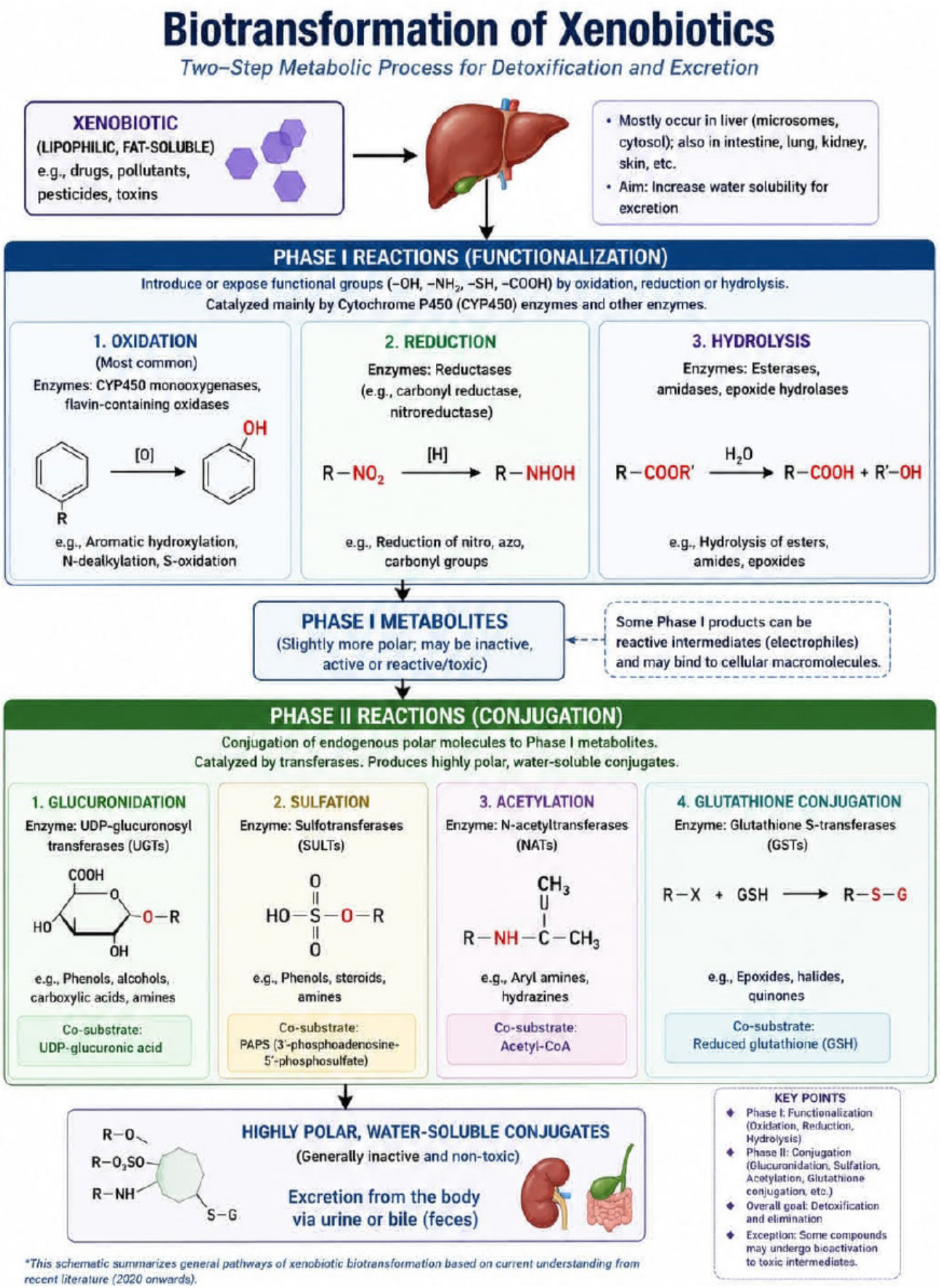


Figure 1: *Biotransformation of xenobiotics.*

Links Researchers

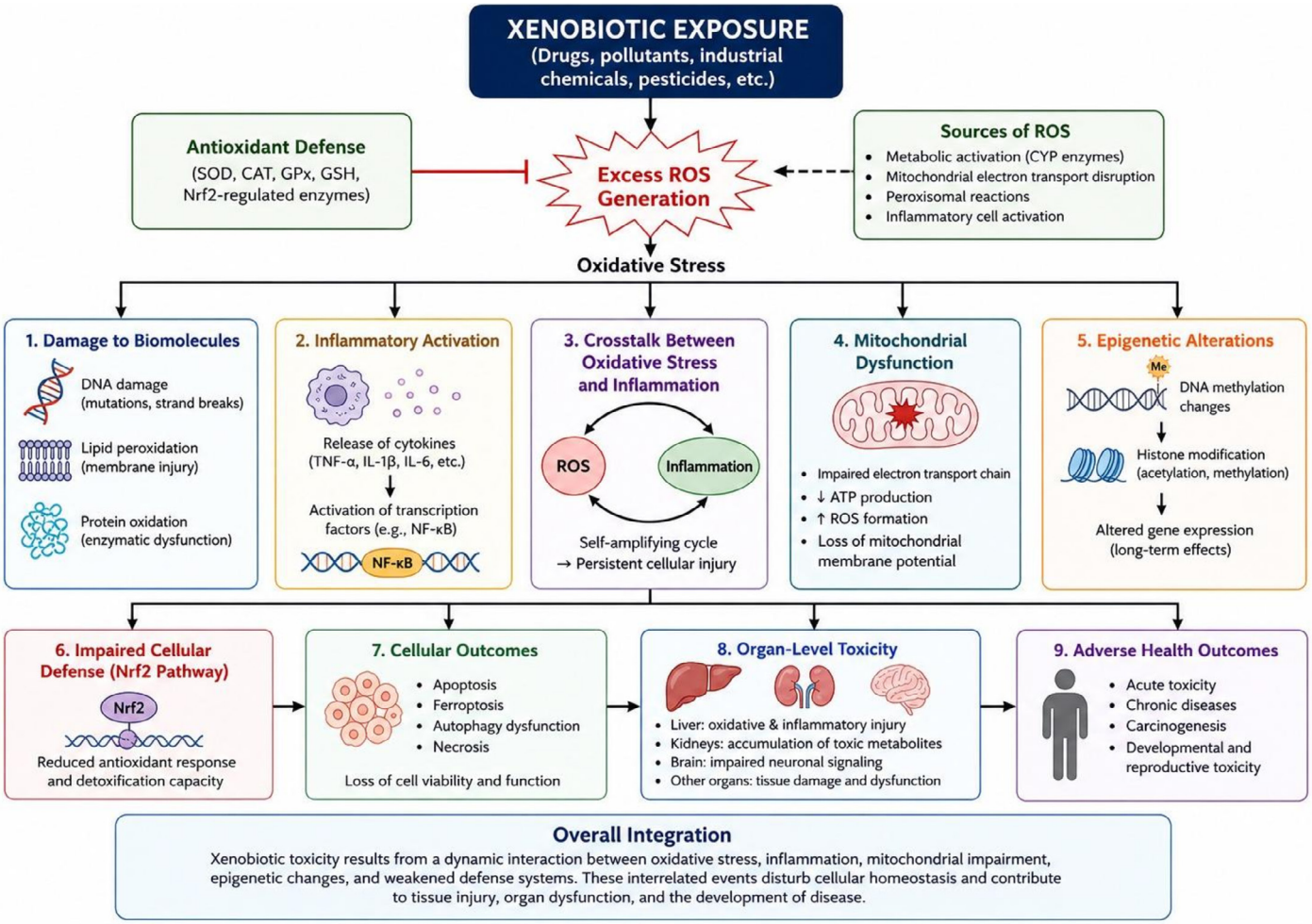


Figure 2: *Overview of xenobiotics toxicity.*

activity, metabolic pathways, and detoxification efficiency.

Environmental exposure

Environmental pollutants, industrial chemicals, pesticides, and cigarette smoke significantly influence xenobiotic metabolism by modulating CYP450 enzyme expression. Polycyclic aromatic hydrocarbons (PAHs) present in cigarette smoke can induce CYP1A1 and CYP1A2 enzymes, increasing the formation of reactive toxic intermediates. Chronic exposure may result in oxidative stress, enzyme dysregulation, and impaired detoxification (Ali *et al.*, 2019).

Gut microbiota

The gut microbiota contributes to xenobiotic metabolism through hydrolysis, reduction, and deconjugation reactions. Microbial enzymes can activate, inactivate, or modify xenobiotics before or after hepatic metabolism. Dysbiosis may disrupt these metabolic pathways, affecting drug efficacy and toxicity through the gut–liver axis (Dikeocha *et al.*, 2022).

Genetic factors

Genetic polymorphisms in CYP450 enzymes such as CYP2D6, CYP2C19, and CYP2E1 cause major inter-individual differences in metabolic capacity. Variations in Phase II enzymes, including GSTs and UGTs, also affect detoxification efficiency and susceptibility to xenobiotic toxicity (Zhou and Lauschke, 2022).

Diet and lifestyle

Dietary habits and lifestyle factors strongly influence xenobiotic metabolism. Cruciferous vegetables may induce detoxification enzymes, whereas high-fat diets alter xenobiotic distribution. Alcohol consumption induces CYP2E1 activity and increases oxidative stress, while smoking promotes enzyme induction and modifies metabolic pathways.

Disease conditions

Liver diseases such as hepatitis, cirrhosis, and fatty liver disease impair xenobiotic clearance by reducing enzyme activity. Obesity, metabolic syndrome, and chronic inflammation can further alter metabolic

pathways and increase vulnerability to toxic effects even at lower exposure levels (Wang *et al*., 2022).

The combined influence of genetic, physiological, environmental, and microbial factors creates considerable variability in xenobiotic metabolism among individuals. As a result, susceptibility to toxic effects may differ substantially even under similar exposure conditions. This complexity represents a major challenge in toxicological risk assessment and highlights the need for personalized approaches to evaluating chemical safety and exposure-related health risks.

Bioactivation of xenobiotics

Bioactivation is a metabolic outcome in which relatively inert xenobiotics are converted into highly reactive intermediates during enzymatic processing. This process is primarily mediated by CYP450 enzymes and is considered a critical toxicological event rather than a protective mechanism (Liu *et al*., 2025).

These reactive intermediates can interact with cellular macromolecules such as DNA, proteins, and lipids, leading to oxidative stress, covalent binding, and cellular dysfunction. Bioactivation therefore represents the harmful branch of xenobiotic metabolism that contributes to toxicity, carcinogenesis, and organ damage (Gonzalez *et al*., 2026).

The toxicological significance of bioactivation lies in its ability to transform relatively harmless compounds into highly reactive and potentially damaging metabolites. This phenomenon presents a considerable challenge for drug development and chemical safety evaluation, as adverse effects may arise not from the parent compound itself but from its metabolic products. Understanding the mechanisms governing bioactivation is therefore essential for predicting toxicity and designing safer chemical entities.

Mechanisms of xenobiotic toxicity

Xenobiotic toxicity is not solely a consequence of reactive metabolite formation but results from the dynamic interplay between oxidative stress, inflammation, and mitochondrial dysfunction. Variations in chemical properties, exposure intensity, and endogenous defense capacity further influence these responses, underscoring the complexity of predicting toxic outcomes. Figure 2 illustrates these interconnected mechanisms.

Oxidative stress as a key mechanism for toxicity

Oxidative stress plays a major role in how xenobiotics cause toxicity inside the body. When there is excessive ROS production, it disrupts cellular redox homeostasis. The oxidants build up faster than the body's own antioxidants can handle them, which seems like a problem. That leads to damage in biomolecules like lipids, proteins, and DNA, all of which are important cell parts. Ultimately, cells get injured, and it spreads to tissues too (Jomova *et al*., 2023). A wide range of xenobiotics, including environmental pollutants, therapeutic drugs, and industrial chemicals, contribute to this imbalance. The extent of oxidative damage is not uniform; it varies depending on exposure dose, duration, and the chemical nature of the compound (Møller *et al*., 2010).

Oxidative stress is a key driver of xenobiotic toxicity but acts in concern with inflammatory signaling, mitochondrial dysfunction, and epigenetic alterations. This interplay highlights xenobiotic toxicity as a multifactorial process governed by interconnected molecular mechanisms rather than a single pathogenic pathway.

Damage to cellular components

The endurance of oxidative stress leads to progressive damage of key cellular components. Nucleic acids are particularly susceptible, and oxidative modifications to DNA can result in mutations and genomic instability. In parallel, lipid peroxidation compromises membrane integrity, while protein oxidation alters enzyme activity and structural organization (Lang *et al*., 2025). When cellular repair processes are insufficient, cells may activate regulated death pathways, such as apoptosis or ferroptosis, to contain damage (Wang *et al*., 2023).

Inflammatory responses and signaling pathways

In addition to direct oxidative injury, xenobiotics can initiate inflammatory signaling cascades that worsen tissue damage. Increased production of cytokines and other inflammatory mediators disrupts normal cellular communication and encourages dysfunction (Liu *et al*., 2025). Among the key regulatory systems, the NF-κB pathway plays a key role by controlling the expression of genes associated with inflammation and stress responses.

Interconnection between oxidative stress and inflammation

Oxidative stress and inflammation are closely entangled processes that reinforce each other. ROS can activate inflammatory pathways, while inflammatory responses further enhance ROS production, creating a self-amplifying cycle of cellular damage (Olaniyan *et al*., 2023).

Mitochondrial dysfunction

Mitochondria are a primary target of xenobiotic toxicity due to their central role in energy production and redox regulation. Disturbance in the mitochondrial electron transport chain leads to decreased ATP synthesis and increased ROS generation (Martins *et al*., 2023).

Organ-level toxic effect

The cumulative impact of these molecular events becomes evident at the organ level. The liver is particularly susceptible due to its central role in detoxification, frequently exhibiting oxidative and inflammatory injury following xenobiotic exposure (Zhang *et al*., 2022). The kidneys are also affected, as their filtration function promotes the accumulation of toxic metabolites. Furthermore, the brain is highly sensitive to oxidative imbalance, which can disrupt neuronal signaling and function.

Role of cellular defense systems (Nrf2 pathway)

The Nrf2 (Nuclear factor erythroid 2-related factor 2) signaling pathway plays a crucial protective role by regulating antioxidant and cytoprotective gene expression. Under normal conditions, Nrf2 helps maintain redox homeostasis; however, its impairment reduces the cell's ability to counteract oxidative stress.

Although Nrf2 activation strengthens cellular defense against oxidative stress, sustained or dysregulated activation may support the survival of damaged cells and facilitate cancer progression. Therefore, Nrf2-targeted therapies require careful evaluation to balance their protective benefits against potential adverse effects (Hammad *et al*., 2023).

Epigenetic modifications

Emerging evidence suggests that xenobiotics can induce epigenetic alterations, including DNA methylation and histone modifications, which influence gene expression without altering the DNA sequence (Sobral *et al*., 2025). These changes may persist even after the initial exposure has ceased, contributing to long-term cellular dysfunction and increased disease susceptibility (Stoccoro *et al*., 2024).

Toxic effects on the human body

Xenobiotics are highly harmful to the human body. They affect multiple organs by disrupting normal cell function and inducing oxidative stress. Over time, they can damage the liver, kidneys, and nervous system. Long-term exposure to xenobiotics leads to the death of millions of people annually.

Liver (Hepatotoxicity)

The Liver is the major organ in the human body responsible for the detoxification and metabolism of xenobiotics. Xenobiotics such as heavy metals (cadmium, lead, arsenic), and chemical effluents containing polycyclic aromatic hydrocarbons, are the main causes of toxicity in the liver (Li *et al*., 2023).

The detoxification of xenobiotics in the liver occurs through CYP450. During this process, intermediates are produced that include ROS, resulting in oxidative stress that affects the normal functioning of the liver. (Mahajan *et al*., 2024).

Long-term vulnerability to xenobiotics can slowly damage the liver. With the passage of time, it can lead to multiple issues like fat buildup in the liver (fatty liver), death of liver cells(apoptosis), and, in severe cases, scarring of the liver (fibrosis) (Massart *et al*., 2022). These harmful effects mainly happen because too much oxidative stress can damage the energy-producing parts of liver cells (mitochondria), which makes the liver work poorly and gradually get injured.

Kidney (Nephrotoxicity)

Kidneys are also susceptible to toxicity due to xenobiotics because of their involvement in processes like filtration, excretion, and concentration of harmful contaminants. Xenobiotics such as toxic metals, pharmaceutical drugs, and industrial chemicals are responsible for nephrotoxicity (Sharma and Singh, 2023). These pollutants, like cisplatin and other chemicals, accumulate in renal tissue, especially in the proximal tubular part of the kidney, and result in oxidative degradation of lipids, protein damage, and DNA injury, and disrupt the normal functioning of renal tubular cells (Tang *et al*., 2023).

When the kidney is long-term exposed to these xenobiotics, it results in acute kidney injury, i.e., it impairs the blood flow to the renal part and can also result in tubular epithelial cell death (Xue *et al.*, 2026).

Neurotoxicity

Xenobiotics such as pesticides, heavy metals, and air pollutants overcome the blood-brain barrier (BBB) and accumulate in the brain tissues, producing excessive ROS and causing neurotoxicity (Trussel and Brad, 2024). These toxins disturb the proper functioning of mitochondria, reduce ATP production, and can cause neuronal cell death (Maciejska *et al.*, 2022). Furthermore, xenobiotics lead to the release of cytokines that further worsen the neuronal injury (Rahman *et al.*, 2025).

Endocrine disruption

Toxins such as bisphenol A (BPA), phthalates, pesticides, and industrial chemicals disrupt the endocrine system, i.e, cause hormonal imbalance. These toxins mimic or block natural hormones, specifically estrogen and thyroid hormone, and cause endometriosis in women, declining sperm health in men, and affect the growth in children (Evans, 2022). Endocrine disruption produces oxidative stress and can lead to physiological disruption (Vanivska *et al.*, 2025).

With the passage of time, exposure to these toxins causes problems such as infertility, menstrual or reproductive dysfunction, and developmental issues (Khalil *et al.*, 2025).

Carcinogenic effects

Industrial pollutants, pesticides, heavy metals, and certain drugs damage normal cells and increase the chances of cancer. These toxins increase the production of ROS and damage the DNA and proteins. This increases the chances of mutation in the cell and increases the chances of cancer development in different organs of the body, like the liver, lungs, kidneys, and bloodstream (Bharti *et al.*, 2026).

Xenobiotic toxicity extends beyond isolated organ damage, as oxidative stress, inflammation, and metabolic disturbances can propagate systemic effects across multiple tissues. This integrated perspective is reflected in Table 3, which summarizes the principal mechanisms of xenobiotic-induced organ toxicity and their contribution to both acute and chronic pathological conditions.

Prevention and risk management of xenobiotics

The increasing environmental burden of xenobiotics highlights the urgent need to prioritize prevention over remediation in chemical risk governance.

Effective prevention of xenobiotic pollution requires a shift from conventional end-of-pipe treatment toward source-oriented chemical design and exposure reduction. Green chemistry provides a foundational framework for this transition by promoting the design of chemicals and processes that minimize

Table 3: *Overview of the toxic effects of xenobiotics on different organs of the human body.*

Toxic effect	Xenobiotics	Toxic effect on humans	Reference
Hepatotoxicity (Liver)	Heavy metals (cadmium, lead, arsenic) Chemical effluents Air contaminants	Fatty liver, Apoptosis, Fibrosis	Li *et al.*, 2023
Nephrotoxicity (Kidney)	Pharmaceutical drugs (cisplatin) Heavy metals Industrial chemicals	Kidney injury, Tubular epithelial cell death	Sharma *et al.*, 2023
Neurotoxicity (Brain)	Pesticides Heavy metals Air pollutants	Neuronal injury, Neuronal cell death	Trussel *et al.*, 2024
Endocrine disruption	Bisphenol A (BPA) Phthalates Pesticides Industrial chemicals	Infertility, Developmental issues, Reproductive dysfunction	Evans *et al.*, 2022
Carcinogenic effect	Certain drugs like Cyclophosphamide or Diethylstilbestrol Industrial pollutants Pesticides Heavy metals	Cancer (liver, lungs, kidney, blood stream)	Bharti *et al.*, 2026

toxicity, persistence, and bioaccumulation from the outset. Different microbes (e.g., algae, bacteria, fungi, actinomycetes, and viruses) are used to remove the toxicity of xenobiotics (Ganguly *et al*., 2024).

In addition to preventive design, wastewater treatment remains an essential control strategy. Advanced oxidation processes (AOPs), including ozonation, Fenton chemistry, and photocatalytic degradation, are widely applied for removing emerging contaminants resistant to conventional biological treatment. These processes rely on highly reactive radicals, particularly hydroxyl radicals, which degrade complex organic pollutants. However, their efficiency depends strongly on operational conditions, and complete mineralization is not always achieved, often resulting in intermediate transformation products that may retain toxicity. High energy requirements and operational costs further restrict their large-scale implementation (Pandis *et al*., 2022).

Another important preventive strategy involves environmental monitoring and early-warning detection systems. Continuous surveillance of water, soil, and food matrices using advanced analytical techniques such as chromatography and mass spectrometry enables early identification of xenobiotic contamination before it reaches harmful levels (Murray *et al*., 2023). This allows timely regulatory intervention and prioritization of high-risk chemicals for restriction or substitution. However, implementation of such systems remains uneven globally due to limited infrastructure, financial constraints, and insufficient technical capacity in many developing regions.

Risk assessment approaches are also evolving from single-substance models toward mixture toxicity and cumulative exposure frameworks. This shift reflects real-world conditions where multiple xenobiotics coexist and interact, producing synergistic or antagonistic effects that cannot be predicted by traditional models. As a result, conventional toxicological approaches may underestimate actual environmental and human health risks. Modern frameworks increasingly integrate computational toxicology, environmental monitoring, and probabilistic risk assessment to improve predictive accuracy (Gruszecka-Kosowska *et al*., 2022).

At the regulatory level, global coordination is essential for effective risk management. International organizations emphasize persistent gaps in chemical governance, particularly in developing countries where monitoring and enforcement systems remain weak.

Despite advances in monitoring and regulation, widespread use of synthetic chemicals makes complete prevention of xenobiotic exposure unrealistic. Future strategies should prioritize exposure reduction, sustainable chemical design, and predictive toxicology to identify hazards before environmental release and human exposure.

Future perspective

Recent advances in genomics, proteomics, metabolomics, and computational toxicology have created new opportunities to improve the understanding of xenobiotic-induced toxicity. The integration of these approaches may facilitate the identification of novel biomarkers, improve the prediction of toxicological responses, and provide deeper insight into the molecular pathways involved in toxicity. In addition, the application of artificial intelligence and machine-learning tools may enhance the assessment of chemical safety and support more accurate risk prediction models. AI and machine learning can help researchers identify potentially toxic chemicals earlier and make more accurate predictions about their health risks, improving chemical safety evaluation and public health protection.

Future research should also address the health consequences of chronic low-dose exposure and emerging contaminants, including microplastics, nanomaterials, and newly developed synthetic chemicals. Furthermore, the development of advanced human-relevant experimental models may improve toxicological evaluation and reduce the limitations associated with conventional testing methods.

Additionally, future toxicological studies should focus on the combined effects of multiple xenobiotics rather than isolated compounds, as this approach will provide more realistic risk assessments and support more effective strategies for protecting human health in the face of increasing chemical exposure.

Conclusion

Xenobiotics are an unavoidable aspect of human life,

resulting from ongoing exposure to pharmaceuticals, food additives, industrial chemicals, pesticides, and environmental pollutants. While the human body has effective metabolic systems for detoxifying and eliminating these foreign substances, their biotransformation may produce highly reactive intermediates that interfere with normal cellular processes. These metabolites induce oxidative stress, damage proteins, lipids, and nucleic acids, and contribute to the onset of conditions such as cancer, liver injury, neurotoxicity, and vascular dysfunction.

This review presents a comprehensive synthesis of xenobiotic metabolism and its toxicological effects by integrating current knowledge of metabolic pathways, bioactivation processes, and oxidative stress mechanisms. It demonstrates how chemical structure and metabolic transformation affect biological activity, thereby enhancing understanding of the molecular basis of xenobiotic-induced toxicity and its relevance to human health.

From a chemical perspective, this review contributes by bringing together key concepts of metabolic reactions, enzyme-mediated biotransformation, and structure–toxicity relationships into a single framework. This integrated approach serves as a valuable reference for researchers and students and supports the rational design of safer pharmaceuticals, industrial chemicals, and environmentally sustainable compounds. Furthermore, it emphasizes the importance of advancing analytical chemistry, toxicology, and predictive risk assessment to identify hazardous metabolites and minimize chemical-induced health risks. Continued research in this field will not only improve the prediction and prevention of toxicity but also drive the development of safer chemicals and innovative strategies for protecting both human health and the environment.

Acknowledgement

Thankful to the Department of Chemistry, University of Sialkot, for its support and the researchers whose published work served valuable references for this review.

Novelty Statement

Unlike previous reviews that focused on individual aspects of xenobiotics, this review provides a comprehensive overview of interconnected processes like metabolism, biotransformation, detoxification, along with organ-specific toxic effects and emerging risk-management strategies within a single framework.

Author's Contribution

Sadia Altaf: Conceptualized, supervised and reviewed.
Nawaira Fatima: Conducted the literature review and collected, relevant data.
Narmeen Shahzad: Writing the original draft.
Syrut Nasir: Critically reviewed the manuscript.
Neha Ilyas: Writing the original draft.
Laiba Shakeel: Writing the original draft.

Generative AI and AI assisted technology statement
The authors declare that no generative AI and AI assisted technology was used in the creation of this manuscript.

Conflict of interest
The authors have declared no conflict of interest.

References

Ali, H., Khan, E. and Ilahi, I., 2019. Environmental chemistry and ecotoxicology of hazardous heavy metals: environmental persistence, toxicity, and bioaccumulation. J. Chem., 2019(1): 6730305. https://doi.org/10.1155/2019/6730305

Araújo, F., Dória, M.L., Beliaev, A., Kiss, L.E., Bonifácio, M.J., Holenz, J., Soares-da-Silva, P., Loureiro,A.I.,2024.Metabolism and disposition of zamicastat in rats. Xenobiotica, 54(10): 796-807. https://doi.org/10.1080/00498254.2024.2411993

Bharti, P., Upadhyay, U., Nasrin, T., Kushwaha, B., Pandey, S., Maddheshiya, P.K., Kumari, S., Doharey, P.K. and Mishra, S.K., 2026. Effects of xenobiotics on chemical carcinogenesis and toxicology. Xenobiot. Environ., CRC Press. pp. 92-114. https://doi.org/10.1201/9781003521754-7

Cecati, M., Pozzi, V., Pompei, V., Schiavoni, V., Fumarola, S., Romagnoli, A., Tossetta, G., Montana, A., Polizzi, A., Sartini, D. and Campagna, R., 2026. Cisplatin as a xenobiotic agent: Molecular mechanisms of action and clinical applications in oncology. J. Xenobiot., 16(1): 9. https://doi.org/10.3390/jox16010009

Dhiman, N., Jasrotia, T., Bragta, D., Chaudhary,

S., Singh, A., Ameen, S. and Kumar, R., 2022. Investigating the impact of physiological factors on biomass expansion and enzymatic potential of bjerkandera adusta and fomitopsis meliae. Available at SSRN 4835738.

Dikeocha, I.J., Al-Kabsi, A.M., Miftahussurur, M. and Alshawsh, M.A., 2022. Pharmacomicrobiomics: Influence of gut microbiota on drug and xenobiotic metabolism. FASEB J., 36(6): p.e22350. https://doi.org/10.1096/fj.202101986R

Egwu, O.C., Adama, J.Y., Muhammad, H.L., Ikechukwu, A.A., Ossamulu, F.I. and Anthony, M.H., 2026. 'Toxicological impact and biotransformation of xenobiotics: Novel biological discoveries to combat toxicity'. Ecol. Front., 46(2): 413–433. https://doi.org/10.1016/j.ecofro.2025.10.001

Esteves, F., Rueff, J. and Kranendonk, M., 2021. The central role of cytochrome P450 in xenobiotic metabolism. A brief review on a fascinating enzyme family. J. Xenobiot., 11(3): 94-114. https://doi.org/10.3390/jox11030007

Evans, T.J., 2022. Endocrine disruption. In: Reproductive and developmental toxicology. Academic Press. pp. 1163-1182. https://doi.org/10.1016/B978-0-323-89773-0.00058-8

Ganguly, D., Kumar, P., Kumari, A. and Kumar, M., 2024. Importance of microbial consortia and green chemistry in the removal of xenobiotics from the environment. In role of green chemistry in ecosystem restoration to achieve environmental sustainability. Elsevier. pp. 11-21. https://doi.org/10.1016/B978-0-443-15291-7.00032-8

Garcia-Santamarina, S., Kuhn, M., Devendran, S., Maier, L., Driessen, M., Mateus, A., Mastrorilli, E., Brochado, A.R., Savitski, M.M., Patil, K.R. and Zimmermann, M., 2024. Emergence of community behaviors in the gut microbiota upon drug treatment. Cell, 187(22), pp.6346-6357.

Gonzalez, A.M.K., Powers, M. and Cucullo, L., 2026. Oxidative stress, environmental pollutants, aging, and epigenetic regulation: Mechanistic insights and biomarker advances. Antioxidants, 15(4): 494. https://doi.org/10.3390/antiox15040494

Gruszecka-Kosowska, A., Ampatzoglou, A. and Aguilera-Gómez, M., 2022. Microbiota analysis for risk assessment of xenobiotics: Cumulative xenobiotic exposure and impact on human gut microbiota under a One Health approach. EFSA J., 20: e200916. https://doi.org/10.2903/j.efsa.2022.e200916

Hammad, M., Raftari, M., Cesário, R., Salma, R., Godoy, P., Emami, S.N. and Haghdoost, S., 2023. Roles of oxidative stress and Nrf2 signaling in pathogenic and non-pathogenic cells: a possible general mechanism of resistance to therapy. Antioxidants, 12(7): 1371. https://doi.org/10.3390/antiox12071371

Hassan, A.B., Abbas, A.A., Umr, A., Tanko, H.O., Adgeboye, Y. and Kazeem, F.A., 2024. Importance of liver in the detoxification of xenobiotics. IRASS J. Multidiscip. Stud., 1.

Jomova, K., Raptova, R., Alomar, S.Y., Alwasel, S.H., Nepovimova, E., Kuca, K. and Valko, M., 2023. Reactive oxygen species, toxicity, oxidative stress, and antioxidants: chronic diseases and aging. Arch. Toxicol., 97(10): 2499-2574. https://doi.org/10.1007/s00204-023-03562-9

Khalil, M., Ijaz, M.U., Ghafoor, N., Naz, H., Azmat, R., Jameel, M., Sattar, Q., Tahir, A. and Salar, M.Z., 2025. Xenoestrogens and reproductive health: Implications for fertility and development. Integrated Health and Sustainability: Plants, Wildlife, and Genetic Resilience, pp. 345.

Khan, I.S., Dar, K.B., Ganie, S.A. and Ali, M.N., 2022. Toxicological impact of sodium benzoate on inflammatory cytokines, and oxidative stress and biochemical markers in male Wistar rats. Drug Chem. Toxicol., 45(3): 1345–1354. https://doi.org/10.1080/01480545.2020.1825472

Lang, T., Lipp, A.M. and Wechselberger, C., 2025. Xenobiotic toxicants and particulate matter: Effects, mechanisms, impacts on human health, and mitigation strategies. J. Xenobiot., 15(4): 131. https://doi.org/10.3390/jox15040131

Li, K., Geng, Y., Lin, B. and Zhuge, X., 2023. Molecular mechanisms underlying mitochondrial damage, endoplasmic reticulum stress, and oxidative stress induced by environmental pollutants. Toxicol. Res., 12(6): 1014–1023. https://doi.org/10.1093/toxres/tfad094

Liu, J., Argikar, U.A., Brunetti, P., Chatzopoulou, M., Chen, L., Cho, S., Hauri, S., Kramlinger, V., Lang, J., Ma, B. and Rehm, K., 2025. Bioactivation and reactivity research advances-2024 year in review. Drug Metab. Rev., 57(4): 362-399. https://doi.org/10.1080/036

02532.2025.2530407

Liu, S., Liu, J., Wang, Y., Deng, F. and Deng, Z., 2025. Oxidative stress: signaling pathways, biological functions, and disease. Med. Comm., 6(7): e70268. https://doi.org/10.1002/mco2.70268

Maciejska, A., Skórkowska, A., Jurczyk, J., Pomierny, B. and Budziszewska, B., 2022. Biomarkers of neurotoxicity. In: Biomarkers in Toxicology. 1–30. Cham: Springer International Publishing. https://doi.org/10.1007/978-3-030-87225-0_17-1

Mahajan, P., Palkar, M. and Pingili, R.B., 2024. Drug reactive metabolite-induced hepatotoxicity: A comprehensive review. Toxicol. Mech. Methods, 34(6): 607–627. https://doi.org/10.1080/15376516.2024.2332613

Mahanayak, B., 2024. Biotransformation reactions of xenobiotics: Mechanisms and implications for environmental and human health. World J. Biol. Pharma. Health Sci., 19(1): 158-164. https://doi.org/10.30574/wjbphs.2024.19.1.0406

Martins, A.C., Virgolini, M.B., Ávila, D.S., Scharf, P., Li, J., Tinkov, A.A., Skalny, A.V., Bowman, A.B., Rocha, J.B. and Aschner, M., 2023. Caenorhabditis elegans as a model organism to evaluate xenobiotic-induced mitochondrial dysfunction. Cells, 12(17): 2124. https://doi.org/10.3390/cells12172124

Massart, J., Begriche, K., Corlu, A. and Fromenty, B., 2022. Xenobiotic-induced aggravation of metabolic-associated fatty liver disease. Int. J. Mol. Sci., 23(3): 1062. https://doi.org/10.3390/ijms23031062

Miglani, R., Parveen, N., Kumar, A., Ansari, M.A., Khanna, S., Rawat, G., Panda, A.K., Bisht, S.S., Upadhyay, J. and Ansari, M.N., 2022. Degradation of xenobiotic pollutants: An environmentally sustainable approach. Metabolites, 12(9): 818. https://doi.org/10.3390/metabo12090818

Møller, P., Jacobsen, N.R., Folkmann, J.K., Danielsen, P.H., Mikkelsen, L., Hemmingsen, J.G., Vesterdal, L.K., Forchhammer, L., Wallin, H. and Loft, S., 2010. Role of oxidative damage in the toxicity of particulates. Free Radic. Res., 44(1): 1–46. https://doi.org/10.3109/10715760903300691

Motohira, K., Yohannes, Y.B., Ikenaka, Y., Eguchi, A., Nakayama, S.M., Wepener, V., Smit, N.J., van Vuren, J.H. and Ishizuka, M., 2023. Investigation of dichlorodiphenyltrichloroethane (DDT) on xenobiotic enzyme disruption and metabolomic bile acid biosynthesis in DDT-sprayed areas using wild rats. J. Vet. Med. Sci., 85(2): 236-243. https://doi.org/10.1292/jvms.22-0490

Murray, K.J., Villalta, P.W., Griffin, T.J. and Balbo, S., 2023. Discovery of modified metabolites, secondary metabolites, and xenobiotics by structure-oriented LC-MS/MS. Chem. Res. Toxicol., 36(11): 1666–1682. https://doi.org/10.1021/acs.chemrestox.3c00209

Olaniyan, M.F., Muhibi, M.A. and Olaniyan, T.B., 2023. Oxidative stress and inflammatory response interplay. J. Prevent. Diagn. Treat. Strateg. Med., 2(2): 94–100. https://doi.org/10.4103/jpdtsm.jpdtsm_73_23

Pandis, P.K., Kalogirou, C., Kanellou, E., Vaitsis, C., Savvidou, M.G., Sourkouni, G., Zorpas, A.A. and Argirusis, C., 2022. Key points of advanced oxidation processes (AOPs) for wastewater, organic pollutants, and pharmaceutical waste treatment: A review. Chem. Engin., 6(1): 8. https://doi.org/10.3390/chemengineering6010008

Pietrzak, A., Dąbrówka, B., Popiół, J., Pękala, E. and Słoczyńska, K., 2026. Phase II metabolism in xenobiotic biotransformation: General mechanisms and the underestimated role of microbial systems. Drug Metab. Rev., 58(1): 1-25. https://doi.org/10.1080/03602532.2025.2582864

Rahman, M.A., Khatun, M.T., Mim, A.K. Khandocar, M.P., Rahman, A., Hasan, M.H., Shimki, A.I., Hossain M.S., Shoily, M.S.A., Faraque, A., Amin, M.F., Ferdous, R. and Islam, M.S., 2025. Oxidative stress in DNA damage and neurodegenerative diseases: Unveiling the mechanisms and therapeutic opportunities. Cell Biochem. Biophys., 83: 4233–4252. https://doi.org/10.1007/s12013-025-01845-9

Rathore, S., Varshney, A., Mohan, S. and Dahiya, P., 2022. An innovative approach of bioremediation in the enzymatic degradation of xenobiotics. Biotechnol. Genet. Engin. Rev., 38(1): 1–32. https://doi.org/10.1080/02648725.2022.2027628

Rzeczycki, P., Pęciak, O., Plust, M. and Droździk, M., 2025. Gut microbiota in the regulation of intestinal drug transporters: molecular mechanisms and pharmacokinetic implications. International Journal of Molecular Sciences, 26(24), p.11897.

Sebastian, Mas, Alberto, R.P., Pedro, A., Javier, S., Vanesa, C., Jesús, E., Alberto, O., Emilio,

G.P., Bisphenol, S., 2021. Is a haemodialysis-associated xenobiotic that is less toxic than bisphenol A. Clin. Kidney J., 14(4): 1147–1155. https://doi.org/10.1093/ckj/sfaa071

Sharma, V. and Singh, T.G., 2023. Drug-induced nephrotoxicity: A mechanistic approach. Mol. Biol. Rep., 50: 6975–6986. https://doi.org/10.1007/s11033-023-08573-4

Sobral, A.F., Cunha, A., Costa, I., Silva-Carvalho, M., Silva, R. and Barbosa, D.J., 2025. Environmental xenobiotics and epigenetic modifications: Implications for human health and disease. J. Xenobiot. 15: 118. https://doi.org/10.3390/jox15040118

Stoccoro, A. and Coppedè, F., 2024. Exposure to metals, pesticides, and air pollutants: Focus on resulting DNA methylation changes in neurodegenerative diseases. Biomolecules , 14: 1366. https://doi.org/10.3390/biom14111366

Surendradoss, J., Varghese, A. and Deb, S., 2023. Drug metabolism: Detoxification and xenobiotic biotransformation. In biologically active small molecules. Apple Academic Press. pp. 287-332. https://doi.org/10.1201/9781003283119-17

Tang, C., Livingston, M.J., Safirstein, R. and Dong, Z., 2023. Cisplatin nephrotoxicity: New insights and therapeutic implications. Nat. Rev. Nephrol., 19: 53–72. https://doi.org/10.1038/s41581-022-00631-7

Trussel, M. and Brad, J., 2024. Effects of xenobiotics on the blood-brain barrier and neural gene expression. Asia Pac. J. Pharmacother. Toxicol., 4: 47-54. https://doi.org/10.32948/ajpt.2024.09.20

van Vugt-Lussenburg, B.M., Capinha, L., Reinen, J., Rooseboom, M., Kranendonk, M., Onderwater, R.C. and Jennings, P., 2022. Commandeuring xenobiotic metabolism: Advances in understanding xenobiotic metabolism. Chem. Res. Toxicol., 35(7): 1184-1201. https://doi.org/10.1021/acs.chemrestox.2c00067

Vanivska, K., Dianová, L., Halo, M., Štefunková, N., Lenický, M., Slanina, T., Tirpák, F., Jambor, T., Lukáč, N., Stawarz, R., Jaszcza, K. and Massányi, P., 2025. The impact of endocrine disruptions on animal and human organisms. J. Microbiol. Biotechnol. Food Sci., 14(6): e11855. https://doi.org/10.55251/jmbfs.11855

Wang, B., Wang, Y., Zhang, J., Hu, C, Jiang, J, Li, Y. and Peng, Z., 2023. ROS-induced lipid peroxidation modulates cell death outcome: Mechanisms behind apoptosis, autophagy, and ferroptosis. Arch. Toxicol., 97: 1439–1451. https://doi.org/10.1007/s00204-023-03476-6

Wang, X., Rao, J., Tan, Z., Xun, T., Zhao, J. and Yang, X., 2022. Inflammatory signaling on cytochrome P450-mediated drug metabolism in hepatocytes. Front. Pharmacol., 13: 1043836. https://doi.org/10.3389/fphar.2022.1043836

Xu, H., Jia, Y., Sun, Z., Su, J., Liu, Q.S., Zhou, Q. and Jiang, G., 2022. Environmental pollution, a hidden culprit for health issues. Eco-Environ. Hlth., 1(1): 31-45. https://doi.org/10.1016/j.eehl.2022.04.003

Xue, X., Wu, Y., Sheng, P., Geng, L., Tang, Y., Zhu, X. and Gao, K., 2026. Molecular mechanisms of pyrethroid insecticide-induced acute kidney injury: A network toxicology and molecular docking analysis. Int. J. Environ. Health Res., pp. 1–20. https://doi.org/10.1080/09603123.2026.2657448

Zhang, Y., Qi, Y., Huang, S., Jiang, X., Xiao, W., Wang, L., Liu, Z. and Liu, S., 2022. Role of ER stress in xenobiotic-induced liver diseases and hepatotoxicity. oxidative medicine and cellular longevity, 2022(1): 4640161. https://doi.org/10.1155/2022/4640161

Zhou, Y. and Lauschke, V.M., 2022. Genetic landscape of cytochrome P450 enzymes. Pharmacogen. J., 22: 284–293. https://doi.org/10.1038/s41397-022-00288-2