Toxicology Consequences of Heavy Metal Exposure on Male Fertility

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SUMMARY

Exposure to environmental toxicants such as heavy metals is significantly known for their contribution to numerous health issues; particularly reproductive health is being affected most. Disturbed male reproductive potential and toxicity have pressing concerns now-a-days. Therefore, it is critical to thoroughly investigate, understand, and assess their influence on reproductive toxicity in males. Thus, disrupted redox equilibrium and oxidative stress are major features through which toxicants induced alterations in sperm parameters leading to the affected male reproductive system can be checked. Additionally, epidemiological studies of human populations have shown a strong correlation between heavy metals exposure and several reproductive disorders. However, biomarkers have appeared as valuable tools for the assessment of heavy metal reproductive toxicity, but advanced techniques are required for precise evaluation. To alleviate the detrimental effect of various heavy metals, international policies and remediation technologies have been employed. Despite this, challenges are still arising while resolving these issues effectively. This book chapter will explore potential avenues for future research to address heavy metal-induced reproductive toxicity, including the development of novel targeted therapeutic approaches, diagnostic tools, and biomarkers for better management of these toxicants.

INTRODUCTION

Heavy metals play a significant role in male infertility even at low concentrations; accumulation of bismuth, lead, arsenic, mercury cadmium and other metals has a profound detrimental effect on the reproductive system. Therefore, based on on their pathophysiological effects, trace metals can be classified into two subgroups: first, there are microelements that are necessary for life (such as copper, arsenic, chromium, and cobalt) and are involved in critical metabolic processes, whereas second group constitutes toxic microelements to living things, even at low concentrations, like Cd, Hg, Cr, and Pb. Consequently, these metals have major negative effects on human health; one of them is infertility in men (Bhardwaj et al., 2021).

DEFINITION OF HEAVY METALS

There is still disagreement over the precise definition of "heavy metal" and which natural or chemical components fall under this category. Thus, heavy metals are those metals or metalloids that have potential to be hazardous to the environment, animals, and humans. Leading examples of "heavy metals" are cadmium (Cd), lead (Pb), arsenic (As) and mercury (Hg). Therefore, these are not only significant environmental contaminants but also have relatively large atomic numbers, atomic weights, and densities (>5g/cm^3) (Ilieva et al., 2020).

COMMON SOURCES OF HEAVY METALS EXPOSURE

Prevalence of heavy metal exposure is not only through one's lifestyle choices or place of employment but also due to eating or drinking contaminated food or water. Thus, because of widespread distribution of heavy metals, environmental concerns have gained attention.

Food exposure

Canned foods are a common source of heavy metals thus, includes meat, fish, drinks, fruits, and vegetables Generally, contamination may occur through migration of hazardous heavy metals from metallic packaging material or naturally occurring contaminated foodstuffs (Hamarcu et al., 2010). In addition to this, Solder, which is also used in canning process serves another way of contaminated food because of their manufacturing from aluminum, chromium-coated steel, or tinplate.

Environmental exposure

Exposure to environmental contaminants, such as smoke from cigarettes, burning of fossil fuels, and emissions from metal industry during smelting, refining, and electroplating processes, results in extremely high levels of heavy metals, which can disrupt a person's reproductive system (Sengupta et

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al., 2017). Additionally, these environmental contaminants have transgenerational effects which may influence future generations (Wirth & Mijal, 2010).

Occupational exposure

Construction site workers are at risk of exposure to lead paints, asbestos-containing materials, and other heavy metals. Moreover, employees in agricultural fields may be exposed to pesticides that contain chromium, lead, etc., and those who work in laboratories and other environments where heavy metals are present in reagents or medical devices. Therefore, have a significant risk of developing reproductive dysfunction (Ashiru & Odusanya, 2009).

SIGNIFICANCE OF THE ISSUE

Increased prevalence of environmental toxins has detrimental impact on male fertility due to excessive production of ROS. Studies have shown that amount of lead in blood was directly correlated with a decrease in sperm count (oligospermia), motility, and teratospermia (abnormal increase in sperm production) among lead exposed workers, after analyzing their sperm counts (Telisman et al., 2000). Moreover, investigations conducted on humans have revealed that welders' exposure to chromium is high therefore, have lower-quality sperm (Sheiner et al., 2003). Additionally, heavy metal exposure is responsible for testicular function disruption because of their accumulation in testes. Although it has been evaluated that fetal exposures might have more detrimental effects on future spermatogenesis and general development as compared to exposure during adulthood (Currie et al., 2011).

HEAVY METALS AND MALE REPRODUCTIVE SYSTEM

Overview of male reproductive system

Male reproductive system is considered as intricate and complex system that produces spermatozoa. It consists of internal and external organs. Testis, epididymis, vas deference, seminal vesicle and prostate gland are the internal genitalia, whereas scrotum and penis are known to be external genitalia (Durairajanayagam et al., 2015).

Sperm production and maturation/ spermatogenesis

Spermatocytogenesis and spermiogenesis are two essential steps in the process of spermatogenesis. Spermatocytogenesis (sperm production) takes place in seminiferous tubules in the presence of testosterone and follicle-stimulating hormones. While spermiogenesis—the process by which sperms become functionally mature—occurs gradually in epididymis where the sperms reside (Mawhinney & Mariotti, 2013).

Heavy metals implicated in male fertility issues

Heavy metals such as cadmium, lead, mercury, arsenic are most alarming metalloids, therefore, cause reproductive toxicity because of having influence on the HPG axis, testicular function, spermatogenesis, HPG axis and sperm processing (Patwa et al., 2022).

Sources of lead exposure

Lead is frequently used in different construction sites (such as in ceramics), cosmetics, toys and industrial fields, for instance, fuel, printing, galvanization and paint industry therefore may dissolve through pipes into drinking water or directly from occupational places (Gerhard et al., 1998).

Effects on sperm quality and quantity

Lead exposure even at low concentration poses serious risk on reproduction including reduced sperm motility, lower semen concentration and viability in workers in smelting industries (Ashiru & Odusanya, 2009). Furthermore, research involving lead exposure to experimental animals has revealed macroscopic alterations in testes, which disrupt sperm production and result in decreased sperm counts. Additionally, decreased weight of ventral prostate, seminal vesicles, and epididymis, changes in semen quality and testicular atrophy have all been observed (Bonde, 2010; Akbar & Ijaz, 2024).

Male mice having intrauterine exposures had lower amounts of neonatal sex steroids consequently leading to detrimental effects on male sexual development. Furthermore, high levels of lead exposure throughout male puberty, caused decreased plasma LH and reduction in testosterone concentrations, indicating secondary effects related to hypothalamic-pituitary axis, with further changes in FSH levels resulting in lower-quality sperm (Telisman et al., 2007).

Occupational and environmental sources of cadmium exposure

Cadmium is obtained from fertilizers containing phosphates used in agricultural fields where rice and fish have been grown in contaminated groundwater. Furthermore, over 1,500,000 workers in the United States alone are impacted by cadmium exposure annually, making it a highly pertinent issue, released from Batteries, paint manufacturing, rubber processing, insecticides, and galvanizing industries (Alaee et al., 2014). Additionally, it has a half-life of 10–30 years and is persistent and bio accumulative in the environment. Cadmium is ingested with food, such as fish and rice from areas with contaminated groundwater (Chabchoub et al., 2021).

Impact on testicular function and sperm parameters

The effects of high dosage of Cd on reproduction have been extensively studied in in-vivo experimental animal models. The results showed increased expression of inflammatory markers (TNF-α, NF- κB, COX-2, heme oxygenase-1, and iNOS) in the testis, which led to seminiferous epithelium cell vacuolization, interstitial tissue edema and hemorrhage followed by widely distributed necrosis. These pathological alterations in testes impair the process of spermatogenesis. Furthermore, positive correlation has been demonstrated by epidemiological research between Cd and male infertility. Male exposure to cadmium decreased testosterone level, LH, and FSH secretions, which led to dysfunctional Sertoli cells, the source of sustenance for sperm cells, and finally stopped spermatogenesis (López-Botella et al., 2021).

Mercury exposure

There are three types and routes of mercury exposure: (1) organic mercury, which comes from wood preservatives, seafood, fish, herbicides and fungicides (2) inorganic mercury, comes from dermatological and antiseptics products; and (3) elemental mercury, which comes from fluorescent tubes, batteries, and thermometers (Drasch et al., 1997).

Mercury effects on sperm motility and morphology

Higher levels of mercury have been associated to male subfertility, according to a recent systematic review by Martinez et al. (2014). Due to disruptions in sperm flagella function which results in decreased sperm motility, makes them unable to swim efficiently toward eggs for fertilization (Martinez et al., 2014). Furthermore, Human sperm treated with Hg (at concentrations ranging from 10.0 to 160.4 mg/L) have shown changes in number of bio-physiological parameters. These changes include sperm DNA breaks and membrane lipid peroxidation, which cause structural defects in sperm, consequently, reduce their motility and viability thus compromises male fertility.

Moreover, a comprehensive investigation involving 111 males from Hong Kong who were infertile has revealed a connection between high Hg concentrations (mean level 22.1 ± 2.0 nmol/L) in seminal fluid and anomalous sperm motility and sperm morphology mainly abnormalities in the head and midpiece (Wdowiak et al., 2015).

Mechanisms of heavy metal-induced male infertility

Oxidative stress: Oxidative stress is a condition that causes an imbalance between ROS production and the ability of the body to detoxify ROS through antioxidant systems. In addition to causing dangerous events like oxidative DNA damage and lipid peroxidation, it also affects intracellular signal transduction regulation and physiological adaptation processes (Yoshikawa & Naito, 2002).

Generation of reactive oxygen species (ROS): All metals are redox elements; thus, they can produce ROS or OS, which can disrupt cells in many biological systems. However, half of infertile men have OS which highlights the role of heavy metals play in activating transduction signaling pathways to either initiate defensive responses or cause oxidative damage in different cells and tissues (El-Demerdash et al., 2004). Thus, in addition to damaging nucleic acids, preventing DNA repair, starting membrane lipid peroxidation, and inhibiting the synthesis of sulfhydryl antioxidants. ROS can also result in inflammation in several organs (Sheweita et al., 2005). Including testes leads to long term reproductive dysregulations (Fig 1). For instance, in recent experimental work, long-term exposure to Pb and Cd in rats resulted in increased lipid peroxides caused decreased levels of antioxidants such as peroxidase, SOD, catalase, GPx, and GR in testes thus leading to disrupt reproductive processes during hormonal regulations or spermatogenesis (Ilieva & Sainova, 2022).

Damage to sperm DNA and cellular structures: Oxidative stress produces high levels of ROS which oxidizes sperm membrane flexibility and alters the DNA integrity of sperm. This alteration results in abnormal sperm function, such as motility, morphology, and sperm viability thus leading to failure in fertilization (Martinez et al., 2014). Numerous studies have demonstrated the relationship between both essential and nonessential metals causes alterations in male reproductive health including decreased semen quality and DNA integrity at levels above particular thresholds in animals. Thus, these metals include chromium, cobalt, copper, iron, manganese, molybdenum, nickel, selenium, tin, tungsten, and zinc (Zhou et al., 2016).

Disruption of endocrine signaling: Majority of heavy metals function as EDCs, easily mimicking gonadal sex hormones and having the capacity to attach to endocrine receptors to obstruct hormone-generated signals. Therefore, the reproductive system is most susceptible to exposure to EDCs thus, arsenic exposure, for instance, may be the cause of gonadal dysfunction by reducing testosterone synthesis causing necrosis and apoptosis. Moreover, a lot of recent investigations have demonstrated that exposure to arsenic substantially reduces sperm quality, erectile dysfunction, and eventually male infertility (Monneret, 2017).

Interference with hormonal regulation: Regulation of spermatogenesis is greatly influenced by estrogens, especially estradiol, or E2, and any disturbance in these levels or their downstream pathways can result in infertility in men. Therefore, it has been reported that in the testis of rats, Pb markedly reduced the expression of Cyp19 (P450 arom) and reduction in P450 arom enzyme activity could be the assurance of this downregulation at the messenger RNA level. Thus, P450 arom enzyme inhibition is either by forming a complex with cysteine residues or inhibiting ferroxy radical consequently raises androgen (testosterone) and reduces E2 in testis (Anyanwu & Orisakwe, 2020).

Impact on reproductive hormones: Heavy metals cause disruptions in the neuroendocrine system which results in hormonal abnormalities by inhibiting the release of Inhibin B from Sertoli cells or androgens from Leydig cells (Li et al., 2015). Several studies described the impact of heavy metals on hormone levels. For instance, FSH and testosterone levels were found to be lower in the infertile group when exposed to lead, cadmium, copper, and zinc as compared to the control group thus it showed that there is a substantial and positive correlation between elevated blood lead and FSH levels leading to poor quality semen (Chabchoub et al., 2021).

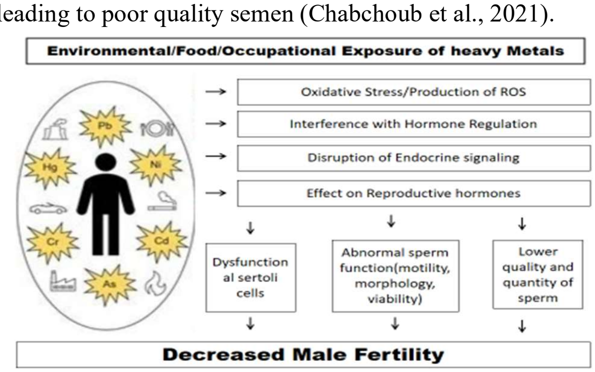

Fig 1. Mechanism of metal induced male infertility

EPIDEMIOLOGICAL STUDIES AND EVIDENCE

Studies on human and animal experimentation have shown that the prevalence of infertility has risen from 8-15% in industrialized nations during the previous 20 years.

Human population studies

Experiments have been performed in order to observe the impact of cadmium exposure on human male fertility especially on spermatozoa acquiring through ejaculation. Therefore, two primary studies assessed the impact of Cd treatment on spermatozoa. In the first research, 150 men with idiopathic infertility and 60 fertile men provided normal semen samples then treated with Cd. Thus, it was discovered that Cd considerably reduced sperm motility in a time-dependent manner. Additionally, a significant dose-dependent and time-dependent drop in sperm vitality was also noted. Whereas, results of the second study demonstrated that Cd exposure have changed activity of important enzymes such as glucose-6-phosphate isomerase, Mg 2+-dependent ATPase, succinic acid dehydrogenase fructose-1,6-diphosphatase glycogen phosphorylase and glucose-6-phosphatase involved in the metabolism of spermatozoa thus affected human semen quality (Pant et al., 2013).

Animal models and experimental research

In vivo studies on animal models have investigated the impact of Cd exposure on male reproduction in animals thus provided evidence of detrimental aspects of Cd on reproductive functioning leads to infertility. These studies showed that Cd is gonadotoxic and spermiotoxic when given as either a single high dose or repeated low doses. Furthermore, it has potential to cause long-lasting and irreversible harm to reproduction such as severe damage to proliferating and differentiating Sertoli cells, which are vital for development of functional testis and spermatogenesis if animals are treated during fetal development, in their early years of life, or before reaching puberty. Moreover, another study has shown that rats were administered orally 5 mg/kg of $CdCl_2$ every single day for almost 30 days, resulted significant decline in testes and epididymis weight, sperm motility, concentration as well as abnormal spermatozoa morphology or dead spermatozoa (El-Demerdash et al., 2004; Hayat et al., 2024).

RISK ASSESSMENT AND REGULATORY FRAMEWORK

Current regulatory limits for heavy metals

WHO, EPA, FDA, OSHA, and other credible international agencies have established maximum contamination levels or permitted limits for specific heavy metals and/or ions, as shown in Table 1.

International standards

Human reproductive health and fertility can be greatly impacted by environmental exposures. Thus, in order to protect the population from environmental risk, advance public knowledge and education about fertility and environment have been established by appropriate laws and regulations by controlling and limiting sources and amounts of environmental. Therefore, some of these guidelines and regulations are as follow:

- An international agreement (Minamata Convention on Mercury) attempts to shield the environment and human health from harmful effects of mercury, a hazardous element that can harm a developing child's or fetuses' reproductive development (Coulter, 2016).
- World Health Organization's (WHO) Air Quality Guidelines are international guidelines that offer suggestions for mitigating the negative effects of air pollution on human health (Kan, 2022).
- A comprehensive framework known as European Union (EU) Regulation on Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) attempts to identify and control compounds of extremely high concern. Additionally, REACH assures safe use of chemicals in the EU market (Petry et al., 2006).

Discrepancies and challenges

Regulating and reducing environmental threats to fertility remains a challenging task, even with the implementation of numerous recommendations and legislation. Several challenges include absence of uniform standards and guidelines for calculating and evaluating environmental exposures and their effects, limited high-quality data on relationship between reproductive outcomes and environmental exposures across various populations and geographical regions, inadequate understanding of thresholds, dose-response relationships, windows of sensitivity, and interactions between various environmental factors on fertility. Additionally, lack of proper consideration of genetic vulnerability, epigenetic alterations, and individual variability that may affect an individual's reaction to environmental exposures. Thus, in order to overcome these challenges public education and awareness campaigns are essential for prevention and minimization of environmental threats to fertility (Skakkebaek et al., 2022).

Critical evaluation of risk assessment methodologies

Methods for risk assessment have been employed to assess the harmful impact of environmental contaminants on human health. Therefore, the panel on contaminants in food chain (CONTAM) of EFSA recently investigated CSAF or (PB-TK) model advised by WHO for risk assessment of cadmium in food and set a PTWI for humans.

FAO/WHO, JECFA, ILSI and EFSA organized an international conference for the introduction of (MOE) approach. Thus, MOE is defined as ratio of human intake data to a certain point on a dose-response curve for adverse effects found in animal research during the absence human epidemiology data. Therefore, BMD and BMDL are recommended reference points for characterizing the dose-response relationship. Moreover, using this methodology; EFSA has carried out a risk evaluation for the metalloid arsenic (O'Brien et al., 2006). In addition to these methodologies, (US-EPA), Norway, and European Union have employed linear extrapolation (LE) technique for industrial chemicals, non-threshold carcinogens, and carcinogens whose mode of action is unknown (Barlow et al., 2006).

Exposure assessment

Exposure assessment refers to "qualitative or quantitative assessment of intake of physical, biological and chemical agents through food or from other relevant sources. Thus, exposure assessment considers both frequency and quantities of chemical pollutants in human diet used by approved analytical methods, as well as patterns of human consumption for many accessible food categories (Dorne et al., 2009).

HQ is defined as ratio of the metal's average daily dose (ADD) to its reference dose (RFD) along the same exposure pathway, therefore, evaluate the harm of heavy metals to human health by using three distinct exposure pathways—inhalation, ingestion, and skin contact. Additionally, RFD is maximum daily dose of a metal at a certain exposure pathway that doesn't cause sensitive people to have any noticeable symptoms over the course of their lifetime (Qing et al., 2015).

Hazard identification and dose-response relationships

Hazard identification is defined as "identification of biological, chemical, and physical agents presents in a particular food or group of foods and have adverse health effects. However, the major goal of hazard identification is to analyze all of the information that is currently available regarding the toxicity and mode of action (genotoxic/non-genotoxic) of the specific metal. Therefore, in order to effectively identify hazards, toxicological studies involving animals—primarily mice, rats, rabbits, and dogs ideally follow international guidelines and good laboratory practices (GLPs), and these studies can be acute, sub-chronic, chronic or focused on more specialized endpoints (such as immunotoxicity, reproductive, neurotoxic and developmental toxicity). Thus, epidemiological human data were available for the majority of heavy metals (lead, cadmium, methylmercury mercury) and metalloids (arsenic) for the establishment of health-based recommendation values.

Hazard characterization (dose–response assessment) consists of ''qualitative or quantitative evaluation of nature of adverse effects due to chemical, physical and biological agents present in food". Thus, BMD is preferred over LOAEL/NOAEL approach because it uses more dose-response data from observational epidemiological studies or through sensitive species of experimental animals in order to estimate the shape of dose-response relationship for a particular endpoint that act as risk for particular toxicant (Gourmelon & Delrue, 2016).

Table 1. Regulatory limit of selected heavy metals (Suparma et al., 2011)

Heavy metals	WHO limits (ppm)	EPA limits (ppm)	FDA limits (ppm)	OSHA limits (µg/m3)
Arsenic	0.05	0.01	0.01	10
Barium	0.7	2.0	2.0	0.5
Cadmium	0.005	0.005	0.005	5
Chromium	0.05	0.1	1	1.0
Lead	0.05	0.15	0.005	50
Mercury	0.001	0.002	1	0.05
Selenium	0.04	0.05	2	0.2
Silver	0.1	0.1	0.1	0.01

MITIGATION AND PREVENTION STRATEGIES

Occupational safety measures

In order to prevent workers at coke oven plants from developing occupational cancer as a result of heavy metal exposure, we need to redesign the engineering process, start thorough medical monitoring, educating employees about the advantages of prohibiting smoking and raise awareness of workplace safety laws. Therefore, it is critically necessary to extend producer responsibility, internalize costs, and apply the precautionary principle generally. Furthermore, OSH specialists in private and public sectors should support these initiatives in order to fulfill their social responsibility to protect the health of their employees. Moreover, numerous food substances have reportedly had their suppressive properties regarding carcinogenesis in each stage such as initiation, promotion, and progression (Kong, 2012).

Personal protective equipment

A preventive strategy to reduce the dust containing metals in our houses is by replacing our carpets with water-cleanable floor coverings. Moreover, in order to stop tiny metal-loaded particles from being released back into the atmosphere, vacuum cleaner equipped with a HEPA filter having cyclone technology is used to capture particles as small as 0.3 ml (Yiin et al., 2002).Therefore, there isn't any scientific evidence for majority of these preventive interventions except one that has been reported. For example, studies have indicated a 40% decrease in cadmium excreted urine after 10 years of replacement of cadmium containing soil in 50 individuals (Kobayashi et al., 2008).

Remediation techniques for heavy metal decontamination

Many techniques for treating and eliminating heavy metals have been developed in last few decades including chemical precipitation, ion exchange, solvent extraction, membrane process, adsorption, and biological removal which includes phytoremediation and removal of metals using microorganisms as shown in Fig 2. Metals can be chemically precipitated by adding coagulants, such as lime, alum, iron salts, and organic polymers. Thus, majority of metals are precipitated chemically by Sulfide (S)2-, carbonate (CO3)2-, and hydroxide (OH) (Wuana et al., 2010).

Ion exchange resins are specific to particular metal ions such as H+ or Na+ for cations and majority of cation exchange resins are synthetic polymers with an active ion group, like SO3H. Therefore, natural minerals like zeolites can be employed as ion exchange medium but the affinity of modified zeolites, such as zeocarb and chalcarb are higher for metals such as Ni and Pb (Pakzadeh & Batista, 2011**)**.

Phytoremediation or "botanical bioremediation", is gaining popularity due to great potential for cleaning up contaminated water and soil. Since different species and cultivars within a species have different mechanisms of ion uptake based on their anatomical, physiological morphological and genetic characteristics. Therefore, the term "phytoremediation" actually refers to a diverse collection of plant-based technologies that use either genetically engineered or naturally occurring plants for cleaning contaminated environments. Thus, on the basis of remediation mechanism, there are several phytoremediation techniques such as phytofilteration, phytovolatilization, phytoextraction and phytostabilization. Moreover, certain genera and families, such as Cu and Co (Lamiaceae, Scrophulariaceae), Ni (Brassicaceae–Thlaspi), *T. rodundifolium*, *Ipomoea alpine* and *T. caerulescens* are recognized as potential sources of certain metal hyperaccumulators (Gabos et al., 2009). Adsorption is the process of adhering one or more ions to the surface of another solid or liquid. Therefore, Adsorption is an affordable cleaning technique for metal removals and water reuse demands of today particularly in situations where sorbents are readily available and inexpensive (Banerjee et al., 2014).

Reduction of heavy metal emissions

The two main possible control strategies for reducing emissions of Cd, Pb, and Hg are primary measures like low-emission process technologies and fuel or raw material substitution and secondary measures like off-gas cleaning and fugitive emission control. Thus, metal emissions can be minimized by handling, storing and discharging raw materials and byproducts inside fully enclosed structures that have appropriate ventilation and de-dusting facilities. Furthermore, improving energy-conservation and energy conversion efficient techniques will lead to a decrease in heavy metal emissions because of less fuel required. Moreover, emissions of heavy metals like mercury would be greatly reduced if natural gas or other fuels with low heavy metal concentration were burned instead of coal. In addition to all these strategies, highly efficient integrated gasification combined-cycle (IGCC) power plant technology can result in lower emissions as compared to large-scale solid fuel-based power production that does not employ IGCC (Park et al., 2021).

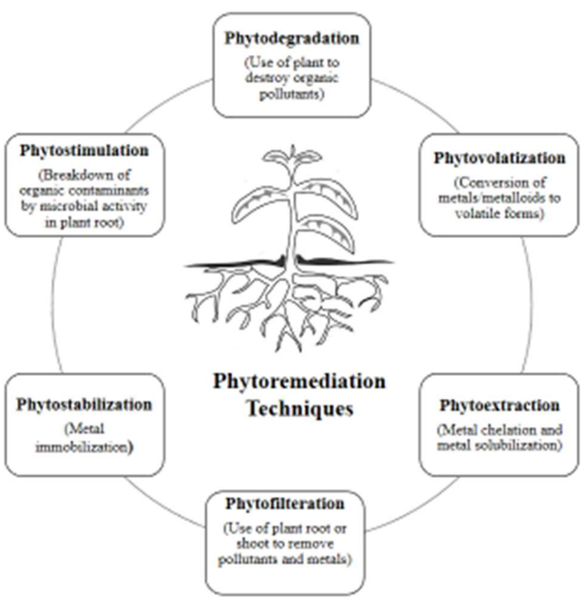

Fig 2. Schematic representation of phytoremediation technique for metals removal

FUTURE DIRECTIONS IN RESEARCH

Identification of novel biomarkers

Recent advancements in non-coding RNAs, such as piRNAs and miRNAs, have identified several pathways that regulate the development of male germ cells. Thus, abnormal expression of these RNAs leads to sperm arrest and apoptosis, which worsens male infertility. Furthermore, Zhou et al. (2017) demonstrated that decreased miR-27a suppress CRISP2 protein expression in post-transcriptional regulation, clinically involve in ATZ and male infertility through affecting sperm morphology and motility. As a result, it indicates a useful biomarker for metal-induced toxicity in male reproductive system (Zhou et al., 2017).

Highly controlled expression of lncRNAs during spermatogenesis was confirmed by analysis of pure spermatogenic cells. Therefore, strand-specific RNA-seq method was used to identify changed lncRNA expression in Cd-treated testes and spermatozoa thus this dysregulation in spermatogenesis results in male infertility. piRNAs may have function in spermatogenesis because they are mostly expressed in pachytene spermatocytes and spermatids in mammalian testis. Thus, according to Cui et al. (2018) men with low sperm counts have downregulated expressions of piR-31704 and piR-39888 in spermatozoa.

Early indicators of heavy metal-induced fertility issues

The presence of 8-hydroxy-2-deoxyguanosine (8-OHdG), is thought to be a sensitive and accurate biomarker of cadmium-toxicity-induced oxidative DNA damage in sperm. Additionally, it has been discovered that high levels of 8-OHdG are adversely connected with sperm motility, density, number, and abnormal sperm morphology. Furthermore, main enzyme involved in catalyzing the condensation of two molecules of ALA into porphobilinogen is d-aminolevulinic acid dehydratase (d-ALAD) may be utilized as possible biomarkers for lead toxicity whose activity is severely inhibited by blood lead levels greater than 20 lg/dL (Gholinezhad et al., 2020). Moreover, Matalliotakis et al. (2006) observed idiopathic infertility patients had higher level of PMN elastase, IL-6, IL-8, IL-1b, TNFa IL-18 in seminal plasma thus may be used as a diagnostic marker in male genital tract related toxicity.

Advancements in diagnostic tools

Advanced diagnostic techniques like fluorescence in situ hybridization, SEM, ELISA, TTS PCR, ultrasound scanning, and ICP-AES are used to assess the toxicity of metals on reproduction. To measure the size of testicles, epididymal cysts, and other genital diseases, a scrotal ultrasound scan of testes has been used. Furthermore, XY probes were used in Fluorescence in Situ Hybridization (FISH) to detect sex chromosomal abnormalities and mosaicism and (ELISA) was used to measure levels of lactate, inhibitor B, and (AMH) in seminal plasma.

Energy Dispersive X-ray Spectrometer (EDXS) and Scanning Electron Microscope (SEM) were used to analyze metals in seminal cells and seminal detritus based on electromagnetic radiation interactions with matter, thus X-rays are released when charged particles strike the matter. For this purpose, 1ml of semen was fixed in a glutaraldehyde solution for two hours, supernatant was discarded after centrifuged for five minutes at 10950g and pellet was rinsed with phosphate buffer saline then coated with metals, two Random areas were chosen for X-ray exposure, thus released energy was measured thus spectrum showing peaks indicates qualitative and quantitative assessment of elements.

Moreover, serum metal concentrations were assessed with Inductively Coupled Plasma-Atomic Emission Spectrometry (ICP-AES). Therefore, hydrogen peroxide and nitric acid were used to breakdown the serum sample, with the help of microwave radiation. Once the samples had cooled, they were diluted to make a 10 ml clear solution thus resultant sample solutions were filtered and ICP software (version 5.2, Horiba Jobin Yvon, Longjumeau, France) was used to choose a wavelength for each element from a predetermined set. Furthermore, GC, LC and most recently capillary electrophoresis (CE) are used for metal detection. For instance, the most often used techniques for arsenic are LC separation, ICP-MS, or AAS. Additionally, many analytical techniques have been proposed for the determination of methylmercury in the situation of mercury detection, such as GC coupled with atomic fluorescence spectrometry (GC-AFS) and LC coupled to ICP-MS (Halder et al., 2014).

Targeted therapeutic approaches

Natural products and medicinal plants have been produced to lessen heavy metal induced toxicity during experimentation on laboratory animals. Therefore, traditional or plant-based medicine appears to have many benefits such as effectiveness, low incidence of severe adverse reactions, and relatively low cost (Bhattacharya, 2018).

Garlic is used as a medicinal herb and contains a variety of vital nutrients and antioxidants that protect the body from harmful effects of heavy metals, including flavonoids, sulfur compounds, allicin, and selenium. However, commercial garlic is sold in a variety of forms, including capsules containing garlic oils, tablets containing aged garlic extracts, liquid, and garlic powder. According to Sajitha et al. (2010) spermatogenesis is improved in lead nitrate exposed humans and animals when ripened garlic extract is taken orally (Sajitha et al., 2010). An active ingredient of turmeric, curcumin, is a yellow-colored polyphenolic compound derived from Centella asiatica and Curcuma longa plants also referred as Indian pennywort. Curcumin is well-known for its several medical uses as well including the treatment of metal toxicity (Agarwal et al., 2010).

Developing interventions to mitigate heavy metal toxicity

Nanotechnological methods have gained attention due to potential advantages in elimination of negative effects of heavy metals by enhanced delivery formulations through liposomes, micelles, phospholipid complexes, and certain others (He et al., 2019). Nanoencapsulation of antioxidants through solubilization improves the bioavailability and biodistribution of medicinal herbs that are poorly soluble. Numerous vehicles, such as solid nanoparticles, micelles, lipid polymer vesicles (polymersomes), and nanohydrogels, have been developed for the encapsulation and delivery of herbal medicines. Later on, biodegradable polymeric nanoparticles have garnered a lot of interest include gelatin, chitosan, albumin, sodium alginate, gums (acacia, guar, etc.), and others made by utilizing polymers and surfactants such as chitosan, polylactic-co-glycolic acid, and alginic acid, (Zigoneanu et al., 2008).

CONCLUSION

Exposure to heavy metals toxicity has adverse effects on male reproductive system causing disruption in testicular germ cells, Leydig cells and Sertoli cells. In addition, these heavy metals may interfere with the normal function of endocrine system leading to reproductive dysfunction, which results in infertility in both humans and animals. Furthermore, downregulation of non-coding mRNAs and alteration in enzyme functioning may serve as biomarkers in response to metal toxicity. Thus, advanced diagnostic techniques have been employed in order to evaluate the extent of its toxicity. For minimal exposure to heavy metals, international organizations have implemented restrictions and provide guidelines. Various mitigation strategies, including the use of natural antioxidants and nanotechnology-based therapeutic approaches have been applied. So, it is crucial to understand molecular mechanisms involved in heavy metal toxicity for the development of advanced therapeutic interventions in order to evaluate specific reproductive influences due to these metals. Consequently, it will enable the scientific community to develop more effective treatments.

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