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Heavy Metal Toxicosis and Male Fertility: The Role of Pentahydroxyflavone Quercetin; a Review

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ABSTRACT: The effect of heavy metals (HMs) has been extensively studied. They cause diverse clinical manifestation through various mechanisms. Male fertility is among the most disturbing effect of HMs affecting family life in human and reproduction in animals. Notably among these effects is interference with the reproductive hormones, morphology and function of reproductive organs, sexual behaviors, and the spermiogram. Quercetin is a dietary flavanoid from edible plants and, has proven pharmacological properties in the treatment and management of many disease conditions. Quercetin ameliorates the adverse effects of HMs on male reproductive hormones by increasing the activity of 3β-hydroxysteroid dehydrogenase (3β-HSD) and 17β-hydroxysteroid dehydrogenase (17β-HSD) in the synthesis of testosterone. Quercetin chelates HMs, scavenge free radicals, and other cytotoxicant capable of disrupting the morphology and function of the male reproductive system. Apart from it neuroprotective activity on the pituitary gland and increased steroidogenesis, quercetin mitigate neurotransmitter that aid in copulation and improve histopathological changes in the brain due to HMs toxicity to improve sexual behavior. Quercetin was also found to be effective in increasing sperm count, daily sperm production, mortility, viability, and also decreased in the percentage of abnormal sperm morphology due to HMs toxicity. In conclusion quercetin was found to be effective in mitigating HMs toxicity that affects male fertility, and so, it is recommended to be incorporated into the treatment and management of HMs toxicity. Individuals who are at risk of HMs toxicity should take dietary plants that contain quercetin to minimize the effects of these metals.

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Heavy metals (HMs) are heterogeneous collection of elements with specific density higher than 5g cm^{-3} (Martin, and Hosam, 2018). HM are widely distribution in the environment, the toxicity of these metals occur naturally or due to human activities (Arif, *et al.,* 2015), due to their toxic effects in plants, animals, and human, they are considered as common environmental pollutants in the developing world (Cheng, 2003). Exposure to HM mostly occurs inadvertently, in some certain occupations, via inhalation of contaminated air or the consumption of contaminated food and water (Wirth, and Mijal, 2010). Activities such as mining and smelting operation and agricultural production involving these metals have contaminated extensive areas of the world (Herawati *et al.,* 2000). Some HMs such as lead (Pb), aluminum (Al), mercury (Hg), arsenic (As), and cadmium (Cd) induce toxicity in humans and other living organisms and this toxicity is considered to be mediated through macromolecules such as proteins with structural catalytic or transport function and DNA (Mathur *et al.,* 2010). Clinical manifestation of HMs toxicity varies in a wide spectrum (Sule, *et al.,* 2018). Many HMs can affect multiple organ systems characterized by the involvement of a particular organ (Haschek, and Porpaczy, 1968), others have carcinogenic, growth, and reproductive toxicities (Shestakova *et al.,* 2016). HM may function via hormonal or genotoxic pathways to disrupt male reproduction (Chowdhury, 2009). They may penetrate the blood testicular barrier to potentially affect spermatogenesis, associated with reduced sperm motility and density, increased morphological anomalies, and consequent infertility in males (Mathur *et al.,* 2010). It is not possible to avoid exposure to HM because of their readily availability in nature and human activities (Wirth and Mijal, 2010; Jahan *et al.,* 2015). Research interest is actively following the characterization of natural products which is not only safe against toxicity caused by HMs but also having health benefits (Kim, *et al.,* 2018). Quercetin, a dietary flavonoid from edible plants such as apple, onion, mulberry, potatoes, broccoli, tea, peanut, soybean, and red wine, it is a potent oxygen free radical scavenger (Jahan *et*

*al.,*2015). Quercetin has many pharmacological properties including antioxidant, neurological, antiviral, anticancer, cardiovascular, antimicrobial, anti-inflammatory, hepatoprotective, anti-obesity, and protection of the reproductive system (Maalik, *et al.,* 2014).

In this review we intend to focus on the reproductive consequence associated with mercury (Hg), lead (Pb), cadmium (Cd), and arsenic (As), how these heavy metals affect male fertility, and the ameleroitive effects of quercetin due to this toxicity in human and animal studies. Using internet search from google scholar, researchgate, scopus and pubMed with keywords such as male fertility, heavy metals, and quercetin.

Mercury: Mercury (Hg) is a HM, it density changes from 13.69 g/cm^3 when liquid to 14.184 g/cm^3 when solid (Simons, 1968). Hg exists in two oxidation states, I and II. Inorganic Hg (Hg salts) has been found in laxatives, cosmetic products, teething powders, diuretics, and antiseptics (Bjorklunda *et al.,* 2017). Hg compounds accumulate along the aquatic food chain.Human exposure occurs most commonly through the consumption of seafood (Clarkson, and Magos, 2006), burning of coal and fuel oil (AMAP, 2004). Hg and its compound exhibited structural and functional alteration of the spermatogenic and leydig cell membrane due to its high affinity towards the hydrolytic enzymes and causing a decrease in ACPase, ATPase, ALKPase resulting to progressive degeneration of peritubular membrane (Roy and Vachhrajani, 1987, 1997). In human studies, high mercury levels have been reported in infertile and sub-fertile than fertile men (Dickman, and Leung, 1998), the report also indicates exposure to Hg is associated with tubular atrophy and Sertoli-cell-only syndrome among infertile patients (Keck, *et al.,* 1993). Reproductive toxicity of mercury among various animal studies has been linked with decreased sperm motility, epididymal sperm count, and normal sperm morphology among rats, mice, and monkeys (Mohamed *et al.,* 1987; Homma-Takeda *et al.,* 2001;). Report on *In vitro* studies have indicate that Hg stimulates DNA breaks in spermatozoa (Arabi, and Heydarnejad, 2007), which also decreased sperm motility, dysfunction, and viability of spermatozoa (Mohamed, *et al.,* 1986).

Lead: Lead (Pb) is also a HM with a density of 11.34 g/cm^3 (Thornton *et al.,* 2001). It is the most common industrial metal that has become widespread in air, water, soil, and food. Lead is slightly soluble in water, and is transported mainly through the atmosphere; it deports like calcium in the body and accumulates in bone, liver, kidney, and other tissues (Mukesh, *et al.,* 2008). Occupational exposure to Pb toxicity occurs via inhalation of lead-containing specks of dusts and fumes (Gittleman et *al.* 1994) and the non-occupational settings, through the consumption of food and drinking water contaminated with Pb leached lead-containing pipes or from natural geological formations (Wirth and Mijal, 2010). Apart from other toxicity associated with lead (EPA, 2010), it is also considered a male reproductive toxicant (ATSDR, 2007). Pb toxicity occurs through the generation of reactive oxygen species (ROS), displacement of zinc in metal- lothionein (MT) resulting in the alteration of zinc bioavailability and also disrupting blood testicular barrier by replacing calcium in zona adherence junction (Bridges and Zalups, 2005). In a human comparative study, infertile men with low or no sperm or with sperm with low motility had significantly higher mean seminal fluid Pb levels (mean lead levels 104 – 150 mg/L) compared to men of proven fertility (60mg/L) (Pant *et al.* 2003). This was demonstrated in a group of Croatian men occupationally exposed with low to moderate Pb levels (median blood lead 367 mg/L)were compared to men not occupationally exposed to Pb (103 mg/L), their median sperm density, sperm count, and the number of motile sperm were significantly lower in the low to moderately exposed men and also, the blood Pb was negatively correlated with sperm count ($r = -0.177$, $p < 0.05$), progressively motile sperm ($r = -0.179$,$p< 0.05$), and positively correlated with abnormalsperm head morphology ($r = 0.209$, $p<0.01$) (Telisman *et al.* 2000).In an experimental study, the male rats treated with Pb have an alteration in androgen level with a significant increase in serum follicle stimulating hormone (FSH) and testosterone, however, there was no significant change observed in the level of luteinizing hormone (LH) (Ayinde *et al.,* 2012). Wadi and Ahmad, (1999) investigated Pb toxicity in male reproductive system of sexually mature male CF-1 mice by administering two concentrations of Pb (0.25% and 0.5%) via drinking water for 6 weeks. It was observed that the low Pb dose significantly reduced the number of sperm within the epididymis, while the high dose reduced both the sperm count and percentage of motile sperm and increased the percentage of abnormal sperm within the epididymis. Plasma androgen levels were not affected by Pb administration indicating that lead targets testicular spermatogenesis and sperm within the epididymis to produce reproductive toxicity rather than acting at other sites within the hypothalamic-pituitary-testicular axis.

Cadmium: Cadmium (Cd) is a HM with a density of 8.69 g cm^{-3} and oxidative state of 2^+ (Haynes, 2015). Cadmium is one of the HMs that occurs

naturally at low concentrations, commonly associated with ores of zinc, lead, and copper (Wirth and Mijal, 2010). Natural sources of Cd include weathering of rocks, volcanic activity, sea aerosols, forest fires, and gathering from soils, and landfills (Ekaterina and Nina 2018). Cd toxicity occurs through inhalation and ingestion mainly from nickel-cadmium batteries, pigments in paints, chemical stabilizers, metal coatings, alloys, pesticides and fertilizers. Other sources of Cd poisoning includes photovoltaic devices, rubberprocessing, galvanization process, fossil combustion and waste incineration (Anju *et al.*, 2014). Following absorption, Cd is predominantly deposited inthe liver and kidney, which is considered a critical target of its toxicity (Rafati *et al.*, 2017). Workers in the metal refining industries that handle Cd have been shown to suffer from ailments such as damaged lungs, gastric disorders, bone fracture, reproductive failure, infertility, and damage of the central nervous system, psychological disorder, DNA damage, or development of cancer among others (Singh, *et al.*, 2007). The most hazardous effect of Cd is its ability to accumulate in the body systems throughout alifetime due to its long biological half-life (Hideaki *et al.* 2008). The toxicodynamics of Cd includes, interference with DNA repair mechanism, production of ROS, induction of apoptosis, binding to mitochondria, and inhibition of both cellular respiration, and oxidative phosphorylation at low concentration (Rani *et al.*, 2014). The Agency for Toxic Substances and Disease Registry (ATSDR), established there was inadequate data to ascertain the effects of inhaled Cd on reproductive outcomes in human (ATSDR 2008). However, results from several studies conducted to assess the effects of its low exposure in humans and in various species of mammals, have provided some facts in support of its effect on some male reproductive indices (Wirth and Mijal, 2010; Marettov *et al.*, 2015). In humans, the effect of Cd on the male reproductive system is age-dependent and, also dose and time dependent with many effect elevated after the fourth decades of life (Oldereid *et al.*,1993;). Smoking of cigarettes containing Cd has been associated with a decrease in testicular size (Jurasovic *et al.*, 2004) which is associated with low sperm count due to apoptosis of sperm cells (Chia *et al.*, 1994). Telisman *et al.* (2000) report that there were significant positive correlations between blood Cd levels and pathologic sperm (r ¼ 0.158, $p < 0.05$), and leutinizing hormone (r ¼ 0.158, $p< 0.05$) and testosterone (r ¼ 0.1295, $p < 0.01$) levels and a negative correlation with prolactin level (r ¼ -0.168, $p< 0.05$) among 98 industrial workers (median blood Cd level 3.40mg/L) and 51 subjects not occupationally exposed (median Cd level 1.83mg/L) . In animal *in-vitro* studies, Cd affect male reproduction from embryonic to adult stage, with an adverse effect on the development of the gonads (Thompson and Bannigan, 2008). Tam and Liu, (1985) report sub-fertility and aberrant maturation of gametes due to the administration of Cd to mouse embryo. Cd readily crosses the testicular blood- barrier and cause a reduction in germ cells numbers which lead to infertility due to disruption of the blood-testis barrier, testicular necrosis and dystrophy as well as a decrease in the plasma testosterone level (Chung and Cheng, 2001). A Study on the intraperitoneal administration of Cd to adult rats for 16 days indicates a decrease in the volume and viability of cauda epididymis sperm, the quantity of free serum testosterone, cell proliferation, and Johnsen Scores in the seminal tubules (Yari *et al.*, 2016). *In vitro* addition of Cd to Sertoli cell culturesandspermatocytes facilitate the mean of entry into cells due to its ability to disrupt the occludin junctions between cells. (Chung and Cheng 2001; Siu *et al.*, 2009).Once Cd enters into a cell, it causes cellular damage which has been attributed mainly to its interference with zinc mediated metabolic processes (Bridges and Zalups 2005), indirectly increases levels of ROS, and induce oxidative stress (Valko *et al.*, 2005) leading to lipid peroxidation (El-Demerdash *et al.*, 2004), and also increase the level of apoptotic biomarkers (Thompson and Bannigan 2008).

Arsenic: Arsenic (As) appears in three allotropic forms: yellow, black and grey; the stable form is a silver-gray, brittle crystalline solid. It tarnishes rapidly in air, and at high temperatures burns to form a white cloud of arsenic trioxide. Arsenic is a HM with a density of 5.7 gcm^{-3} (Wirth Mijal, 2010). Arsenic poisoning occurs through inhalation, skin absorption and, primarily, by ingestion of contaminated food and water (Ratnaike, 2003). Natural exposure to arsenic toxicity includes trace quantities in rock, soil, water, and air and anthropogenic activities such as metal mining and smelting, fossil fuel combustion, sawdust or smoke from wood treated with arsenic, toxic waste sites, and traditional medicines (Naujokas *et al.*, 2013). As and its compounds are exploited productively in pharmaceutical, agriculture, mining, and glass-making industries for centauries (Hughes *et al.*, 2011). As is desired for the safeguarding of dietary, and health conditions of humans at low dosage (Renu, et *al.*, 2018). Contamination with As causes various health challenges such as cancer (Chayapong, *et al.*, 2017), cardiovascular diseases (Chiou *et al.*, 1997), diabeticpathophysiology (Renu, *et al.*, 2017), and reproductive toxicity (Kim and Kim, 2015). Toxicity due to As involved inactivation of up to 200 enzymes, most commonly those associated with cellular energy pathway, DNA replication and repair,

substitution of phosphate in high energy compounds such as ATP and generation of ROS that cause lipid peroxidationand DNA damage (Cobo and Castineira, 1997; Abernathy, *et al.,*1999).Epidemiological observational studies in humans exposed to As has been linked to reproductive dysfunction in males through a reduction in testicular weight, accessory sex organ weight, viability, and motility of sperm, epididymal sperm count, decreased gonadotrophins level, decreased testosterone, and steroidogenesis (Renu, *et al.,* 2018). A report by a Chinese cohort study, indicate positive correlation between As concentration and decreased sperm concentration due to environmental exposure of 96 males with an age range between 32 and 36 years to As (Xu, *et al.,* 2012). In a similar study, the exposure of As > 50 ppb in drinking water to males in Taiwan (177 in number, age ≥50 years), indicates increased risk of erectile dysfunction with reduced circulating testosterone level (Hsieh, *et al.,* 2008). Animal and *In-Vitro* Studies; Sudha, (2012), reported that As caused the reduction in antioxidant enzymes by increasing oxidative stress, and this was corroborated by the damages of the sperm DNA and instability in nuclear constituents(Rajesh *et al.,* 2002). The administration of 5 mg sodium arsenite/kg body weight for 12 weeks to Teddy buck goat caused a significant reduction in sperm count, motility, and male reproductive hormones (Zubair *et al.,* 2016). Male rats exposed to sodium arsenite at 5 mg/L for 4 weeks in drinking water also resulted in decreased testicular weights, accessory sex organ weights, and epididymal sperm counts, as well as extensive degeneration of a wide variety of germ cells at stage VII of the spermatogenic cycle (Jana *et al.,* 2006). Administration of sodium as orally at the dose of 0.4ppm to pregnant and lactating mice, resulted in a reduction in spermatogenesis and steroidogenesis in the next generation of adult mice (Reddy *et al.,* 2011). Lin *et al.* (2002), also reported a reduced sperm motility and fertilization in inseminated semen with increased malondialdehyde (MDA) concentration in testicular tissue of Ducks exposed to 1.2ppm as trioxide for 8 weeks.

Ameliorative effect of quercetin on HMs induced reproductive toxicity in males: Some of those key factors that serve as indices for the evaluation of male fertility are: male reproductive hormones, morphology, and function of the reproductive organs, sexual behavior, and spermiogram. These are discussed in the following context considering the impact of HMs toxicity on male's fertility and how quercetin possibly mitigate these effects.

Male reproductive hormones: Reproductive function in male is mediated by different hormones (Sengupta and Arafa, 2019). The hypothalamopituitary-gonadal/testicular axis also known as the 'master' regulator hormonal axis is led by the pulsatile release of a hypothalamic gonadotropic releasing hormone (GnRH). This, in turn, stimulates the anterior pituitary trophic hormones, the leutinizing hormone (LH) and follicular stimulating hormones (FSH) which act upon the testicular cells, the Leydig cells for steroidogenesis, and Sertoli cells to aid spermatogenesis, respectively (Dutta *et al.,* 2019). Some of these HMs as mention earlier are capable of interfering with reproductive hormone, and invariably affect fertility (Sokol *et al*., 1985; Laskey and Phelps 1991; Jahan *et al.,* 2015). In an experimental study, co-administration of quercetin with sodium arsenites, yielded a significant increase in serum, and intratesticular testosterone (Ciftci *et al.,* 2012; Jahan 2015), this suggest the supplementation of quercetin serves to attenuate the adverse effects of As intoxication by inhibiting ROS and reactive nitrogen species (RNS) generation in increasing testosterone level (Jahan *et al.,* 2015). The enzymes 3β-hydroxysteroid dehydrogenase (3β-HSD) and 17βhydroxysteroid dehydrogenase (17β-HSD) are important enzymes required for steroidogenesis, they are involved in the biosynthesis of the substrate cholesterol to testosterone (Abarikwu and Farombi, 2014). Cds compounds decreased the activities of 3β-HSD and 17β-HSD leading to increased testicular cholesterol concentration with the corresponding decrease in testosterone concentration (Sadik, 2008). Ujah *et al.,* (2017), reported that quercetin attenuates negative changes in rats experimentally induce with $CdCl_2$ by improving the suppressed steroidogenesis, penile erection, and sexual behavior. In a similar study, the increase intra-testicular concentration of testosterone was observe in quercetin plus As treated rats, this may be possible due to quercetin inducing androgenic enzyme activity (Jahan *et al.,* 2015).

Morphology and function of reproductive organs: The male reproductive system is divided into primary, and secondary reproductive organs. Primary reproductive organs include the gonads (responsible for gamete and hormone production), while the secondary organs include the ducts and glands, which play an important role in the growth, maturation, and transmission of gametes (Ampatzidis *et al.,* 2019). Heavy metals toxicosis interfere with the morphology, and functions of these organs, by inhibiting the protective mechanism against free radicals and other cytotoxic mechanisms (Kanter *et al.,* 2016) thereby affecting fertility (Mathur, *et al.,* 2010). Pant *et al.,* (2004) report a decrease in absolute and relative testicular weight due to the administration of sodium arsenites via drinking water at the dose of 4ppm day^{-1} for 365

days in the mouse. Sarkar *et al.,* (2003) also a report similar findings with a relative decrease in testicular weight, seminiferous tubular diameter, gametogenic cell population with atrophy of the leydig cells observed in dose-dependent manner due to sub-chronic administration of sodium arsenic at 30 and 40 mg L^{-1} via drinking water to mice (Sarkar *et al.,* 2003). Ragan and Mast (1990) in a human study, report testicular necrosis due to occupational exposure to Cd. Acute intraperitoneal administration of lead nitrate ($PbNO_3$) at 50, 25, and 12.5 mg kg^{-1} b.wt, increase the incidence of apoptosis in spermatogenic cells, and germinal epithelium with empty spaces (Massanyi *et al.,* 2007). Previous studies also indicate quercetin ameliorate HMs toxicity by chelation and scavenge free radicals and other cytotoxicants (Bros, *et al.,* 1990; Anjaneyulu, and Chopra, 2004; Ravichandran *et al.,* 2014).These protective effects of quercetin in HMs toxicoses affecting the morphology, and function of the males reproductive system may be attributed to it proliferative capacity, increase in the tubular epithelial height and sperm number (Jahan *et al.,* 2015).

*Sexual behavior:*Male normal sexual function is characterized primarily by the erection of the penis and ejaculation, however, persistent absence of these hallmarks could be referred to as male sexual dysfunction (MSD) (Guay *et al.,* 2003). MSD could manifest as a lack of desire, persistent delay in/absence of orgasm, erectile dysfunction, quick ejaculation, and priapism (Yakubu and Akanji, 2011). These among other causes of MSD are associated with HMs toxicoses (Ujah *et al.,* 2017). Research findings have indicated that neurotransmitters such as norepinephrine (NE), dopamine and nitric oxide (NO) are involved in sexual behavior and performance in male (Mokhtari, and Zanboori, 2001). Dopamine participates in the dopaminergic system that is involve in the regulation of cognition and triggers penile erection by acting on oxytocinergic neurons located in the paraventricular nucleus of the hypothalamus, and perhaps on the pro-erectile sacral parasympathetic nucleus within the spinal cord (Giuliano, and Allard, 2001). Previous work demonstrates HMs inference with dopamine (Lafuente *et al.,* 2005; Fang-I, *et al.,* 2008). NO is an atypical regulatory molecule that acts as a second messenger and a neurotransmitter, it is synthesized via the stimulation of the enzyme nitric oxide synthase (NOS),it has been implicated in diverse physiological activities including mediator of male sexual behavior (Forstermann *et al.,*1990;). NO, mediate penile erection by inhibiting smooth muscle of the corpora cavernosa, thereby allowing vasodilation of the corpora, but it increased the number of ex copula seminal emissions and decreased the latency to the first seminal emission which helps prevent premature ejaculation (Hull *et al.,* 1994). NO synthesis and biochemical functions are affected by HMs (Kumagai, and Pi, 2004; Jennrich, 2013). Sexual behavior is also affected by HMs via interference with the $GABA_A$ receptors in the production of adrenal, and gonadal steroids (Iavicoli *et al.,* 2008). As mentioned earlier HMs are also capable of causing oxidative stress and brain damage which possibly affect sexual behavior due to altered spatial memory and locomotor activities. (Nageshwar *et al.,* 2019). Marked impairment in sexual activity, territorial aggressive behavior and anxiety– like behavior was observed in males Wistar rats exposed to $CdCl_2$ (Mervat *et al.,* 2011). Also, Mokhtari and Zanboori (2011) report similar findings in rats exposed to lead acetate. Sharma *et al.,* (2018) in an experimental study, observed the protective activity of quercertin on the pituitary gland, and increased in steroidogenic enzymes 3ß-HSD and 17ß-HSD, responsible for enhanced biosynthesis of testosterone. It has also been documented that quercetin has neuroprotective efficacy in progressive dopaminergic neurodegenerative MitoPark transgenic mouse model of Parkinson's disease (Muhammet *et al.,* 2017). According to Nageshwar *et al.,* (2019), quercetin abrogates histopathological alterations in the brain, ameliorates motor coordination, and decreased the latency period against sodium arsenate induced behavioural deficit in the rat.

Spermiogram: The spermiogram serves as a basis for the diagnosis of possible fertility problems in males. It involves the assessment of various characteristics of the ejaculatory fluid (semen). However, the most important characteristics considered for the analysis of the ejaculate are; Quantity, pH level, Sperm concentration (in million sperm/ml), Morphology (percentage of normally formed sperm cells), and motility (movement, expressed as a percentage). (https://www.kinderwunschteam.berlin/en/infertility/ diagnostik/diagnostik spermiendiagnostik/). Human and animal evidence suggests that HMs may have adverse impacts on male reproductive health at relatively low levels with semen quality (Meeker *et al.,* 2008). These metals are also found in seminal plasma of individuals exposed to theses toxicants which may be poor indicators of andrological parameters (Hovatta, *et al.,* 1998). For example, Cd has been linked to poor semen quality, and DNA damage in humans, and animals' studies (Telisman *et al.* 2000; Xu *et al.,* 2003). Pb adversely affects the shape of the spermatozoa, its motility, and DNA integrity (Eibensteiner *et al.* 2005). Xu, *et al.,* (2012) report a decrease in sperm count, viability and motility due to as toxicity. Previous studies also reveal Hg toxicities affect semen quality (Mohamed, *et al.,* 1986;

Choy et al. 2002). Al-Omair *et al.,* (2017) in an experimental study, report significant increase in sperm count, motility, and a decrease in percentage of abnormal sperm in rats co-treated with lead, and quercetin compared with lead acetate treated group. Also, in a similar study, Jahan *et al.,* (2015) report quercetin was found to be effective against as induced reduction of daily sperm production and DNA damage. Abnormal changes observed in spermiogram due Cd toxicity were reverse to near normal in quercetin co-treatment, thus indicating ameliorative activities of these compounds (Farombi, *et al.,* 2012). It was also reported that quercetin protects both goat sperm and preimplantation embryos from Cd^{2+}-induced oxidative stress (Mao *et al.,* 2018).

Conclusion: Unrestrained industrialization and urbanization without proper emission controls of HMs disposal are the attributable factors that have exposed human lives to risk of infertility in males. Quercetin apart from its other pharmacological activities is proven to ameliorate HMs toxicity affecting male fertility. Consumption of dietary food rich in quercetin may be of benefit most especially in individuals at high risk of HMs toxicity, and thus, could be of clinical usefulness in the management and treatment of these environmental toxicants.

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