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Molecular Mechanisms of Arsenic and Microplastic-Induced Male Reproductive Toxicity and Potential Protective of Imperatorin: A Narrative Review

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Abstract **Background:** Environmental contaminants such as arsenic and microplastics are increasingly associated with male reproductive dysfunction. This article reviews the mechanisms through which arsenic and microplastics affect male reproductive health and highlights the potential protective effects of imperatorin against co-exposure toxicity. **Methods:** A narrative literature review was conducted using studies published up to June 2026. Relevant experimental and observational studies were identified from major scientific databases to evaluate the effects of arsenic and microplastic exposure on male reproductive health. The review focused on the Nrf2/Keap1, NF-κB, p53 and steroidogenesis signalling pathways and their associated molecular markers involved in oxidative stress, inflammation, apoptosis, hormonal imbalance and impaired spermatogenesis. The potential cytoprotective mechanisms of imperatorin against environmentally induced testicular injury were also examined. **Results:** Exposure to arsenic and microplastics negatively impacts male reproductive function by inducing excessive reactive oxygen species production, inhibiting antioxidant defence mechanisms, causing mitochondrial damage, activating inflammation, disrupting endocrine balance and impairing spermatogenesis. Simultaneous exposure exacerbates oxidative stress, activates nuclear factor-kappa B-mediated inflammatory pathways, disrupts nuclear factor erythroid 2-related factor 2/Kelch-like ECH-associated protein 1 signalling and intensifies p53-dependent apoptosis. Microplastics may enhance the transit and storage of arsenic in testicular tissue, thus exacerbating its harmful effects on the male reproductive system. **Conclusion:** The presence of arsenic and microplastics in the environment may significantly affect male reproductive function. Growing evidence suggests that oxidative stress along with interconnected molecular pathways substantially contribute to the toxic effects observed during co-exposure.

Key Words Arsenic, Microplastics, Male Reproductive Toxicity, Testicular Toxicity, Oxidative Stress, Apoptosis, Bcl-2, Nrf2/Keap1, NF-κB, Imperatorin

INTRODUCTION

Infertility has become an important reproductive health issue worldwide, with male-related factors contributing substantially to unsuccessful conception among couples [1]. In recent decades, there has been increasing apprehension regarding the effects of environmental factors and occupational contaminants on male reproductive function. This is particularly relevant in industrial and urban regions where continuous exposure to multiple toxic substances has become unavoidable [2]. Among the various environmental contaminants, arsenic and microplastics have recognized as significant pollutants because to their widespread dispersion, persistence and capacity to damage physiological systems, particularly the male reproductive system [3].

Arsenic occurs naturally in the environment and is commonly found in water, soil, atmospheric particles and food sources [4]. Prolonged arsenic exposure can produce toxic effects in various organ systems, such as nervous, cardiovascular, hepatic, renal and reproductive systems [5]. Both experimental and epidemiological investigations suggests that arsenic exposure adversely affects male reproductive function by disturbing spermatogenesis, altering steroid hormone synthesis, disrupting endocrine regulation, increasing oxidative stress and impairing mitochondrial activity, thus rendering testicular tissue highly susceptible to damages [6]. Microplastics are generally described as small plastic fragment less than 5 mm in size, which are now largely arising as environmentally significant pollutants associated with various biological and health consequences [7]. Microplastics gets collected inside the biological systems because of their environmental persistence, large surface area and capacity to bind to toxic substances, leading to oxidative imbalance, inflammation, hormonal disruptions and tissue damage [8].

Individuals are often exposed to multiple contaminants simultaneously rather than a single toxicant under natural environmental conditions. Among these pollutants, arsenic and microplastics frequently coexist in water bodies, agricultural soils, food materials and drinking water systems [9]. Because microplastics possess strong surface-binding properties, they can carry heavy metals such as arsenic across biological barriers and promote their accumulation within organs. Such combined interactions may intensify reproductive toxicity, a process often referred to as the "Trojan horse effect" [10]. Studies performed under co-exposure conditions indicates that the combined presence of arsenic and microplastics produces more pronounced reproductive toxicity beyond that produced by individual exposure [11-13]. The enhanced toxicity has been associated with excessive generation of reactive oxygen species, mitochondrial damage, inflammatory alterations, apoptotic cell death, endocrine imbalance and impairment of steroid hormone synthesis [11-13]. Furthermore, modified regulation of signalling pathways involving nuclear factor and tumour suppressor protein p53 (p53), mitogen-activated protein kinase (MAPK) and mitochondrial apoptotic signalling appear to play important roles in spermatogenic impairment and male fertility dysfunction [14].

Plant-derived bioactive compounds have attracted considerable interest due to their ability to counteract toxic effects induced by environmental pollutants [15]. Among these natural compounds, imperatorin, a bioactive linear furanocoumarin with diverse pharmacological properties has reported from experimental studies that they possess antioxidant, anti-inflammatory, anti-apoptotic and cytoprotective effects [16]. Emerging evidence further suggests that imperatorin may influence oxidative stress-related and inflammatory pathways involved in reproductive toxicology [17].

Considering the increasing environmental burden of arsenic and microplastics, this review aims to summarize the basic molecular pathways associated with male reproductive toxicity, particularly under co-exposure conditions and highlights the potential protective effects of imperatorin.

METHODS

This narrative review was conducted to summarize current evidence on the effects of arsenic and microplastic exposure on male reproductive health and the potential cytoprotective role of imperatorin. A comprehensive literature search was performed in PubMed, Scopus, Web of Science and Google Scholar for studies published from January 2000 to June 2026. The search strategy combined Medical Subject Headings (MeSH) and free-text keywords, including arsenic, microplastics, male reproductive toxicity, testicular damage, oxidative stress, apoptosis, Nrf2/Keap1, NF-κB, p53, steroidogenesis, imperatorin and related terms using Boolean operators (AND/OR). After removing duplicates, titles and abstracts were screened for relevance, followed by full-text assessment of potentially eligible articles. Studies were selected based on predefined eligibility criteria. Inclusion criteria comprised peer-reviewed original research articles, experimental animal studies, in vitro studies, observational human studies and relevant review articles published in English that investigated arsenic, microplastics, their combined exposure, molecular mechanisms of reproductive toxicity or the protective effects of imperatorin. Exclusion criteria included non-English publications, conference abstracts without full text, editorials, letters, studies unrelated to male reproductive toxicity, studies lacking mechanistic relevance and publications with insufficient methodological detail.

The review primarily synthesized evidence related to oxidative stress, inflammation, apoptosis, endocrine disruption and steroidogenesis, with particular emphasis on the Nrf2/Keap1, NF-κB, p53 and steroidogenic signalling pathways. The review was prepared in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) recommendations to improve methodological transparency and reporting quality.

Arsenic and Male Reproductive Toxicity

Sources and Human Exposure: Human exposure to arsenic is through various environmental and occupational sources. Among these, drinking contaminated groundwater remains the most important source of exposure, particularly in regions where naturally occurring arsenic leaches into aquifers. Other sources include mining and smelting operations, industrial discharges, pesticide application, fossil fuel combustion and contaminated food products [18,19]. Higher concentrations of arsenic in groundwater have been observed in several parts of the world, remarkably in India, Bangladesh, China, Pakistan and certain areas of South America. Long-term use of contaminated groundwater for agricultural irrigation further facilitates the entry of arsenic into the food chain. Rice and other staple crops cultivated under such conditions can accumulate considerable amounts of arsenic, thereby contributing to chronic dietary exposure

[20]. Although ingestion represents the predominant exposure pathway, inhalation can also contribute to arsenic uptake. As individuals located around industrial areas with substantial fossil fuel combustion may be exposed to arsenic-containing particulate matter released into the atmosphere. Occupational settings involving mining, metal processing and other industrial activities can further increase the probability of airborne exposure [21].

Metabolism and Cellular Uptake

Once absorbed into the body, inorganic arsenic undergoes a series of metabolic transformations that influence its toxicity and biological fate. Inside cells, arsenate (As^{5+}) is reduced to the more reactive arsenite (As^{3+}), a process largely dependent on cellular reducing agents such as glutathione [22]. As arsenic is further metabolized through methylation reactions, generating intermediates such as monomethylarsinic acid (MMA) and dimethylarsinic acid (DMA). Although methylation has traditionally been considered a detoxification mechanism, several methylated arsenic metabolites retain considerable biological reactivity and may contribute to cellular damage. These metabolites can persist within tissues and participate in processes that promote oxidative stress and cellular dysfunction [23]. The testes are particularly vulnerable to arsenic contamination because of their rich blood supply, high metabolic demand and continuous requirement for cellular proliferation during spermatogenesis [6]. Consequently, arsenic and its metabolites can accumulate within testicular tissue, where they may interfere with normal reproductive function by promoting oxidative damage, disrupting cellular homeostasis and impairing the integrity of developing germ cells [22,23].

Molecular Processes Behind Arsenic Induced Reproductive Toxic Effect

Arsenic exposure disrupts the balance between reactive oxygen species (ROS) generation and the antioxidant defence mechanism resulting in the excessive accumulation of free radicals within cells. Concurrently, the activity of antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GSR) and glutathione-S-transferase (GST), is diminishing the cellular ability to counteract oxidative damage [24]. Research indicates that arsenic disrupts mitochondrial function by impairing electron transport chain activity, diminishing adenosine triphosphate (ATP) production and compromising mitochondrial membrane integrity. These alterations result in increased reactive oxygen species (ROS) generation and trigger lipid peroxidation, thereby damaging proteins, membrane lipids and nucleic acids in reproductive organs [25]. Numerous experimental studies have demonstrated elevated malondialdehyde (MDA) levels alongside diminished antioxidant enzyme activity in animals exposed to arsenic [26]. Such modifications are often associated with aberrant spermatogenesis, diminished sperm count, compromised sperm motility and a decline in overall sperm quality [24,26]. Programmed cell death is initiated by increased levels of reactive oxygen species (ROS), which subsequently induce mitochondrial membrane permeabilization and the release of cytochrome c into the cytosol, resulting in the activation of caspase-dependent apoptotic pathways [27]. The downregulation of these steroidogenic regulators negatively impacts germ cell development and compromises spermatogenesis, ultimately resulting in male infertility [28]. Inflammation serves as a crucial mechanism in arsenic-induced reproductive toxicity, primarily via the activation of nuclear factor-kappa B (NF-κB), which facilitates the production of pro-inflammatory mediators including tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β). The resultant inflammatory milieu can exacerbate oxidative stress, facilitate cellular damage and impair normal testicular function [29]. In addition to oxidative and inflammatory damage, arsenic has been associated with epigenetic modifications, including as abnormalities in DNA methylation, histone modification patterns and the expression of genes related to reproductive control. Molecular changes may endure long after exposure and are thought to contribute to poor spermatogenesis, reproductive dysfunction and negative fertility outcomes [30].

Human and experimental evidence of arsenic-induced male reproductive toxicity

Epidemiological studies demonstrate correlations between arsenic exposure and several detrimental reproductive consequences, including diminished sperm count, compromised sperm motility and reduced viability, hormonal disturbances and abnormalities in spermatogenesis [31,32]. Also, increase in arsenic concentrations in biological specimens such as urine, blood and seminal plasma have been linked with poor semen quality among exposed individuals [31-33]. Experimental investigations provide further support for these observations. Exposure to sodium arsenite has demonstrated structural and functional modifications in testicular tissue, such as decreased testicular weight, abnormal sperm morphology, degeneration of seminiferous tubules, damage to Sertoli cell as well as reduced testosterone levels has also been reported in animal models. These effects have largely been attributed to oxidative stress, steroidogenic dysfunction and activation of apoptotic pathways involving p53 and caspase-3 signalling [26-28]. Overall, the evidences from both human and experimental studies indicates that the testes represent an important target of arsenic-induced toxicity, with potential consequences for male fertility and reproductive function.

Microplastics and Male Reproductive Toxicity

Sources and Characteristics of Microplastics: Microplastics, defined as small plastic particles of less than 5 mm, come from the decomposition of bigger plastic trash or from goods deliberately produced in microscopic sizes [7]. They consist of many polymer kinds, including polystyrene (PS), polyethylene (PE), polypropylene (PP),

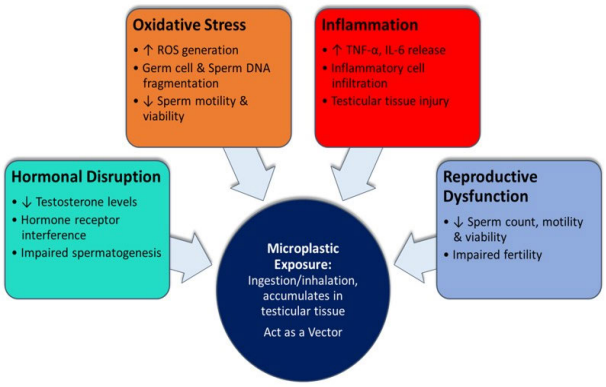


Figure 1: Analysis of molecular processes behind male reproductive damage produced by microplastics

polyvinyl chloride (PVC) and polyethylene terephthalate (PET) [34]. Microplastics, owing to their widespread utilization and environmental durability, have been detected in aquatic ecosystems, agricultural soils, food products, potable water, air particulates and indoor settings. Due to their extensive dispersion, human exposure is inevitable and occurs through the consumption of contaminated food and drink, inhalation of airborne particles, and, to a lesser degree, skin contact [35]. Due to their environmental durability and capacity to infiltrate biological systems, microplastics have raised significant concerns about their potential effects on human health, especially reproductive health.

Molecular Mechanisms of Microplastic Induced Reproductive Toxicity

Excessive reactive oxygen species generation resulting from surface reactivity, inflammatory activation and release of toxic additives, including phthalates and bisphenol compounds, promotes lipid peroxidation, sperm DNA fragmentation, reduced antioxidant enzyme activity and impaired sperm motility [36,37]. Both experimental and human studies have reported associations between microplastic exposure and structural as well as functional alterations in the male reproductive system, including seminiferous tubular degeneration, hormonal imbalance and increased testicular apoptosis [38]. Endocrine disruption represents another important mechanism underlying microplastic-induced reproductive toxicity. Alterations in hypothalamic-pituitary-gonadal axis activity have been reported due to microplastic exposure, resulting in impaired androgen signalling and reduced testosterone biosynthesis. Also, downregulation of steroidogenic enzymes activity involved in hormone production has been observed in several experimental models [39,40]. These endocrine disturbances may compromise normal spermatogenic processes and contribute to reproductive dysfunction and fertility impairment [40]. Thus, current evidence suggests Oxygen-mediated stress, inflammatory processes, endocrine dysfunction and mitochondrial damage apoptosis play important roles in microplastic-associated reproductive dysfunction [36]. The major pathways involved are summarized in Figure 1.

Human Evidence

Evidence of human exposure to microplastics has increased substantially in recent years, with these particles being detected in biological samples such as blood, placenta, seminal plasma and semen. The detection of microplastics in reproductive tissues and other fluids suggests that they are capable entering the reproductive tract and accumulating within reproductive organs [41]. Recent studies have analysed associations between the presence of microplastics in semen and also differences in sperm quality such as reduced motility and other abnormalities in seminal parameters [42]. Hormonal imbalance has also been observed which rises concerns regarding their possible effects on male reproductive system. Although there remains limited human evidence and still the underlying mechanisms are not yet fully understood, current findings highlight the need for further investigation into the reproductive consequences of microplastic exposure [41-43].

Combined Exposure to Arsenic and Microplastics

Environmental exposure of arsenic and microplastics often occurs simultaneously because both contaminants are commonly isolated in the aquatic ecosystems, agricultural soils, food chains and drinking water sources [3,9]. Arsenic can be adsorbed onto microplastic surfaces and transported across biological barriers, resulting in enhanced bioavailability and tissue accumulation, including within the testes [3,10].

Enhanced oxidative stress, mitochondrial damage, inflammatory response, apoptosis, endocrine disruption and steroidogenic dysfunction may result in more pronounced reproductive effects have been observed, in combined exposure compared to individual contaminant exposure [12,13]. Persistent testicular damage may be resulted from excessive generation of ROS, which weakens the antioxidant defence system stimulating the NF-κB-mediated inflammatory pathways [13,24,29]. At the same time, activation of p53-associated apoptotic pathways due to mitochondrial dysfunction and oxidative DNA damage leading to germ cell loss and degeneration of seminiferous tubules [13,14,25,27].

Expression of steroidogenic enzymes are highly decreased, including steroidogenic acute regulatory protein (StAR), 3β-hydroxysteroid dehydrogenase (3β-HSD) and 17β-hydroxysteroid dehydrogenase (17β-HSD), has also been noted under co-exposure conditions when compared with individual toxicant exposure. This may contribute to reduced testosterone production and impaired spermatogenesis [13,28]. And also, in the experimental models combined exposure had shown impaired sperm parameters, seminiferous epithelial degeneration, Leydig cell injury and hormonal imbalance in experimental studies [13,26]. These observations emphasize the importance of studying environmental contaminants under realistic mixed-

exposure scenarios rather than as isolated toxicants [12,13]. As a result, the reproductive toxicity associated with arsenic and microplastic co-exposure has been interconnected with several molecular pathways like oxidative stress, dysregulation of nuclear factor erythroid 2-related factor 2/Kelch-like ECH-associated protein 1 (Nrf2/Keap1) signalling, nuclear factor-kappa B (NF-κB)-mediated inflammation, p53-dependent apoptosis and suppression of steroidogenic processes.

Oxidative Stress and Nrf2/Keap1 Signalling

Cellular protection against oxidative stress is largely regulated by the Nrf2/Keap1 signalling pathway. As normally, Nrf2 is retained in the cytoplasm where it always binds with Keap1 and continuously targeted for degradation. But Nrf2 is released from Keap1 in response to oxidative stress and will be translocated into the nucleus, where it activates genes encoding antioxidant and detoxifying enzymes such as heme oxygenase-1 (HO-1), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione-S-transferase (GST). Combined exposure of these contaminants impairs this signalling pathway and suppress antioxidant defences, thereby enhancing oxidative damage within testicular tissue [44-47].

NF-κB-Mediated Inflammatory Signalling

A critical function in the modulation of inflammation responses is majorly due to the initiation of NF-κB signalling under enhanced oxidative stress which further amplifies the expression of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1β. As a result, Sertoli cell function may be weakened along with compromise in the stability of the blood-testis barrier (BTB) leading to the disruption of spermatogenesis [48-50].

p53 and Apoptotic Signalling

Cellular responses to DNA damage and stress are regulated primarily by the tumour suppressor protein p53. Activation of p53-dependent signalling pathways may occur during co-exposure under conditions of excessive oxidative stress and mitochondrial dysfunction. This activation promotes the expression of pro-apoptotic mediators, including Bax and caspase-3, thereby facilitating apoptotic cell death within testicular tissue. Hence, germ cell depletion, impaired spermatogenesis and reproductive dysfunction may occur [51-53].

Steroidogenic Dysfunction

Arsenic and microplastics suppress steroidogenic pathways involved in testosterone synthesis. The combined exposure potentially modifies the expression of essential hormonal regulators such as StAR, 3β-HSD, 17β-HSD and CYP17A. Reduced activity of these proteins may interfere with androgen synthesis and disturb the hormonal balance required for normal spermatogenesis. Hormonal imbalance further contributes to infertility and testicular dysfunction [54-56].

Integrated Pathway Crosstalk

Oxidative stress, inflammation, apoptosis and endocrine disruption function as interconnected signalling networks rather than independent processes [13]. Co-exposure to arsenic and microplastics may enhance ROS generation, leading to increased oxidative stress. The resulting redox imbalance can activate NF-κB-mediated inflammatory signalling while simultaneously promoting p53-dependent apoptotic pathways and suppressing steroidogenic function. As a result, these interconnected molecular pathways contribute to enhanced reproductive toxicity [13,44,48,49,54]. The major signalling pathways, molecular markers, exposure types and biological outcomes associated with arsenic- and microplastic-induced reproductive toxicity are summarized in Table 1.

Therapeutic Potential and Molecular Mechanisms of Imperatorin

Natural Sources and Extraction: Among naturally occurring phytochemicals, imperatorin has emerged as a compound of interest because of its diverse biological activities, particularly its antioxidant, anti-inflammatory, anti-apoptotic and cytoprotective effects [16,17]. Plant-derived bioactive compounds, including furanocoumarins, have gained increasing attention because of their diverse pharmacological activities and potential translational relevance [57]. Imperatorin may protect cells from damage induced by environmental pollutants under conditions of cellular stress, indicating it may have the potential to preserve the structural and functional integrity of reproductive tissues [58]. Activation of the Nrf2/Keap1 signalling pathway has been linked to elevated expression of antioxidant enzymes, including SOD, CAT, GPx, GST and HO-1. Furthermore, inhibition of NF-κB signalling has been associated with reduced inflammatory activity and lower levels of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1β [16,58]. Imperatorin may also influences mitochondrial apoptotic pathways by promoting Bcl-2 expression together with reduced levels of Bax and caspase-3, thereby supporting testicular integrity and normal spermatogenic function under environmental toxicant exposure under arsenic- and microplastic-induced toxic conditions [17]. Natural sources of imperatorin include medicinal plants belonging to the Apiaceae and Rutaceae families, such as *Angelica dahurica*, *Angelica archangelica*, *Cnidium monnieri*

Table 1: Signalling pathways, molecular markers, and biological outcomes associated with arsenic and microplastic exposure in male reproductive tissues

Pathway	Change	Key Markers	Main Outcome	Evidence	Refs.
Nrf2/Keap1	↓ Downregulated	HO-1, SOD, CAT, GPx	Oxidative stress; impaired antioxidant defence	Human, animal	[24,28,44]
NF-κB	↑ Activated	TNF-α, IL-6, IL-1β	Inflammation; blood–testis barrier disruption	Rodent	[13,48,50]
p53	↑ Upregulated	Bax, Caspase-3	DNA damage; apoptosis	Animal, in vitro	[36,45,49]
Steroidogenesis	↓ Downregulated	StAR, 3β-HSD, 17β-HSD	Reduced testosterone; impaired spermatogenesis	Rodent	[40,54–56]

and *Peucedanum praeruptorum* [16,59]. It is commonly extracted using solvent-based extraction methods followed by chromatographic purification techniques [60].

Regulation of Oxidative Stress and Redox Homeostasis

One of the major factors involved in reproductive toxicity associated with arsenic and microplastic exposure is oxidative stress. Antioxidant effects of imperatorin have been linked to regulation of the Nrf2/Keap1 signalling pathway, through which the cellular antioxidant defence system is strengthened by increased production of enzymes such as SOD, CAT, GPx, GST and HO-1 [61,62]. As a result, excessive accumulation of ROS, lipid peroxidation and mitochondrial damage may be attenuated. Suppression of NADPH oxidase-dependent oxidative stress has been reported, while regulation of mitogen-activated protein kinase (MAPK) pathways, including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38 MAPK, has also been associated with imperatorin treatment. Through these mechanisms, maintenance of cellular redox homeostasis may be facilitated under toxicant-induced stress conditions [63,64].

Modulation of Inflammatory Signalling

Regulation of inflammatory signalling has been identified as an important mechanism related to the protective actions of imperatorin. Imperatorin treatment may suppress NF-κB nuclear translocation followed by the inhibition of IκB degradation and downregulation of pro-inflammatory cytokines, TNF-α, IL-6 and IL-1β. Through attenuation of inflammatory responses, preservation of Sertoli cell integrity, maintenance of blood-testis barrier function and reduction of chronic inflammatory damage within reproductive tissues may be preserved [65,66].

Anti-Apoptotic and Cytoprotective Mechanisms

Excessive oxidative stress and mitochondrial dysfunction activate intrinsic apoptotic pathways, leading to germ cell loss and seminiferous tubular degeneration. Imperatorin exerts anti-apoptotic effects by increasing Bcl-2 expression while suppressing Bax, caspase-3 and caspase-9 activation. Through modulation of apoptotic pathways, mitochondrial integrity may be maintained and cytochrome c release may be lessened, thereby reducing testicular cell damage during toxicant exposure [67-69].

Regulation of Ferroptosis and Mitochondrial Function

Recent studies indicate that imperatorin may help counteract ferroptosis by reducing oxidative damage and supporting cellular antioxidant defence mechanisms. Imperatorin modulates the aryl hydrocarbon receptor/Nrf2/HO-1/glutathione peroxidase 4 signalling axis, thereby reducing lipid peroxidation and preserving mitochondrial integrity during oxidative stress [70,71].

Support for Endocrine and Steroidogenic Function

Imperatorin may help preserve reproductive endocrine function under toxicant-induced oxidative stress conditions through its antioxidant and anti-inflammatory activities. Maintaining the oxidative stress balance and mitochondrial dysfunction may indirectly support steroidogenic pathways, Leydig cell function, testosterone synthesis and spermatogenesis [16,17,53].

Pharmacokinetics and Safety Profile

Imperatorin demonstrates favourable membrane permeability because of its lipophilic structure and undergoes metabolism primarily through CYP450-mediated pathways. Although generally well tolerated in experimental studies, its bioavailability, long-term safety, dose-response profile and potential phototoxicity require further investigation [72,73].

Potential Relevance in Environmental Reproductive Toxicology

The multifunctional molecular mechanisms of imperatorin support its potential therapeutic relevance in reproductive damage induce by arsenic- and microplastic-induced reproductive toxicity. Preservation of testicular structure and reproductive function may be achieved through modulation of multiple interconnected pathways involving oxidative stress, inflammation, apoptosis, ferroptosis and impaired steroidogenesis during environmental toxicant exposure [58,61,71,74]. The major molecular targets, pathway-level effects and biological outcomes associated with imperatorin are summarized in Table 2.

Research Gaps and Future Perspectives

Despite increasing evidence regarding arsenic- and microplastic-induced reproductive toxicity, several limitations remain. Current knowledge of co-exposure is mainly based on laboratory-based animal and cell culture studies conducted at comparatively high concentration of doses, which may not accurately reflect the complex exposure conditions experienced by humans in the environment. Comparisons among studies remain challenging because of their substantial differences in microplastic size, polymer composition, surface characteristics and exposure protocols. Furthermore, direct

Table 2: Molecular targets and protective effects of imperatorin against toxicant-induced cellular injury

Pathway	Molecular target(s)	Effect of imperatorin	Biological outcome	References
Nrf2/HO-1	Nrf2, HO-1	Activation	Enhanced antioxidant defence	[61,62]
Oxidative stress	ROS, NADPH oxidase	Suppression	Reduced ROS generation and lipid peroxidation	[17,65]
NF-κB	IκB, NF-κB	Inhibition	Suppressed inflammatory cytokine expression	[63–66]
MAPK	ERK, JNK, p38	Modulation of phosphorylation	Attenuated stress signalling	[63,66]
Apoptosis	Bax, caspase-3, caspase-9	Anti-apoptotic modulation	Regulation of programmed cell death	[67,68]
Ferroptosis	GPX4, SLC7A11	Regulation	Reduced lipid peroxidation and ferroptotic injury	[70,71]

human evidence on the reproductive effects of combined arsenic and microplastic exposure is not much explored. Even though imperatorin has shown potential protective effects in experimental model, more investigations are to be carried out to clarify its pharmacokinetic behaviour, long-term safety, dose-response relationship and potential clinical applicability. Future research should focus on environmentally relevant co-exposure models, standardized microplastic characterization, biomarker identification, omics-based approaches and clinical evaluation of imperatorin as a potential protective agent against environmental reproductive toxicity.

CONCLUSIONS

Arsenic and microplastics are important environmental toxicants that impair male reproductive function through oxidative stress, inflammation, mitochondrial dysfunction, apoptosis, endocrine disruption and steroidogenic impairment. Combined exposure may further exacerbate reproductive toxicity by enhancing reactive oxygen species generation and dysregulating key signalling pathways, including Nrf2/Keap1 and NF-κB. Although experimental studies suggest that imperatorin possesses antioxidant, anti-inflammatory, anti-apoptotic and cytoprotective properties that may mitigate toxicant-induced testicular injury, the current evidence is largely limited to preclinical models. Therefore, further mechanistic, dose-response, safety, translational and clinical studies are required before any therapeutic role of imperatorin in environmental reproductive toxicology can be established.

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