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Counteracting effects of heavy metals and antioxidants on male fertility

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Abstract Infertility is regarded as a global health problem affecting 8–12% of couples. Male factors are regarded as the main cause of infertility in 40% of infertile couples and contribute to this condition in combination with female factors in another 20% of cases. Abnormal sperm parameters such as oligospermia, asthenospermia, and teratozoospermia result in male factor infertility. Several studies have shown the deteriorative impact of heavy metals on sperm parameters and fertility in human subjects or animal models. Other studies have pointed to the role of antioxidants in counteracting the detrimental effects of heavy metals. In the currents study, we summarize the main outcomes of studies that assessed the counteracting impacts of heavy metal and antioxidants on male fertility. Based on the provided data from animal studies, it seems rational to administrate appropriate antioxidants in persons who suffer from abnormal sperm parameters and infertility due to exposure to toxic elements. Yet, further human studies are needed to approve the beneficial effects of these antioxidants.

Keywords Heavy metal · Antioxidant · Male infertility · Animal models · Reactive oxygen species · ROS · Oxidative stress

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Introduction

Being defined as a failure to achieve the clinical pregnancy after at least 12 months of regular unprotected sexual intercourse (Zegers-Hochschild et al. 2009), infertility is estimated to globally affect 8–12% of couples (Kumar and Singh 2015; Sciarra 1994). Male factors are regarded as the main cause of infertility in 40% of infertile couples and contribute to this condition in combination with female factors in another 20% of cases (Kumar and Singh 2015). Male factor infertility generally results from abnormalities in the semen; therefore semen quality is regarded as a marker for measurement of male fecundity (Cooper et al. 2010). The most important parameters pointing to the male factor infertility are low sperm count, poor sperm movement, and anomalous sperm morphology being described as oligospermia, asthenospermia, and teratozoospermia, respectively (Kumar and Singh 2015). A vast body of evidence indicates a deterioration of sperm quality in at least some regions in the world (Kumar and Singh 2015) in addition to a remarkable difference in the semen quality in different regions (Kumar and Singh 2015). The latter might be caused by various environmental, nutritional, or socioeconomic factors (Fisch and Goluboff 1996). Therefore, identification of the role of environmental factors on male infertility is a practical method for decreasing the exposure to these factors to improve male fertility. Several studies have shown the deteriorative impact of heavy metals on sperm parameters and fertility in human subjects or animal models. Defined origins of heavy metals in the environment comprise geogenic, industrial, agronomical, medical and atmospheric origins as well as domestic wastes (He et al. 2005). On the other hand, several antioxidants have been demonstrated to compensate for such effects. Lead and cadmium as representative of heavy metals are regarded as factors that disturb endocrine functions and influence the levels of hormones accountable for sperm biogenesis. These defects are mainly induced by oxidative stress (Benoff et al. 2000). Such overproduction of reactive oxygen species (ROS) surpluses the capacity of antioxidants, leading to abnormal sperm parameters. The spermatozoa are extremely vulnerable to the degenerative effects of ROS due to the presence of large quantities of membrane polyunsaturated fatty acid (PUFA) and their aptitude to produce ROS (Nabil et al. 2008). ROS-induced peroxidation of PUFA and oxidative DNA damages have detrimental effects on sperm parameters such as activity, motility, capacitation, and acrosome reaction (Venkatesh et al. 2009). On the other hand, seminal fluid contains a number of antioxidants such as catalase, superoxide dismutase (SOD), glutathione (GSH), vitamin C vitamin E, and some trace minerals such as zinc and selenium to counterbalance the effects of ROS and maintain the sperm activity (Atig et al. 2012). Exogenous administration of these antioxidants is expected to exert the same beneficial effects. Figure 1 depicts the role of heavy metals in induction of male infertility and the importance of antioxidants to prevent these effects. In the currents study, we summarize the main outcomes of studies which assessed the impact of heavy metal and antioxidants on male fertility. For the purpose of identifying relevant literature, we searched PubMed and Google Scholar with keywords "Heavy metal" and "male infertility". We retrieved articles from 2011 until 2020. Then, we tabulated the obtained data and discussed the results of articles focusing on Aluminum, Lead, Mercury, Cobalt, Nickel, Potassium dichromate, Arsenic, and Cadmium, since the obtained data was mostly focused on these agents.

Heavy metals

Several studies have assessed the impact of heavy metals on male infertility. We have summarized these data in the Tables and explained a number of more important ones with mechanistical data in the text.

Aluminum

Aluminum phosphide has been shown to exert detrimental effects on male infertility as observed in a rat model. These effects include low counts of spermatid resulted from spermatogenic arrest, thin basement membrane, the atypical configuration of the spermatids, and hypertrophy of the seminiferous tubules. These features were slightly reversed by the administration of garlic (*Allium sativum*) (Eric et al. 2020). Another study in Wistar rats demonstrated defects in the bonds between the germinal epithelial cells in several tubules after exposure to Aluminum. Administration of vitamin E in this group of rats has beneficial effects as demonstrated by the preservation of the full germinal epithelium cells and reduction of

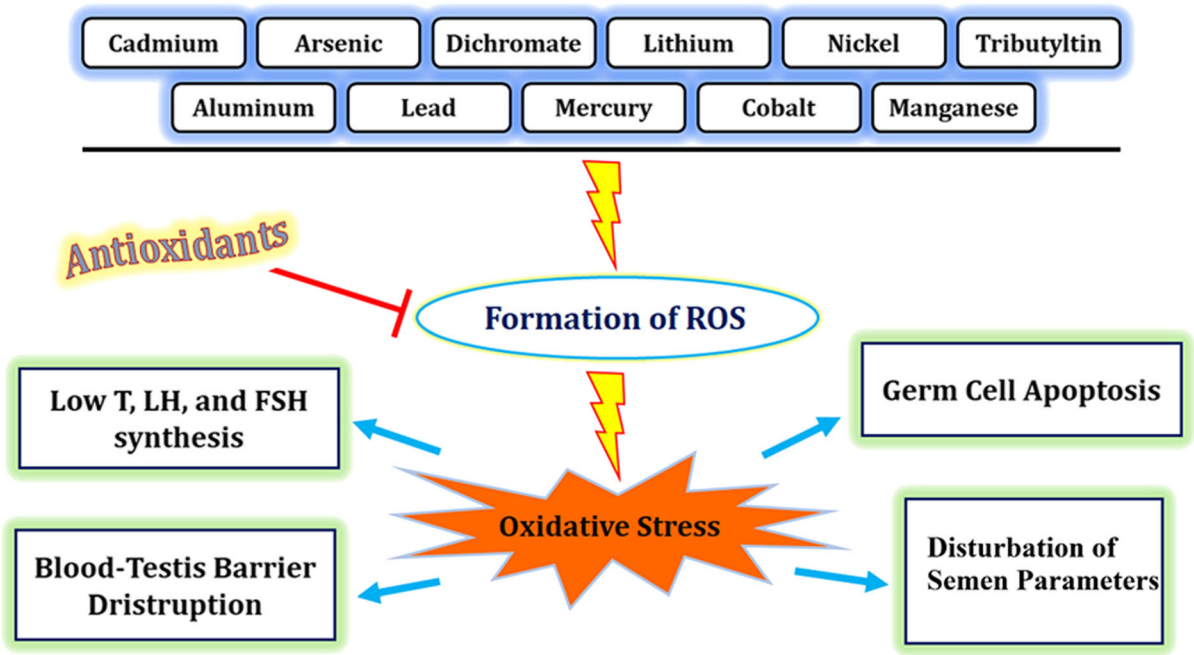

Fig. 1 Toxic metals, which are widely found in our environment, lead to an increase in the production of reactive oxygen species (ROS) including hydrogen peroxide (H_2O_2), superoxide radical ($O_2^{\cdot -}$), and/or hydroxyl radical (HO.) (Ercal et al. 2001). Toxic metals via ROS generation, caspase-3 upregulation, Bcl-2 downregulation, p53 deficiency, decreasing testosterone (T), LH, and FSH synthesis, disrupting BTB (blood-testis barrier) function, disrupting sperm parameters, and testicular germ cells, Sertoli cells, and Leydig cells apoptosis could result in subfertility/infertility in males (Habib et al. 2018). However, antioxidant supplementations could be involved in abating some hazards of heavy metals by suppressing ROS generation, thus improving reproductive function in males (Agarwal et al. 2004)

apoptosis rate (Ulfanov et al. 2020). Aluminum chloride ($AlCl_3$) has also been shown to exert detrimental effects on male infertility including the disturbing architecture of testes, impaired sperm motility in addition to diminished GSH levels, catalase activities, and down-regulation of Nrf-2, HO-1, and BCL-2 expressions. These effects were accompanied by overexpression of caspase-3 and malondialdehyde (MDA) levels as well as atypical dead/live sperm proportion. Yet, tyrosol has been shown to partially reverse these abnormal alterations (Güvenç et al. 2020). Table 1 shows the results of studies that assessed the effect of Aluminum on male infertility.

Lead (Pb)

Investigations in a mouse model of Pb-associated testicular damage have shown that this metal could prompt a series of injuries, such as low litter size, smaller testes, and abnormal spermiogenesis. This element suppresses lysine acetylation and succinylation and subsequently hinders the replacement of transition proteins in the elongating sperm which leads to aberrant configuration of germ cells in the seminiferous tubule. Inhibition of lysine acetylation occurs in the meiotic spermatocyte and round spermatid, especially in the course of meiosis. Moreover, Pb can inhibit the activity of key enzymes to suppress the TCA cycle and decrease the levels of acetyl-CoA and succinyl-CoA (Yang et al. 2020). Pb has also been shown to induce degenerative alterations in spermatids including vacuolization. Besides, it decreases the number of cytoplasmic organelles in Leydig cells and impairs the stereocilia of epididymal epithelium. Notably, vitamin E can reduce these detrimental effects in spermatids, epididymal epithelial, and Leydig cells (Fahim et al. 2013). Besides, Pb has been demonstrated to increase oxidative stress in the testes as verified by a remarkable reduction in the activity of SOD, GSH peroxidase, and catalase, and a decrease in GSH levels while increasing MDA levels. These effects were entirely reversed by thymoquinone

Table 1 Summary of the results of studies that assessed the effect of aluminum on male infertility

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
Aluminum phosphide (ALP), *Allium sativum (ALS)*	ALP (0.014 mg) ALS (250 and 500 mg), daily, for 7 days	Orally	Rat	–	Treatment with AL led to the hypertrophy of the seminiferous tubules, spermatogenic arrest, and abnormal structure of the spermatids, while the administration of garlic could ameliorative the testicular toxicity induced by AL	Eric et al. (2020)
Aluminum sulfate, Vit E	ALS (10 mg/kg) Vit E (500 mg/kg) 3 times/week, for 4 weeks	IP	Rat	–	Treatment with AL led to the formation of bonds between the germinal epithelial cells, increased the number of unidentified cells in the lumen of tubules, apoptotic index, and abnormal sperm, and also decreased JS, while treatment with the VitE could ameliorate the testicular toxicity induced by Al	Ulfanov et al. (2020)
Aluminum chloride ($AlCl_3$)	$AlCl_3$ (34 mg/kg), daily, 10 weeks	Orally	Rat	Nrf-2, HO-1, Bcl-2, Caspase-3	Treatment with $AlCl_3$ could increase MDA level, caspase-3 expression, abnormal and dead/live sperm ratio, while decrease sperm motility, CAT activity, GSH level, Johnsen score (JS), Nrf-2, HO-1, Bcl-2 expressions	Güvenç (2020)

(TQ) supplementation (Mabrouk and Ben Cheikh 2015). Pb also decreases epididymal sperm count and motility, testes and epididymis weights, spermatogenesis score, and serum testosterone levels. These alterations were accompanied by remarkable reductions in SOD and GSH levels, while the increase in MDA and NO levels. Furthermore, Pb down-regulates CYP19 gene expression enhances Caspase-3 levels and induces degenerative and necrotic alterations in the testis. However, co-administration of Pb and diallyl sulfide ameliorated the Pb-induced histological changes and normalized CYP19 and Caspase-3 levels (Hassan et al. 2019). Lead acetate has reduced expression of PGC-1α, enhanced the intracellular level of ROS, and decreased the level of ATP in mouse Sertoli cells. Such effects were attenuated in PGC-1α(+) Sertoli cells indicating the protective role of PGC-1α against PbAc-associated oxidative stress (Liu et al. 2017). Another study has shown the protective effect of zinc chloride against lead nitrate-induced degenerative changes in rat testes (Hanan and Abd 2015). Table 2 shows the results of studies that assessed the effect of Pb on male infertility.

Mercury (Hg)

Mercuric chloride has been shown to increase serum levels of TNF-α, IL-6, caspase-3, and testicular MDA. On the other hand, serum levels of testosterone, dehydroepiandrosterone, GSH level, and SOD activity were reduced following treatment with this agent. Expression and histological assays showed down-regulation of Nrf2 while up-regulation of Bax and DNA fragmentation in the testicular tissues. Notably, alpha-tocopherol (α-toco) and/or Lactobacillus Plantarum (LCB) amended the abnormal biochemical parameters and reversed tissue injury (Fadda et al. 2020). This agent also elevated MDA levels, TNF-α, and COX-2 expressions, increased necrotic and degenerative changes in spermatogonium, induced abnormal histological changes, reduced antioxidant enzyme activities, and decreased sperm motility. These abnormal changes were reduced by the

Table 2 Summary of the results of studies that assessed the effect of Pb on male infertility

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, Pathways, Biochemical factors	Observations	References
Lead chloride (Pb)	Pb (1.5 mg/ kg), every two days, for 50 days	IP	Mouse	PK, Kac, Ksuc, Tnp, Prm	Pb treatment could inhibit the activity of pyruvate kinase, reduce the acetyl-CoA and succinyl-CoA which caused to restrain polarization of acetylation and the replacement of histone by transition protein and protamine. Consequently, meiosis and elongation of sperm cells could be blocked, thus inducing abnormal spermiogenesis. Also, Pb could decrease the activity of the electron transport chain complex I and II to reduce ATP levels, which could lead to spermiogenesis failure. The combined negative effects of Pb on acetylation, succinylation, and energy production could induce reproductive injury	Li (2020)
Pb, Green tea extract (GTE)	Pb (0.4%), GTE (1.5% w/v), daily, for 6 weeks	Orally	Rat	–	Pb administration could induce toxicity and testes tissue damage, which was reduced by the beneficial effect of GTE treatment	Tarek et al. (2009)
Pb, Vit E	Pb (1 mg/kg), 5 days per week, for 3 weeks, Vit E (100 mg/kg), 5 days per week, for 3 weeks	IP	Mouse	–	Pb administration could cause degenerative changes in the spermatids of seminiferous tubules of mice testis. It also could reduce the number of stereocilia in the epithelial cells of the epididymis and caused cellular abnormalities in testosterone-producing Leydig cells. Vitamin E treatment could prevent a decrease in the density of spermatozoa observed in the testis of lead-intoxicated mice	Fahim et al. (2013)
Pb, Thymoquinone (TQ)	Pb (2000 ppm), daily, for 5 weeks, TQ (5 mg/kg), daily, for 5 weeks	Orally	Rat	CAT, GPX, GSH, GR, NADPH, GSSG	Pb treatment could induce oxidative stress status in testes by a significant decrease in the antioxidant enzyme activities such as superoxide dismutase, glutathione peroxidase, and catalase, and in the reduced glutathione content and a significant increase in the level of malondialdehyde	Mabrouk and Ben Cheikh (2015)

Table 2 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, Pathways, Biochemical factors	Observations	References
Pb, TQ	Pb (2000 ppm), daily, for 5 weeks, TQ (5 mg/kg), daily, for 5 weeks	Orally	Rat	–	Pb administration could induce impairment of testicular steroidogenic and spermatogenic functions, which could improve by TQ treatment	Mabrouk and Ben Cheikh (2016)
Pb, Telfairia occidentalis (TO)	Pb (75 mg/kg), daily, 15 days, TO (300 mg/kg), daily, 15 days	Orally	Rat	–	Telfairia occidentalis administration could improve the deleterious histological testicular and epididymal changes, low plasma testosterone with concomitant low levels of packed cell volume, which induced by Pb	Falana et al. 2019)
Pb, Diallyl sulfide (DAS)	Pb (20 mg/kg), daily, for 49 days, DAS (200 mg/kg), daily, for 49 days	Orally	Rat	CYP19, MDA, NO, SOD, GSH, Caspase-3	Pb administration could cause a decline in epididymal sperm number and motility, testes and epididymal weights, spermatogenesis score, and testosterone level, also a significant decrease in SOD and GSH level, and a significant increase of MDA and NO	Hassan et al. (2019)
Pb, Selenium (Se)	Pb (350 mg/L), daily, for 90 days, Se (1 mg/kg), daily, for 90 days	Orally	Chicken	Dio1, Dio2, Dio3, GPx1, GPx2, GPx3, GPx4, SelH, SelI, SelK, SelM, SelO, SelPb, SelS, SelT, SelU, SelW, Sep15, SepN1, Sepp1, SepX1, SPS2, Txnrd1, Txnrd2, Txnrd3, HSP27, HSP40, HSP60, HSP70, HSP90	Pb poisoning could increase the mRNA expressions of HSPs in the chicken testes, and decrease the mRNA expressions of Selenoproteins in the chicken testes. HSP70 may be a biomarker of Pb poisoning in the chicken testes. Se could alleviate the changes of five HSPs and 25 Selenoproteins caused by Pb by regulating mRNA expressions of HSPs and Selenoproteins	Huang (2017)
Pb, Se	Pb (350 mg/L), daily, for 90 days, Se (1 mg/kg), daily, for 90 days	Orally	Chicken	iNOS, NF-κB, TNF-α, PE, HSP 60, HSP70, HSP90	Pb administration could cause inflammatory damage by decreasing the expression of inflammatory factors and heat shock proteins in the chicken testes, which, Se treatment could improve these effects	Wang et al. (2017)

Table 2 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, Pathways, Biochemical factors	Observations	References
Pb, Se	Pb (350 mg/ L), daily, for 90 days, Se (1 mg/kg), daily, for 90 days	Orally	Chicken	CHOP/caspase-3, GSH, MDA, GPx, GST, SOD, GRP78, PERK, eIF2α, ATF4, CHOP, caspase-3/12	Pb poisoning could cause increased MDA, decreased GSH, and the activities of GPx, GST, and SOD; and upregulated mRNA expressions of ER-related and apoptosis-related genes in the chicken testes Se could alleviate Pb-induced oxidative stress, ER stress, and apoptosis via the CHOP/caspase-3 signal pathway	Huang (2018)
Pb	0, 3.675, 7.35, 14.7, 29.4, 58.8 mg/L, daily, 1 week	Environmental in water	Crab	SOD, GPx, CAT, MDA	Pb exposure could reduce the survival rate of sperm and cellular harmful effects in crab testes, which may be related to Pb-induced oxidative stress	Li (2015)
Pb	1% aqueous solution of Pb, daily, for 9 months	Orally	Rat	EPR, TAS, ROS	Pb administration could cause disturbances in the metabolism of male rat reproductive system organs. This exposure may lead to an imbalance between ROS generation and removal by a decrease of L-ascorbic acid level and an increase in lipid peroxide concentration in the tissues of the male reproductive system	Marchlewicz (2007)
Pb	0, 10, 20, 40, 80, 160 μM, for 24 h, 1 day	In vitro	Mouse	PGC-1α, ROS, Sirt3	Pb administration could result in cell injury through oxidative damage and energy metabolism dysfunction in mouse TM4 cells. Overexpression of PGC-1α could ameliorate lead-induced toxicity	Liu (2017)
Pb	50, 100 mg/ kg, single-dose, 7 days	IP	Blackbird	–	Pb administration could cause oxidative damage and reduce the reproductive quality; loss of membrane integrity, mitochondrial functionality, and DNA integrity	Leidens (2018)
Pb, Se	Pb (350 mg/ L), Se (1 mg/kg), daily, for 90 days	Orally	Chicken	H_2O_2, CAT, TAOC, GSH, SOD, Beclin 1, Dynein, LC3-I/II, mTOR	Pb could cause an increase in H2O2, decrease CAT, TAOC, and SOD activities and GSH and increase mRNA and protein levels of the autophagy-related genes except for that mTOR decrease in chicken testes, which Se could alleviate these changes	Huang (2019)

Table 2 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, Pathways, Biochemical factors	Observations	References
Pb, Ascorbic acid (AA)	Pb (0.2% /kg), AA (500, 1000, 1500 mg/kg), daily, for 8 weeks	Orally	Rat	TBARS, TAC, NO, GSH	Pb administration could cause a significant decrease in spermatogenesis quality, an increase in FSH and LH, and a decrease in testosterone hormones. For antioxidant activity, Pb could cause a significant increase in NO and TBARS levels, in which AA treatment can protect the reproductive system of male rats from lead toxicity	Abd-Allh et al. (2017)
Lead acetate (LA), DMSA, Vit C Vit E	LA (100 ppm in drinking water), DMSA (50 mg/kg), Vit C (160 mg/kg), Vit E (50 mg/kg), two times/ week for 6 weeks	Orally	Rat	–	Lead acetate could cause degenerative changes in spermatogenesis, seminiferous tubules, and the interstitial blood vessels in rats, which could remove by a combination of DMSA, as a chelating agent, and both vitamin E and C, as antioxidants	Mohamed et al. (2015)
LA, AA, Thiamine	LA (0.2% in drinking water), AA (140, 420, 1260 mg/kg), Thiamine (10, 30, 90 mg/kg), daily All treatments for 14, 28 and 42	Orally	Mouse	TGFβ1, caspase-3, AI	LA administration in drinking water could result in increased expressions of TGFβ1 and caspase-3, apoptotic index (AI), and DNA damage Treatment with thiamine and AA at lower doses effectively could inhibit testicular cells from apoptosis by LA, but higher doses could aggravate the testicular lesion	Wang (2006)

Table 2 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, Pathways, Biochemical factors	Observations	References
LA	LA (0.5, 1.0, 1.5 g/L), daily, for 60 days	Orally	Mouse	Usp9y, Ddx3y, Uty	LA administration could inhibit spermatogenesis and sperm development and downregulate the expressions of the Ddx3y gene in mice testes	Wang (2013)
LA, Punicalagin (PU)	LA (100 mg/kg), PU (9 mg/kg), daily, for 4 weeks	IP, Orally	Mouse	ROS, GSH, Nrf2	Lead administration could induce OS and a direct effect on the differentiation of spermatogonial cells, following by a significant decline in sperm count Supplementation of PU could change values of LPO and GSH with a concomitant increase in sperm count, decrease in the abnormal sperms, and a decline in the morphologically abnormal sperm population	Rao et al. (2016)
LA, Ficus carica	LA (30 mg/kg), daily, 57 days, Ficus carica (80 mg/kg), daily, 57 days	Orally	Rat	–	Lead acetate could make important disruption of the basement membrane in testis seminiferous tubules of adult rats but the subsequent treatment of Ficus carica could reduce the effects in the short term	Asad et al. (2018)
LA, Clomiphene citrate (Clomid)	LA (10 mg/kg), daily, for 35 days, Clomid (0.35 mg/kg), daily, for 35 days	Orally	Rat	SOD, MDA	LA administration could result in reproductive toxicity, which clomiphene citrate treatment may stimulate testicular testosterone synthesis, sperm motility, and viability via LH	Wahab (2019)
LA	20, 100, 300 mg/kg, daily for 19 days, 6 months	Orally	Rat	–	Maternal lead acetate exposure during lactation in female rats could cause a significant decrease in testis weight and volume of offspring, seminiferous tubules diameter, and germinal epithelium height, mean sperm density of offspring at puberty, and testosterone levels	Dorostghoal et al. (2011)

Table 2 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, Pathways, Biochemical factors	Observations	References
LA, Vit C	LA (20 mg / kg), daily, for 56 days, Vitamin C (20 mg /kg), daily, for 56 days	Orally	Rat	MDA, GSH, SOD, Catalase	Administration of lead acetate to rats for 2 months could have a bad effect on testes by causing a decline in sperm count and viability. Furthermore, it causes to decrease in the antioxidant levels in testes as glutathione, superoxide dismutase, and catalase and results in increased lipid peroxidation Administration of Vit C as a natural antioxidant in combination with lead acetate for 2 months could improve semen quality, testosterone level, and antioxidant status	Mohamed et al. (2020)
LA, Curcumin	LA (25 mg/L), daily, for 2 months, Curcumin (15 mg/kg), daily, for 2 months	Orally	Mouse	ROS	Curcumin could increase the level of serum FSH and reduce the negative effects of lead in the oxidative status of lead-treated mice	Adelinik and Papian (2016)
LA, Propolis	LA (20 mg/ kg), Propolis (200; 400, 800 mg/kg), daily, for 35 days, 6 weeks	Orally	Mouse	–	Propolis administration could maintain the number of spermatocytes, spermatids, and Sertoli cells of mice testes from cell damage induced by lead acetate, but couldn't maintain the seminiferous tubules epithelium thickness that is induced by lead acetate	Tuti et al. (2017)
LA	0, 10, 20, 40, 80, 100 M for 12 or 24 h, 1 day	–	Mouse TM4 cell line	MK571, GSH, BSO, mrp1	Lead excretion could be mediated by Mrp1 and GSH in TM4 cells. Mrp1 could be one of the important targets for lead detoxification	Huang (2014)
LA	0.1 mg/kg, daily for 20 days, 6 weeks	IP	Mouse	–	Administration of lead acetate could result in a decrease in the body and testicular weights, birth rate, and inverse changes in all semen parameters of experimental male animals	Sodani and Nisreen (2011)

Table 2 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, Pathways, Biochemical factors	Observations	References
LA	18 mg/kg, daily, for 21 days, 3 weeks	Orally	Mouse	ROS	Lead acetate treatment could increase the number of abnormal sperms and enormous ROS	(Abd 2016)
LA	10, 30, and 70 mg/dL, daily, for 21 days	Orally	Rat	–	Lead acetate exposure could result in testicular atrophy and other histological anomalies in rats	Olajide et al. (2018)
LA	532 mg/kg, daily, for 11 days, 3 weeks	Orally	Mouse	–	LA administration could cause a significant decrease in body weight, change the arrangement and shape of spermatogonia cells, and reduced the number of Sertoli cells, and reduce the development of Leydig cells	Sharma and Garu (2012)
LA, Nigella sativa (NS)	LA (10 mg/kg), daily, 3 months, NS (100, 150, and 200 mg/kg), daily, 3 months	Orally	Rat	SOD, GSH	Exposure to low-dose chronic LA administration could induce gonadal spermatogenesis suppression, decreased TS, and reduced antioxidant defense in rats. Graded dose NS administration could improve the adverse effects of LA in the rats	Assi (2017)
LA, Gallic acid	LA (60 mg/kg), Gallic acid (50 mg/kg), daily, for 14, 35 days	Orally, IP	Rat	LDH, MDA	Lead acetate administration could result in degeneration and reduction in spermatogenic activity in seminiferous tubules. These effects on the male reproductive organ could be reverse significantly by Gallic acid due to its ability to scavenge for oxidative stress caused by Lead	Bello and Idris (2018)

Table 2 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, Pathways, Biochemical factors	Observations	References
LA, Bee pollen	LA (30 mg/ kg), daily, for 15 days Bee pollen (100 mg/kg), daily, for 15 days	Orally	Rat	–	Lead acetate administration could cause rat body weight loss which is exhibited by nutritional potential, lipid-lowering activity, and the anti-inflammatory response of bee pollen extract. Bee pollen supplementation could maintain the spermatogenesis progress at the first level with the ameliorative proliferation of spermatogonia and spermatocytes, marked by the thickness of the germinal epithelium and the normal Sertoli cells	Sofiane et al. (2018)
LA, Nigella sativa(NS) Eurycoma longifolia	LA (20 mg/ kg), NS (300 mg/ kg), Eurycoma longifolia (500 mg/kg), daily, for 30 days	Orally	Rat	–	Lead acetate has could reduce the sperm quality of rats, while pretreatment with Nigella sativa and Eurycoma longifolia could play an important role in reducing these harmful effects	Assi (2019)
LA, Ferulic acid	LA (20 mg/ kg), Ferulic acid (25 mg/kg), daily, for 10 days	Orally	Rat	ROS, LPO, TAC, CAT	Administration of LA could induce oxidative stress by reduction of LH, total testosterone, and FSH levels in serum, also increase the ROS level, lipid peroxide levels, as well as lysosomal enzyme activity such acid phosphatase and N-acetyl-β-glucosminidase Ferulic acid treatment could reduce the deleterious effects induced by LA	Kelainy et al. (2019)
LA, Quercetin (QE)	LA (150 mg/ kg), QE (75 mg/ kg), daily, for 35 days	Orally	Mouse	claudin 11, occludin, Cx 43	LA administration could affect the BTB by decreasing BTB related protein genes and the level of testosterone in rats, which couldn't improve by co-administration of quercetin	Dolati et al. (2020)

Table 2 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, Pathways, Biochemical factors	Observations	References
Lead sulfide nanoparticles (PbS NPs)	25, 50, 100 mg/kg, five days/ week, for 6 weeks	Orally	Rat	–	PbS NPs increased damage of spermatogenic cells and seminiferous tubules. It also decreased sperm count	Cao (2016)
Lead nitrate, Mercury chloride	Lead nitrate (45 mg/kg), Mercury chloride (0.02 mg/ kg), daily, for 32 days, 4 weeks	Orally	Rat	MDA, SOD, CAT, GPx, GST	Low doses of lead nitrate and mercury chloride could cause testicular toxicity in male rats. It may be related to the oxidative effects of them on the testis cell membranes and also testis tissues. Mercury chloride treatment could induce more increases in SOD, CAT, GST, GPx activities, MDA levels, and histopathological changes than lead nitrate treatment. Also, treatment with a combination of lead nitrate and mercury chloride could cause more harmful effects than the use of them alone	Bas et al. (2016)
Lead nitrate	8, 18, and 28 mg/L, daily, for 30, 60, and 90 days	Environmental in water	Fish	–	Exposure to lead nitrate could cause disorganization and shaping the changing of seminiferous tubules, centralization of spermatozoa, and reduction in the number of spermatozoa in fishes	Shivani (2018)
Lead nitrate, Coriander	Lead nitrate (40 mg/kg), daily, for 40 days, Coriander (300 mg/kg), daily, for 33 days	Orally	Mouse	SOD, CAT, GSH	Lead nitrate administration could induce oxidative stress, which could improve by Coriander treatment	Sharma et al. (2010)
Lead nitrate, Zinc chloride, QE	Lead nitrate (20 mg/kg), Zinc chloride (2 mg/kg), QE (50 mg/ kg), daily, for 21 days, 3 weeks	Orally, IP, Orally	Rat	–	Lead nitrate treatment could induce shrinkage of seminiferous tubules with degeneration and marked widening of interstitial spaces, disturb the arrangement of germinal epithelium, which could improve by quercetin or zinc chloride	Hanan and Abd (2015)

Table 2 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, Pathways, Biochemical factors	Observations	References
Lead chloride, Cadmium chloride	Lead chloride (74 mg/kg), Cadmium chloride (1 mg/kg), single-dose, 1 day	Subcutaneous (SC)	Mouse	–	A combination of lead and cadmium could disrupt the BTB, and then cause histopathological lesions within the testis	Maria de Lourdeset al. (2012)

administration of rutin, a glycoside of the flavonoid quercetin (Kandemir et al. 2020). Hg exposure has also reduced testosterone levels, and sperm speed, motility, and vitality in rat models. Vitamin C could ameliorate Hg effects on the spermatozoa's speed and motility, while date palm exerted beneficial effects on the testosterone and spermatozoa speed. Yet, the combined administration of these two agents has only amended the testosterone level and spermatozoa speed (Moumen et al. 2011). Hg vapor has also decreased the total size of the testis, diameters of seminiferous tubules, and the total size of seminiferous tubules. This agent remarkably reduced the quantity of Sertoli cells, spermatogonia, spermatocytes, and spermatids inducing degenerative changes in the spermatogenic cells and atrophy of seminiferous tubules (Altunkaynak et al. 2015). Table 3 shows the results of studies that assessed the effect of Hg on male infertility.

Cobalt (Co)

Intra-articular injection of high dose cobalt–chromium (CoCr) nanoparticles has led to a remarkable decrease in epididymal sperm motility, viability, and concentration, which were accompanied by elevation of abnormal sperm proportion and pathological alterations in the testis through induction of oxidative stress (Wang et al. 2013). Chronic ingestion of cobalt chloride ($CoCl_2$) by male mice has resulted in decreased fertility, a lower number of viable fetuses in females mated with these male mice, and reduction of the epididymis and testes weights. Moreover, sperm counts and daily sperm biosynthesis were considerably reduced in these male mice. These effects were accompanied by hypertrophy of the interstitial Leydig cells, degenerative changes in the spermatogonial cells, and necrotic alterations in the seminiferous tubules and the interstitial tissue (Elbetieha et al. 2008). Co_3O_4 nanoparticles have also induced sperm abnormalities, and DNA damage, while decreasing sperm motility and concentration. Yet, the administration of Omega-3 has weakened the genotoxic ability of these nanoparticles (Hussien and Mohamed 2018). Table 4 summarizes the results of studies that assessed the effects of Cobalt on male infertility.

Table 3 Summary of studies that assessed the effect of Hg on male infertility

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
Mercuric chloride (MCH), Alpha-tocopherol (α-toco), Lactobacillus Plantarum (LCB)	MCH (5 mg/kg), daily, for 5 days, α-toco (100 mg/kg), daily, for 3 weeks LCB (6 × 10 10 CFU 1.8701/kg), daily, for 3 weeks	SC, Orally, Orally	Rat	TNF-α, IL-6, caspase-3, Nrf2, Bax, STAR, 17β-HSD, 3β-HSD	MCH administration could induce testicular dysfunction by altering the expression of the STAR, 17β-HSD, 3β-HSD, Bax, and Nrf2 The LCB andα-toco combination could be considered a promising candidate for the treatment of effects induced by MCH	Fadda et al. (2020)
MCH, Ziziphus Spina-christileaf extract (ZSCLE)	MCH (0.4 mg/kg), ZSCLE (300 mg/kg), daily, for 28 days	Orally	Rat	NO, SOD, CAT, GPx, GR, TNF-α, IL-1β, Bcl-2, Bax, Caspase-3	MCH administration could cause a disturbance in the testicular function by increasing its accumulation, testis index loss, hormonal alterations, oxidative reactions induction, enhancing inflammatory and immune responses, and triggering the apoptotic pathway. ZSCLE treatment besides with MCH could reduce the alterations in the testicular tissue	Almeer (2020)
MCH, Rutin	MCH (1.23 mg/kg), Rutin (50, 100 mg/kg), daily, for 7 days	IP, Orally	Rat	MDA, TNF-α, COX-2	MCH administration could cause histopathological changes and reproductive damage due to oxidative stress and inflammation in testes and that rutin could improve the adverse effects of MCH	Kandemir (2020)
MCH, Pb, Cadmium ($CdCl_2$), Costus afer, Zinc chloride ($ZnCl_2$)	MCH (0.40 mg/kg), Pb (20 mg/kg), $CdCl_2$ (1.61 mg/kg), Costus afer (750, 1,500, 2,250 mg/kg), $ZnCl_2$ (0.80 mg/kg), daily, for 90 days	Orally	Rat	SOD; catalase, CAT, glutathione, GSH, malondialdehyde, MDA	Low-dose heavy metal mixture include Pb + $CdCl_2$ + MCH could reduce the antioxidant biomarkers, the lipid peroxidation marker and increase abnormal sperm morphology and plasma prolactin level and decrease epididymal sperm count, viability, FSH, LH, and testosterone. Costus afer treatment could reduce the heavy metal mixture-mediated toxicity	Anyanwu et al. (2020)

Table 3 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
MCH, Coconut oil (CO), Moringa oleiferaoil (MO)	MCH (5 mg/kg), CO (2 ml/kg), MO (2 ml/kg), daily, for 15 days	IP, Orally, Orally	Rat	17β-HSD, GSH, GSH-Px, MDA, CAT, SOD	MCH administration could induce reproductive dysfunction and oxidative damages, which MO and not CO could decrease the deleterious effects of MCH	Abarikwu et al. (2017)
MCH	0, 50, 100 ppm, daily, for 90 days	Orally	Rat	TBARS, SOD, CAT	MCH administration could induce oxidative stress, and antioxidant enzymes could be the effectiveness of as key regulators of basic testicular-cells processes, during the intoxication by MCH	Boujbiha (2009)
MCH, Sodium selenite, Vit E	MCH (1 mg/kg), Sodium selenite (0.25 mg/kg), Vit E (100 mg/kg), daily, for 4 weeks	Orally	Rat	TBARS, SOD, CAT, GPx	MCH exposure could result in an increase in the TBARS level and a decrease in the SOD, CAT, GPx activities, leading to testicular toxicity, which could be inhibited by sodium selenite and/or vitamin E treatment	Kalender et al. (2013)
MCH, Vit E	MCH (1.25 mg/kg), Vit E (2 mg/kg), daily, for 45 days	Orally	Mouse	SDH, ALKPase, ATPase, LPO, GSH, MDA	MCH administration could induce adverse effects on the testis, vas deferens, and epididymis by inducing androgen deficiency through direct toxic effects on these issues. However, These changes could not observe with co-administration of vitamin E and MCH	Rao and Sharma (2001)
MCH, Cilantro, Garlic extract	MCH (0.12 mg/kg), daily, for 2 months, Cilantro (25 mg /kg), daily, for 1 month, Garlic extract (50 mg /kg), daily, for 1 month	Orally	Rat	–	MCH administration could cause severe toxic tissue damage in testis and epididymis by reactive oxygen species produced by mercury within the animal's body. Cilantro and garlic extract as antioxidant vegetables could interact with mercury ions, neutralize them or bind with transition metals and prevent the ROS-mediated oxidative damage in the testis and protect the tissue in a manner that depends on the duration of treatment	El-Desoky et al. (2013)

Table 3 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
MCH, Moringa oleifera leaf extract	MCH (0.11, 0.13, 0.02, 0.03, 0.07, 0.05 ml), daily, for 21 days, Moringa oleifera leaf extract (0.6, 0.5, 0.4, 0.3 ml), daily, for 21 days	Orally	Rat	–	MCH administration could induce testicular damage, necrosis of seminiferous tubules and interstitial tissues, loss of spermatid, and the presence of multinucleated giant cells with sperm cell depletion, which M. Oleifera could reduce its deleterious effect	Asomugha et al. (2014)
MCH, Spirulina platensis	MCH (5 mg/kg), single-dose, 3-time a week, for 60 days, S. platensis (300 mg/kg), daily, for 2 months	SC, Orally	Rat	SOD, CAT, GPx, GSH, MDA	Spirulina platensis treatment could ameliorate the MCH-induced testis damages and sperm quality deteriorations	El-Desoky (2013)
MCH, Ginseng	MCH (2.0 mg/kg), Ginseng (100 mg/kg), daily, for 6 weeks	Orally	Rat	–	Ginseng treatment could protect the testis tissue from oxidative damage due to exposure to MCH and improve the histological and histochemical changes induced by it	Omayma et al. (2014)
MCH	4.6 mg/kg, 0.07 mg/kg, daily, for 30 days	IM	Rat	GPx1, GPx4	MCH administration could induce reproductive toxicity and reduce sperm quality by selenoproteins GPx1 and GPx4	Martinez (2017)
MCH	0.01, 0.05 or 0.1 mg/ml, daily, for 1–7 months	Orally	Rat	IFN-γ IL-4	MCH administration could induce arrest in spermatogenesis at the spermatocyte stage, hypo-spermatogenesis, and possibly impair steroidogenesis which together could affect male fertility	Penna (2009)
Mercury vapor	1 mg/m^3, daily, for 6 weeks	Environmental exposure	Rat	–	Exposure of rat testes to mercury vapor could significantly decrease the total volume of the testis, diameters of seminiferous tubules, and the total volume of seminiferous tubules, and the numbers of Sertoli cells and germ cells	Altunkaynak (2015)

Table 3 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
Methyl mercury	0.26 mg, every 48 h for 6 weeks	IP	Rat	–	Methyl mercury poisoning could disturb testicular steroid hormone secretion, which could be a part of the diminished stress tolerance and decreased sexual activity observed in the mercury-intoxicated animals	Burton and Meikle (1980)
Methyl mercury	20 mg/Lit, daily, for 8 weeks	Orally	Rat	–	Oral administration of methyl mercury oral administration could reduce the testosterone synthesis and decrease plasma testosterone level, but the sperm count and histological characterizes haven't been affected and no changed	Moussa et al. (2010)
Methyl mercury chloride	1 mg, weekly, for 20 days	SC	Mouse	–	Methyl mercury chloride administration could have minimal effect on the male reproductive tract weight	Choe et al. (2003)
Mercury, Selenium (Se)	Mercury (0.04, 0.12 ppm), Se (0.1 ppm), daily, for 30 days	Environmental in water	Fish	TAO, SOD, CAT, GPx, LPO, CP, NO	Mercury administration could induce oxidative stress in the testis of C. gariepinus and reduce antioxidant enzymes leading to histopathological alterations, disruption of hormone production, and diminished sperm quality. Se co-exposure could show protective effects by restoring the hormone levels, the antioxidant and oxidative stress markers and reducing histopathological alterations,	Ibrahim et al. (2019)
Mercury, $ZnCl_2$	Mercury (4 ppm), $ZnCl_2$ (800 ppm), daily, for 12 weeks	Orally	Mouse	–	Zinc could prevent mercury-induced testicular damage in the mouse, reducing testicular weights and epididymal sperm number	Orisakwe et al. (2001)
Mercury, Egg white, hydrolysate (EWH)	Mercury (0.07, 4.6 µg/kg), EWH (1 g/kg), daily, for 60 days	IM, Orally	Rat	ROS	Mercury treatment could decrease sperm number, impaired sperm morphology, increase ROS levels, lipid peroxidation, and antioxidant capacity in testis and epididymis. These harmful effects could be prevented by EWH	Rizzetti (2017)

Table 3 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
Mercury, Vit C, Date palm (DP)	Mercury (500 mg/kg) Vit C (8 mg/ animal in water), DP (100 g/kg), daily, for 6 weeks	Orally	Rabbit	–	Mercury administration could induce testicular toxicity by a decrease in speed, motility, and vitality of sperms and testosterone levels, which could be prevented by Vit C and DP	Moumen et al. (2011)
Mercury	5, 10, 20 mg/ kg, single-dose, 2 days	IP	Rat	–	Mercury administration could induce a negative effect on seminiferous tubules as well as interstitium; the place of blood vessel and steroidogenesis	Massanyi (2007)
Mercury	0.5, 1, 2 mg/kg, daily, for 10 days, 2 months	Orally	Rat	–	Mercury administration to pregnant rats could exhibit deleterious effects on male gonads during fetal life by alterations in the hormones and testicular cell quantity and this disorder could remain persistent during the post-neonatal period	Hematian (2014)
Mercury (Hg), Lead (Pb), Arsenic (As), Cadmium (Cd), Iron (Fe), Copper (Cu)	Hg (0.011 ppb), Pb (0.188 ppm), As (0.038 ppb), Cd (0.016 ppb), Fe (1.792 ppm), Cu (1.67 ppm), daily, for 28 days	Orally	Rat	GSH, LPO, MDA, CAT, SOD, SDH, 17β-HSD, ACP, GGT, LDH, ROS	Metal mixtures administration could induce oxidative stress and ROS generation that might be associated with altered histoarchitecture of testicular tissues The toxicity of the metal mixture was dose-dependent, while concurrent treatment of curcumin could reduce oxidative damage and maintain antioxidant activity in the tissues	Zoheb (2014)

Nickel (Ni)

Ni nanoparticles have induced apoptosis in Sertoli-germ cells through modulation of expression of LOC102551356, Insulin-like growth factor-binding protein 3 (Igfbp3), and alterations in mitochondrial apoptosis pathway (Kong et al. 2019). Intraperitoneal administration of Nickel sulfate ($NiSO_4$) has resulted in abnormal changes in the rat testes. However, oral administration of Nano-Selenium could reverse the $NiSO_4$-induced pathological changes, attenuate $NiSO_4$-induced apoptosis in rat testes, and decrease expressions of Bak, cytochrome c, caspase-9, and caspase-3 while increasing Bcl-2 expression (Liu et al. 2019). Table 5 summarizes the results of studies that assessed the effects of Nickel on male infertility.

Table 4 Summary of studies that assessed the impact of Cobalt on male infertility

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, Pathways, Biochemical factors	Observations	References
Cobalt chromium (CoCr)	20, 100, 500 µg/kg, once/week, for 10 and 11 weeks	Intra-articular injection	Rat	–	CoCr nanoparticles administration could reduce epididymal sperm motility, viability, and concentration, increase abnormal sperm rate and Co and Cr ions levels in serum and the testis, and induce testicular damage and pathological changes by oxidative stress	Wang (2013)
Cobalt chloride	200, 400, 800 ppm, daily, for 12 weeks	Orally	Mouse	–	Cobalt chloride administration could reduce fertility quality, the number of pregnant females, the number of viable fetuses, epididymal and testes weight, epididymal and sperm counts and daily sperm production, and several abnormalities including hypertrophy of the interstitial Leydig cells, congested blood vessels, degeneration of the spermatogonial cells and necrosis of both the seminiferous tubules and the interstitial tissue	Elbetieha et al. (2008)
Cobalt chloride	75, 125 mg/kg, daily, for 25 days	Orally	Mouse	–	Cobalt administration during the perinatal and postnatal periods could affect body weight during puberty but not significantly reduced reproductive organ growth	Madzharova et al. (2010)
Cobalt, Omega-3	Cobalt (20 mg/kg), Omega-3 (250 mg/kg), daily, for 3 days	Orally	Mouse	–	Cobalt administration could increase the number of micronucleated polychromatic erythrocytes (PCEs)/ 1000 PCEs, sperm abnormalities, and DNA damage could decrease sperm motility and concentration. Omega-3 administration in the accompany cobalt could modulate the genotoxic potential cobalt	Hussien and Mohamed (2018)

Nickel (Ni): Ni nanoparticles have induced apoptosis in Sertoli-germ cells through modulation of expression of LOC102551356, Insulin-like growth factor-binding protein 3 (Igfbp3), and alterations in mitochondrial apoptosis pathway (Kong 2019). Intraperitoneal administration of Nickel sulfate (NiSO4) has resulted in abnormal changes in the rat testes. However, oral administration of Nano-Selenium could reverse the NiSO4-induced pathological changes, attenuate NiSO4-induced apoptosis in rat testes, and decrease expressions of Bak, cytochrome c, caspase-9, and caspase-3 while increasing Bcl-2 expression (Liu 2019). Table 5 summarizes the results of studies that assessed the effects of Nickel on male infertility

Potassium dichromate

Exposure of male rat pups to Potassium dichromate has led to the induction of histological pathologies in the genital organs and reproductive accessory glands (Savici et al. 2020). This agent also has induced biochemical, cytogenetic, and sperm abnormalities resulting in the disruption in reproductive functions. These abnormalities were attenuated by the administration of Selenium or vitamin E (Mohammed and Abd-Elwahab 2020). Another study in male Wistar rats demonstrated induction of histopathological

Table 5 Summary of studies that assessed the impact of Nickel on male infertility

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
Nickel nanoparticle (Ni NPs)	(low dose 50, mid-dose 100 and high dose 200 µg/ml) for Sertoli cell culture (24 h)	In vitro	Rat	LOC102551356, Igfbp3, Bax, Bcl-2, Caspase3/9	Ni NPs by upregulating the expression of LOC102551356 could activate the mitochondrial apoptosis pathway via Igfbp3 in the P53-induced apoptosis pathway in Sertoli cells	Kong (2019)
Nickel sulfate (NiSO4)	1000 µM NiSO4 for Leydig cell culture (24 h)	In vitro	Rat	Ets1, Sik1, Bmp2, Src, Atf6, Smurf1, Mapk14, Cyp27a1, Acat2, Hsd17b7, Tgfa, Stat5b, Cyp1b1, Nr1h3, Wnt4, miR-130b-3p,	Nickel by targeting, mRNAs, miRNAs, and lncRNAs could induce steroidogenesis disturbance in rat Leydig cells	Qiannan (2020)
$NiSO_4$, Nano-Selenium	5 mg/kg ($NiSO_4$), daily, for 14 days, 0.5, 1, and 2 mg (Se/kg), daily, for 14 days	IP, Orally	Rat	GPx, MDA, Bak, Cytochrome-C, Caspase-3/9, Bcl-2	Nickle led to degenerative damage in testis tissue, increased germ cell apoptosis, while treatment with nano-Se via regulating mitochondria-mediated apoptotic pathway could protect the testicles against $NiSO_4$.	Liu (2019)
$NiSO_4$	0, 250, 500, and 1000 µmol/L (NiSO4) for Leydig cell culture (24 h)	In vitro	Rat	Bak, Cytochrome-C, GRP78, Caspase-3/9/12, GADD153,	Nickel via targeting mitochondria and endoplasmic reticulum stress (ERS) pathways could induce ROS generation and apoptosis in rat Leydig cells	Zou (2017)
Ni NPs	5, 15, and 45 mg/kg (Ni NPs), daily, for 30 days	Orally	Mouse	AKP, ACP, and LDH	Treatment with Ni NPs dose-dependently decreased the body weight and sperm motility index, and also increased the testicular enzyme assay and cell apoptosis in seminiferous tubules	Hu (2019)
Nickel chloride	5 mg/kg, daily, for 14 days	IP	Mouse	CatSper 1, CatSper 2	Treatment with nickel led to congestion of blood vessels, Leydig cell hyperplasia, maturation arrest, the disintegration of germ cells from their basement membrane, and	Mohammadi (2018)

abnormalities in testis tissue including disorganization of spermatogonial cell layers and deformation of Leydig cells following exposure with this agent. Yet, authors have shown amelioration of Potassium dichromate-induced abnormalities in male sex hormones levels in plasma, testicular antioxidant markers, sperm

Table 6 Summary of studies that assessed the impact of Potassium dichromate on male infertility

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, Pathways, Biochemical factors	Observations	References
Potassium dichromate ($K_2Cr_2O_7$)	25, 50, 75 ppm ($K_2Cr_2O_7$)	Orally	Rat	–	Exposure to $K_2Cr_2O_7$ during the suckling period produced severe congestive and degenerative lesions in genital organs and sexual accessory glands and led to Leydig cell necrosis, epithelial smoothing, and epithelial necrosis	Savici et al (2020)
$K_2Cr_2O_7$, Selenium (Se), Vit E	8 mg/kg ($K_2Cr_2O_7$), 0.5 mg/kg (Se), 200 mg/kg, (Vit E), daily, for 6 weeks	Orally	Rat	–	Exposure to $K_2Cr_2O_7$ increased total sperm abnormality and decreased sperm viability and serum testosterone level. Treatment with Se or vit. E improved all these effects	Mohammed and Abd-Elwahab (2020)
$K_2Cr_2O_7$, N-acetyl-L-cysteine (NAC), Taurine (Tau)	20 mg/kg($K_2Cr_2O_7$), 200 mg/kg (NAC), 1 mg/kg (Tau), for one day	IP	Mouse	GSH, MDA, NPSH	Exposure to $K_2Cr_2O_7$ increased lipid peroxidation in testicles and NPSH levels were decreased. NAC and taurine could ameliorate $K_2Cr_2O_7$-induced oxidative damage in testis	Boşgelmez and Güvendik (2019)
$K_2Cr_2O_7$, Citrus reticulata peel extract (C reticulata peel)	10 mg/kg ($K_2Cr_2O_7$), 200 and 400 mg/kg (C reticulata peel), daily, for 2 months	Orally	Rat	MDA, CAT, SOD, GP_X, TNF-α, IL6, p53	Exposure to K2Cr2O7 decreased sex hormones concentrations, testicular antioxidant parameters (TAC), sperm motility, and sperm count. Also, it increased sperm abnormalities, FSH concentration, testicular MDA, TNF-alpha, and nitric oxide levels. Disorganization of spermatogonial cell layers and deformation of Leydig cells was observed after K2Cr2O7 exposure. Treatment with Citrus reticulata peel improved the testicular histology and decreased p53 positive immune-reaction	Bashandy et al. (2019)
$K_2Cr_2O_7$	1/25, 1/50, 1/100 mg/kg ($K_2Cr_2O_7$), daily, for 90 days	Orally	Rat	–	Exposure to K2Cr2O7 decreased total sperm count and motility in rats	Saha et al. (2017)
$K_2Cr_2O_7$	1 and 2 mg/kg ($K_2Cr_2O_7$), daily, for 15 days	IP	Rat	MDA, CAT, Bax, Bcl-2	Exposure to K2Cr2O7 increased apoptosis in germinal cells, and Bax expression was induced in spermatogonia and spermatocytes cells	Marouani (2017)

Table 6 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, Pathways, Biochemical factors	Observations	References
$K_2Cr_2O_7$, ZnO-NPs	10.5 mg/kg ($K_2Cr_2O_7$), 5 days/ week, for 10 weeks, 5 mg/kg (ZnO-NPs), 3 days/week, for 10 weeks	Orally, P	Rat	MDA, GSH, SOD	Treatment with ZnO-NPs could increase the serum level of testosterone, sperm count, and decrease sperm abnormalities	Ibrahim et al. (2017)
$K_2Cr_2O_7$	20, 60, and 100 mg/ kg ($K_2Cr_2O_7$), daily, 6 weeks	Orally	Mouse	–	Exposure to K2Cr2O7 decreased sperm count and increased sperm abnormalities, dose-dependently	Cheaid yousif AL-fatlawi
$K_2Cr_2O_7$, Vit c	2 mg/kg ($K_2Cr_2O_7$), 1 ml, (Vit C), per day for 14 days	IP, Orally	Rat	–	Treatment with vitamin could ameliorate the harmful effects of K2Cr2O7 on the somniferous tubules, prostate, and seminal vesicle in the male rats	Al-Mukhtar et al. (2016)
$K_2Cr_2O_7$	5.0 mg/kg ($K_2Cr_2O_7$), daily, for 60 days	Orally	Mouse	MDA GPx, CAT, SOD	Exposure to K2Cr2O7 reduced the number of sperm count and let to the destruction of spermatids, Leydig cells, and Sertoli cells	Rasool et al. (2014)

motility, and sperm count by Citrus reticulata peel extract. Furthermore, the peel extract lessened the increase in sperm anomalies, follicle-stimulating hormone, testicular MDA, TNF-α, and NO concentrations induced by potassium dichromate (Bashandy et al. 2019). Table 6 summarizes the results of studies that assessed the effects of Potassium dichromate on male.

Arsenic (As)

Prepubertal exposure to low doses of sodium arsenite has led to significant abnormalities in spermatogenesis and histopathological changes in the epididymis in rats (da Cunha de Medeiros et al. 2019). Also, Sodium arsenite has diminished the sperm count and GST levels in the testis of mice. This agent also increases the abnormal configuration of the spermatozoa and lipid peroxidation levels. Notably, *Mucuna (M.) pruriens* has significantly alleviated the arsenite-induced effects on sperm count, GST levels, sperm abnormality, and lipid peroxidation levels (Concessao et al. 2020). Mitochondria have been identified as the major organelle that is affected by arsenite. This agent has induced obvious mitochondrial oxidative impairment in the testis, being demonstrated by iron buildup as well as accumulation of ROS and lipid peroxidation products (Fig. 2). Arsenite also induces ferroptosis-associated signaling pathways in the testis of mice. The effects of arsenite on the induction of ferroptosis cell death have been verified in vitro. Moreover, in vitro studies indicated that suppression of ferroptosis by ferrostatin-1 can reduce these adverse impacts in cells (Meng et al. 2020). Table 7 summarizes the results of studies that assessed the effects of as on male infertility.

Cadmium (Cd)

Cd has been shown to exert several adverse effects on male fertility including reduction of the relative testicular weight and induction of pathological alterations in the testes. These effects are exerted through the induction of oxidative stress and autophagy. Cd has also increased the MDA levels and reduced SOD,

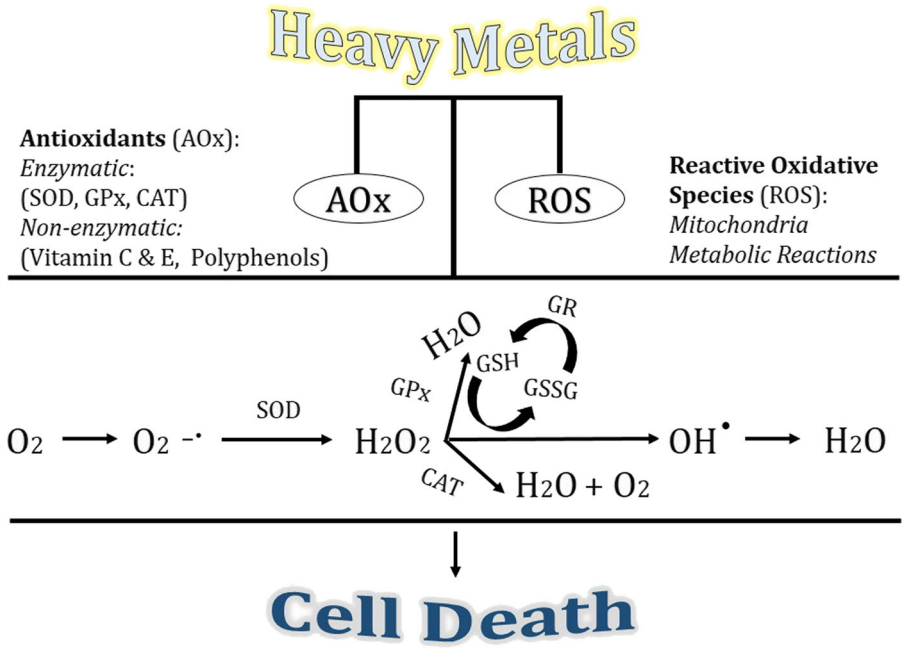

Fig. 2 The amount of ROS increases under heavy metal treatment. However, exogenous and endogenous antioxidants could protect cells against oxidative stress

GST peroxidase, catalase, and GST levels. Besides, Cd has enhanced expression levels of P62 and LC3-II. Notably, quercetin has been demonstrated to ameliorate these Cd-induced adverse effects (Wang et al. 2020). The adverse effects of Cd on the activity of antioxidant enzymes, serum levels of total SGT and thiol, and the size of seminiferous tubules have been verified in other studies as well. Yet, curcumin treatment has been shown to alleviate these toxic effects through compensating the adverse effects of Cd on lipid and protein peroxidation, enhancing the activity of the antioxidant system, and amending several morphological changes in the testis (Momeni and Eskandari 2020). Table 8 shows the results of studies that assessed the effect of Cd.

Other agents

Several other agents such as Tributyltin (TBT), lithium, and manganese have been shown to affect testicular morphology and antioxidant system. Table 9 shows the results of studies that assessed the effects of these agents on male fertility.

Antioxidants

Antioxidant effects of Selenium (Se)

Se is among the mostly assessed agents with antioxidant activity. This agent has been shown to ameliorate the toxic effects induced by Pb and Cd. In vitro studies have shown that Se can increase the viability of Sertoli cells and expression of structural proteins of the blood-testis barrier. Moreover, this agent has a potent role in the induction of anti-inflammatory cytokines (Adegoke et al. 2018). Moreover, oral administration of Se has enhanced the quantities of various types of spermatogenic cells and increased the expression of growth factors and steroids in diabetic rats (Moghazy et al. 2016). Table 10 summarizes the results of studies that assessed the beneficial effects of Se on male fertility parameters.

Other antioxidants

Zinc, carthinine, arginine, and vitamin B12 are other agents that enhance sperm quantity and motility

Table 7 Summary of studies that assessed the impact of as on male infertility

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, Pathways, Biochemical factors	Observations	References
Sodium arsenite ($NaAsO_2$), Mucuna (M) pruriens (aqueous seed extract)	40 mg/L (SA), 500, 1000, and 2000 mg/kg (M), daily, for 45 days	Orally	Mouse	GSH, TBRAS	$NaAsO_2$ decreased the sperm count and testicular glutathione levels increased TBRAS content and led to the abnormal architecture of the spermatozoa. Treatment with M. pruriens could ameliorate the adverse effects of $NaAsO_2$	Concessao et al. (2020)
Arsenite	0.5, 5, and 50 mg/L, daily, for 6 months	Orally	Mouse	MDA, GSH, GSSG, GPX4, ATP, ROS, GPX4, IREB2, SLC7A11, VDAC3, p-JNK1/2, p-ERK1/2, CHOP,	Arsenite reduced the number of sperm, led to severe damage of seminiferous tubules, enhanced ROS, and activated ferroptosis-related signal pathways. Moreover, in vitro study (GC-2spd cells) showed that arsenite could trigger ferroptosis cell death	Meng (2020)
Arsenic (As)	0, 0.2, 2, and 20 ppm (As2O3), daily, for 6 months	Orally	Mouse	TDRD-1/6/7, DDX25, CRM1, HMG2, PGK2, H4	As reduced sperm count, the ratio of elongated/round spermatids, while increased the sperm malformation ratio. It also by altering the expression of some genes could disrupt spermatogenesis	Han (2020)
Sodium arsenite ($NaAsO_2$), Caryopteris grata grata	10 mg/kg ($NaAsO_2$), 150, 300, and 400 mg/kg (C. grata), daily, for 10 days	Orally	Mouse	CAT, POD, SOD, GSH, GSR	$NaAsO_2$ reduced serum testosterone levels and testicular antioxidant enzymes (CAT, POD, SOD, GSH, and GSR). Treatment with crude extract of C. grata leaves could attenuate the deleterious effects of arsenic	Ullah (2019)
Sodium arsenite ($NaAsO_2$), Chromolaena odorata (CA) (ethanolic leaf extract)	2.5 mg/kg ($NaAsO_2$), 200 mg/kg (CA), daily, for 2 weeks	Orally	Rat	-	$NaAsO_2$ reduced serum testosterone levels, sperm parameters, and testicular weight, while increased LH and LDH levels. However, CA had sperm protective properties via protecting testicles against arsenic toxicity	Ola-Davies and Oloye (2019)
Sodium arsenite ($NaAsO_2$), Selenium (Se or Na_2SeO_3), Diphenyl diselenide (DPDS)	60 µg/L ($NaAsO_2$), 0.25 mg/kg (Se), 2.5 mg/kg (DPDS), daily, for 45 days	Orally	Rat	ACP ALP, LDH-X, G6PD, SOD, CAT, GST, GPx, RONS, LPO, NO, MPO, Caspase-3, TNF-α, IL-1β	$NaAsO_2$ reduced hormones (LH, FSH, T, intra-testicular T), enzymes of testicular function (ACP, ALP, LDH, G6PD), sperm parameters, and antioxidant enzymes, while increased Caspase-3 activity, RNOS, LPO, NO, MPO, TNF-α, IL-1β, and testicular arsenic levels. Treatment with Se or DPDS via suppressing caspase-3 activation, inflammation, oxidative stress could improve reproductive function in rats exposed to arsenic	Adedara (2019)

Table 7 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, Pathways, Biochemical factors	Observations	References
Sodium arsenate (Arsenic or As), Phytochemicals (Ellagic and Ferulic)	200 ppm (As), 50 mg (ellagic and ferulic), daily, for 40 days	Orally	Mouse	CAT, GSH, TAC, SOD, LPO, Nfe2l2 StAR, Ppargca1	Treatment with phytochemicals could attenuate the adverse effects of arsenic on reproductive function	Guvvala et al. (2019)
Sodium arsenate (Na_3AsO_4, arsenic or As), Spirulina platensis (Sp)	5 mg/kg (As), 300 mg/kg (Sp), daily, for 2 months	Orally	Rat	MDA, GSH, Caspase-3	Treatment with Sp could attenuate the adverse effects of As on reproductive function	Ahmed et al. (2019)
Sodium arsenite ($NaAsO_2$)	0.01 and 10 mg/L ($NaAsO_2$), daily, for 23 days	Orally	Rat	–	Expose to $NaAsO_2$ led to abnormal seminiferous tubules and decreased the number of Sertoli cells. In $NaAsO_2$-treated animals, spermatogenesis, epididymal histophysiology, sperm quality, and fertility, have been impaired	da Cunha de Medeiros (2019)
Sodium arsenite ($NaAsO_2$)	5 and 50 ppm ($NaAsO_2$), daily, for 180 days	Orally	Mouse	T-SOD, GSH, MDA, ROS, Bax, Bcl-2, Caspase-3, p21, p53, Cyclin B, cdc2	Arsenite reduced sperm count, GSH, T-SOD, cdc2, cyclin B1, Bcl-2, destroyed the structure of the testicles, induce G2/M phase arrest in testes, and increased the expression of some genes (p53, p21, caspase-3, and Bax), the levels of MDA and ROS	Zeng et al. (2019)
Sodium arsenite ($NaAsO_2$)	1, 10, 50, and 100 µM ($NaAsO_2$), 2 h and 24 h for testis organ culture	–	Mouse	CAT, SOD, POD, TBARS, ROS	$NaAsO_2$ could increase ROS and TBARS levels, sperm DNA damage, and also could decrease the levels of CAT, SOD, and POD	Anwar and Qureshi (2019)
Sodium arsenite ($NaAsO_2$), Sodium arsenate (Na_3AsO_4)	0.01 and 10 mg/L ($NaAsO_2$ or Na_3AsO_4), daily, for 56 days	Orally	Rat	SOD, CAT, GST, NO	Both arsenic compounds (10 mg/mL) affected epididymal sperm counts, percentage of sperm with intact membranes, antioxidant enzymes, seminiferous epithelium height, epithelium somatic index	de Almeida Lima (2018)
Sodium arsenite ($NaAsO_2$), Sodium arsenate (Na_3AsO_4)	0.01 and 10 mg/L ($NaAsO_2$ or Na_3AsO_4), daily, for 56 days	Orally	Rat	–	Both arsenic compounds (10 mg/mL) decreased daily sperm production, the number of spermatids, sperm in the epididymal caput/corpus regions, while progressive sperm motility, sperm morphology, and serum level of testosterone remained without change	Souza (2016)

Table 7 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, Pathways, Biochemical factors	Observations	References
Sodium arsenite ($NaAsO_2$),	5 mg/L ($NaAsO_2$), daily, 60 days	Orally	Mouse	LHR, StAR, AB, Bcl-2, MDA, T-SOD, T-AOC, H_2O_2	$NaAsO_2$ reduced body weight, sperm count, spermatogenic cell counts, serum testosterone levels, expression of steroidogenic-related genes (LHR, StAR, and ABP), induced abnormal testicular pathological changes, and increased the percentage of sperm malformation, caspase-3 activity, Bax expression, and TUNEL-positive cells	Li et al. (2018)
Sodium arsenite ($NaAsO_2$), Ellagic acid (EA)	10 mg/kg ($NaAsO_2$), 10 and 30 mg/kg (EA), daily, for 21 days	Orally	Rat	TAC, CAT, MDA, SOD, GPx, NO, GSH, TNF-α, IL-1β,	$NaAsO_2$ reduced serum testosterone levels, GSH, TAC, SOD, GPx, CAT, Seminiferous tubular diameter, luminal diameter, and epithelial height, and also increased NO, MDA, TNF-α, IL-1β. Treatment with EA could reduce oxidative stress parameters, testicular arsenic accumulation and, and improve histological parameters, serum testosterone level, and testicular antioxidant markers	Mehrzadi (2018)
Sodium arsenite ($NaAsO_2$), Baicalin	10 mg/kg ($NaAsO_2$) daily, for 2 days, 10 mg/kg (baicalin), daily, for 7 days	Orally	Rat	NO, SOD, GSH, TNF-α, MDA, NF-κB, Caspase-3	Baicalin reversed the effects of arsenic on levels testicular MDA, NO, TNF-α, NK-κB p65 unit, and caspase-3, increased SOD, GSH, serum level of testosterone, and the testicular histopathological changes	Fouad et al. (2018)
Sodium arsenate (Na_3AsO_4, or As), Imidacloprid (IMI)	50, 100, and 150 ppb (As), 16.9 mg/kg (IMI), daily, for 28d ays	Orally	Rat	TTH, GST, GR GPx, SOD, CAT, MDA	IMI and/or arsenic (150 ppb) increased MDA levels, AOPP, led to severe seminiferous damage (necrosis, tubular shrinkage, decreased lumen diameter, depletion of germ cells), and decreased antioxidant enzymatic activities and total thiols. Imidacloprid had potentiating effects on arsenic-induced testicular toxicity	Mahajan et al. (2018)
Sodium arsenite ($NaAsO_2$), Vit E	5 mg/kg ($NaAsO_2$), 200 mg/kg (Vit E), daily, for 12 weeks	Orally	Goat	–	Treatment with Vit E could increase reduced-testicular measurements (scrotal circumference, width, length, and weight) in animals exposed to arsenic. It could also prevent vacuolations, loss of germinal epithelium, and atrophy of Leydig cells	Zubair (2017)
Sodium arsenite ($NaAsO_2$)	5 mg/kg ($NaAsO_2$), 5 days/week, for 8 weeks	Orally	Rat	–	$NaAsO_2$ reduced seminiferous tubule diameter and testis weight, which may be due to inhibition of the steroidogenesis resulting from disorders of testosterone metabolism due to the activation of immunological responses of macrophages	de Araújo Ramos et al. (2017)

Table 7 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, Pathways, Biochemical factors	Observations	References
Arsenic, Epigallocatechin-3-gallate (EGCG)	200 ppm (As), 20 mg/kg (EGCG), daily, for 40 days	Orally, IP	Mouse	LPO, GSH SOD, CAT	Arsenic reduced sperm parameters, sperm kinematic attributes, structural membrane integrity (SMI), functional membrane integrity (FMI), mitochondrial membrane potential (MMP), and antioxidant enzymes. Treatment with EGCG could restore arsenic-induced adverse effects on reproductive function	Guvvala et al. (2017)
Sodium arsenite ($NaAsO_2$), Curcumin	5 mg/kg ($NaAsO_2$), 100 mg/kg (curcumin), daily, for 5 weeks	IP	Mouse	–	Arsenite reduced sperm parameters (number, motility, viability, and normal morphology) and acrosome integrity of spermatozoa, while treatment with curcumin could attenuate the adverse effects of arsenite on the above-mentioned parameters	Momeni and Eskandari (2016)
Sodium arsenite ($NaAsO_2$), Silymarin	Spermatozoa treated with10 μM ($NaAsO_2$) and 20 μM (silymarin), for 180 min	–	Ram	–	$NaAsO_2$ reduced sperm viability, non-progressive motility, and intact mitochondrial membrane potential, while treatment with silymarin had a protective effect on the mentioned-parameters	Eskandari and Momeni (2016)
Sodium arsenite ($NaAsO_2$), Melatonin (M)	5 mg/kg ($NaAsO_2$), 25 mg/kg (M), daily, for 30 days	Orally, IP	Rat	PCNA, SOD, GPx, MDA, CAT	$NaAsO_2$ increased the number of apoptotic germ cells and MDA levels, and also decreased PCNA-positive germ cells and antioxidant enzymes. Treatment with melatonin could ameliorate testicular injury via suppressing oxidative stress	Uygur (2016)
Sodium arsenite ($NaAsO_2$) Quercetin (QE)	10 mg/kg ($NaAsO_2$), 50 mg/kg (QE), daily, for 15 days	Orally	Rat	PCNA, SOD, CAT, GSH-Px, MDA	A decrease in the SOD, CAT, and GSH -Px activities and the number of spermatogenic cells, also an increase in the number of apoptotic cells and the MDA levels were observed when rats were exposed to $NaAsO_2$. Treatment with quercetin had protective effects against $NaAsO_2$-induced testicular damage	Baltaci (2016)

Table 8 Summary of studies that assessed the effect of Cd on male infertility

Metal/antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
Cadmium chloride (CdCl2), Quercetin (QE)	2 mg/kg (CdCl2), 50 mg/kg (QE), daily, for 4 weeks	IP	Rat	SOD, GPx, MDA, GSH, CAT, p62, LC3-I/III	Cd reduced both body weight and testicular weights and induced pathological changes in testes, while treatment with QE could protect testes against Cd toxicity by alleviating oxidative stress and autophagy	Wang et al. (2020)
CdCl2, Grape seed oil (GSO)	7.48 mg/kg (CdCl2), 1 mL/kg (GSO), daily, for 30 days	Orally	Mouse	–	Treatment with GSO could improve sperm parameters relative to the group exposed to Cd	Elhamalawy (2020)
CdSO4, Raphanussativus (Rs)	15 mg/kg (Rs), 0.15 mg/kg (CdSO4), daily, for 4 weeks	Orally	Rabbit	–	Treatment with Rs could improve sperm parameters and serum level of testosterone relative to the group exposed to Cd	Yasmina (2020)
CdCl2, Euterpe oleracea oil (EO)	4.28 mg/kg (CdCl2), daily, for 1 week, 50, 100, and 150 mg/kg (EO), daily, for 42 days	Orally	Mouse	SOD, MDA, NO, CAT	Cd could reduce the epithelium height, increase both luminal diameter and tubule-epithelium ratio, nucleus and cytoplasm volumes of Leydig cells. Treatment with EO increased germ cell viability, enhanced serum testosterone levels, testicular manganese (Mn), and zinc (Zn) concentrations	Mouro (2020)
CdCl2, Polygonatum sibiricum (PS)	2.5 mg/kg (CdCl2), single-dose, 10 g/kg (PS), daily, for 5 weeks	IP	Mouse	SOD, MDA, GSH, CAT, ROS, TXNIP, NLRP3, Caspase-1/3/9, IL-1β, CytC	Treatment with PS could improve sperm parameters, increase testicular weight, increase serum testosterone level, and also by inhibiting oxidative stress and mitochondria-mediated apoptosis could protect testis against CdCl2 injury	Han (2020)
Cd, Glutamine (G)	5 mg/kg (Cd), 1 g/kg (G), daily, for 30 days	Orally	Rat	G6PD	Cd decreased bodyweight and sperm parameters and serum testosterone level, altered sperm morphology, caused atrophy of the seminiferous tubules, disrupted testicular architecture, lumen, Sertoli cells, and spermatogonia, while treatment with glutamine by targeting G6PD activity could ameliorate the deleterious effects of Cd	Olaniyi (2020)

Table 8 continued

Metal/antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
Cd, Cyanidin-3-O-glucoside (C3G)	5 mg/kg (Cd), 500 mg/kg (C3G), daily, for 30 days	Orally	Mouse	SOD, MDA, GSH, GSSG, HDAC, HAT, Bax, Bcl-2, Bad, Caspase-3, p53, p38, Lys5/8/12, ERK, JNK	Treatment with C3G could improve sperm parameters, increase testicular weight, increase Johnsen's Score, and also via histone ubiquitination and mitigating oxidative damage could restore spermatogenic dysfunction in testicles exposed to Cd	Bao (2020)
Cd, Curcumin	5 mg/kg (Cd), single injection, 100 mg/kg (curcumin), 24 h	IP, SC	Mouse	MDA, SOD, GPx, CAT, thiols, GSH	Treatment with curcumin could protect the testis against Cd-induced oxidative stress and histopathological damages	Momeni and Eskandari (2020)
Cd, Omega-3 oil	40 and 60 mg/L (CdCl2), 4 g/kg (omega-3 oil), daily, for 30 days	Orally	Rat	–	The present investigation concluded that omega-3 oil could play a protective role against cadmium-induced testicular toxicity due to the antioxidant power of the oil	Ismail and Aziz (2020)
CdCl2, Caffeic acid phenethyl ester (CAPE)	1 mg/kg (CdCl2), 1 mg/kg (CAPE), daily, 7 days	IP	Mouse	MDA, SOD, CAT, GSH, LPO, H2O2	CdCl2 reduced body/testis weight ratio and zinc levels in testis. It could also decrease the activity of antioxidant enzymes, while treatment with CAPE could improve the testicular dysfunction induced by CdCl2	Gong et al. et al. (2019)
Cd, Astaxanthin nanoparticles (Ast NPs)	1 mg/100 (Cd), daily, for 7 days, 25 mg/kg (Ast NPs), daily, for 5 weeks	SC, Orally	Rooster	MDA, CAT SOD, TAC, GPX	Ast NPs could act as a potent antioxidant in protecting rooster testes against oxidative stress induced by Cd	Najafi et al. (2020)
CdCl2, Silymarin (SL), Milk thistle (MT)	150 and 300 mg/kg (CdCl2), 250 mg/kg (SL), 10 g/kg (MT), daily, for 60 days	Orally	Quail	–	CdCl2 reduced body weight in quails. Also, testicles atrophied and no active spermatozoa were observed in the lumen of seminiferous tubules, while treatment with MT and SL could ameliorate the rate of mortality, organ weights, spermatogenesis, and histopathological lesions	Saleemi (2019)

Table 8 continued

Metal/antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
CdCl2, Pleurotus tuberregium	3 mg/kg (CdCl2), either 500 or 1000 mg/kg (Pleurotus tuberregium), daily, for weeks	Orally	Rat	SOD, CAT	Treatment with aqueous extract of P. tuberregium reduced the oxidative stress engendered by Cd in the testicle of rats	Lolodi et al. 2019)
Cd, Carpolobia lutea	1 mg/kg (Cd), single-dose, 100 and 200 mg/kg (methanolic root extract of C. Lutea), daily, for 6 weeks	IP, Orally	Rat	–	Cd reduced testicular 17β-HSD activity, testosterone, LH, and FSH levels. On the one hand, treatment with carpolobia lutea increased the levels of mentioned-hormones	Eze (2019)
CdCl2, Vigna angularis	4 mg/kg (CdCl2), single-dose, 300 and 450 mg/kg (aqueous extract of V. angularis), daily, for 12 days	SC, Orally	Rat	SOD, MDA	Cd decreased SOD and sperm count and increased MDA levels, prostate cholesterol levels, serum testosterone, LH, and FSH levels, while treatment with V. angularis was unable to effectively remove the toxic effect of cadmium on the testes of rats	Adaikpoh et al. (2019)
CdCl2, Cinnamomum Zeylanicum	20 mg/kg (CdCl2), 200 mg/kg (aqueous extract of Cinnamon), daily, for 8 weeks	Orally	Rat	Nrf2	Cd reduced testosterone hormone level and sperm viability, led to focal degeneration with loss of spermatogenic series in the seminiferous tubules, and also increased sperm abnormality and Nrf2 gene expression. However, treatment with Cinnamon could decrease testicular damage	Ibrahim and Abo-Kora (2018)
CdCl2, Agaricus blazei polysaccharide (ABP)	140 mg/kg (CdCl2), 30 mg/ml (ABP), daily, for 20, 40, and 60 days	Orally	Chicken	MDA, TNF-α, GSH-Px, SOD, TNF-α, IL-6, IL-1β, HSP60, HSP70, HSP90	ABP could improve Cd-caused testicular tissue damage by decreasing the Cd accumulation and MDA content, protein expressions of HSP60, HSP70, and HSP90, and mRNA levels of TNF-α, IL-1β, and IL-6, and also by increasing the SOD and GSH-Px activities	Song et al. (2018)

Table 8 continued

Metal/antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
CdCl2, Green tea (GT)	1.5 mg/kg (CdCl2), single-dose, 1.5% (w/v) (aqueous extract of GT), daily, for 13, 25, and 49 days	IP, Orally	Rat	MDA, TBA	Cd reduced the number of spermatogonia, Sertoli, and Leydig cells, the thickness of the germinal layer, the mean of the diameter of seminiferous tubes, sperm motility and count, and serum testosterone levels., while treatment with green tea could eliminate the adverse effects of Cd	Mahmoudi (2018)
Cd, Shilajit	2 mg/kg (Cd), 50, 100, and 200 mg/kg (Shilajit), daily, for 5 weeks	Orally	Mouse	-	Treatment with Shilajit could restore spermatogenesis, increase weights of reproductive organs, improve sperm motility and count, and enhance serum level of testosterone and the activities of testicular 3β-HSD and 17 β-HSD enzymes in mice exposed to Cd	Mishra et al. (2018)
CdCl2, D-3-O-methylchiroinositol	2.5 mg/kg (CdCl2), 2 mg/kg (D-3-O-methylchiroinositol), daily, for 3 months	Orally	Rat	-	Cd reduced the volume of spermatozoa in the seminiferous tubules, spermatogenesis, and sperm count and motility, while treatment with D-3-O-methylchiroinositol could restore the testicles to normal spermatogenic activities	Uwagie-Ero (2018)
CdCl2, Ghrelin	2 mg/kg (CdCl2), single dose, 10 nmol/100 µl saline (ghrelin), daily, for 5 and 10 days	IP, SC	Rat	SOD, GPx, CAT, GSH, TBARS	Cd reduced the mean of Johnsen's score, impaired spermatogenesis associated with inter-tubular hemorrhage, and decrease the activity of antioxidant enzymes, while treatment with ghrelin by increasing the activity of antioxidant enzymes could attenuate the testicular injury upon Cd toxicity	Kheradm et al. (2015)
Cd, Pentoxyfiline (P)	2.5 mg/kg (Cd), 100 mg/kg (P), daily, for 30 days	Orally	Rat	SOD, MDA, CAT, GSH	Cd impaired spermatogenesis, reduced weights of body and reproductive organs, semen characteristics, testosterone levels at both serum and testicular source, zinc, and antioxidant enzymes, while increased testicular cholesterol and MDA levels. Pentoxifylline treatment could protect testes against cadmium toxicity	Zakaria and Al-Busadah (2015)

Table 8 continued

Metal/antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
Cd, Propolis	1 mg/kg (Cd), 50 mg/kg (propolis), daily, for 17 days	IP, Orally	Rat	HIF-1α	Cd reduced the mean of Johnsen's score, the diameters of seminiferous tubules, and serum testosterone levels, and also increased tissue levels of MDA and HIF-1α, and the number of apoptotic cells, while treatment with propolis improved histological appearance in rats exposed to Cd	Çilenk, Öztürk and Sönmez (2016)
CdCl2, ZnCl2	2.2 mg/kg (CdCl2), 2.2 mg/kg (ZnCl2), 4 times weekly for 2 months	SC	Rat	TNF-α, NO, GSH, SOD, CAT, iNOS	Cd increased testicular iNOS immunoreactivity and degenerations, testicular MAD, TNF-α, and NO levels, blood H_2O_2 and FSH, while decreased testicular ascorbic acid, zinc, SOD, GSH, CAT, sex organ weight, plasma testosterone, LH, and sperm motility and count. Treatment with Zn could ameliorate the toxic impacts of Cd on spermatogenesis, oxidative stress, and sex hormones	Bashandy et al. (2016)
Cd, Caffeic acid phenethyl ester (CAPE)	1 mg/kg (Cd), 10 μmol/kg (CAPE), daily, for 30 days	SC, IP	Rat	GSH-Px, SOD, CAT, MDA	Treatment with CAPE via its anti-oxidant and anti-apoptotic properties led to a reduction in the number of apoptotic cells in testis tissues and an increase in serum testosterone levels and the activity of antioxidant enzymes	Erboga (2016)
CdCl2, Spirulina platensis (SP)	2 mg/kg (CdCl2), 150 mg/kg (SP), daily, for 10 days	SC, IP	Rat	17β-HSD3, 3β-HSD6, NR5A1	Cd reduced the weight of reproductive organs, sperm count and motility, the levels of testosterone, LH, and estradiol hormones, the expression of steroidogenic genes, and also led to testicular degeneration that was represented by desquamation, necrosis, and severe calculation. Treatment with SP could improve spermatogenesis and steroidogenesis in rats exposed to Cd	Farag et al. (2016)

Table 8 continued

Metal/antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
CdCl2, Flavocoxid	2 mg/kg (CdCl2), 20 mg/kg (flavocoxid), daily, for 14 days	IP	Mouse	ERK, TNF-α, COX-2, 5-LOX, Bcl-2, TGF-β3, Occludin, Claudin-11, N-cadherin, MDA	Cd disrupted the blood-testis barrier, induced structural damages in the testis, increased p-ERK 1/2, TNF-α, COX-2, 5-LOX, Bax, MDA, FSH, LH, TGF-β3, while decreased Bcl-2, testosterone, inhibin-B, occludin, N-Cadherin. Treatment with flavocoxid could decrease the rate of TUNEL-positive cells, and improve testicular germ cell impairment in mice exposed to Cd	Minutoli (2015)
CdCl2, Thymoquinone (TQ)	2 mg/kg (CdCl2), single dose, 10 mg/kg (TQ), daily, for 5 days	IP	Rat	MDA, GSH, NO, SOD, iNOS, TNF-α, COX-2, NF-κB, Caspase-3	Cd reduced serum testosterone level, testicular GSH, and SOD activity, while increased in testicular cadmium ion, MDA, NO. It also led to widespread necrosis and vacuolization of the seminiferous tubular cells and enhanced the expression of iNOS, TNF-α, COX-2, NF-κB, and caspase-3 in the cells of seminiferous. Treatment with TQ could abrogate the toxic effect of cadmium on rat testes	Fouad and Jresat (2015)
CdCl2, strawberry methanolic extract (SME)	6.5 mg/kg (CdCl2), 250 mg/kg (SME), daily, for 5 days	IP, Orally	Rat	NO, LPO, GSH, CAT, CAT, SOD2, GPX1, GR, NFE2L2, HMOX1, Bax, Bcl-2, PCNA, TNF-α, Nrf2, HO-1	Cd increased LPO, NO, Bax, and TNF-α, while decreased GSH, CAT, SOD2, GPx, GR, Bcl-2, PCNA, NFE2L2, HMOX1, and serum testosterone level. Treatment with SME had a protective role against Cd-induced oxidative damage to the testes	Elmallah et al. (2017)

Table 8 continued

Metal/antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
CdCl2, Quercetin (QE)	5 mg/kg (CdCl2), 20 mg/kg (QE), daily, for 4 weeks	Orally	Rat	SOD, CAT, GPx, GSH, Vitamin C and E, TAC, Bax, Bcl-2, Caspase-3	Cd decreased testicular enzymatic (SOD, GPx, and CAT) and non-enzymatic (glutathione, vitamins C and E) antioxidants, Johnsen's score, the weight of reproductive organs, and Leydig cell count, sperm count and motility, and hormones including, GnRH, FHS, LH, and testosterone, while increased testicular glucose, lactate, and lactate dehydrogenase activity, the ratio of Bax/Bcl-2, caspase-3 activity, and abnormal sperm. However, treatment with QE could protect the testis from Cd toxicity	Nna (2017)
CdCl2, Quercetin (QE)	5 mg/kg (CdCl2), 20 mg/kg (QE), daily, for 4 weeks	Orally	Rat	NO, Cholesterol, 3β-HSD, 17β-HSD	Cd increased mount, intromission and ejaculatory latencies, serum NO, and testicular cholesterol, while decreased penile cyclic guanosine monophosphate, 3β-HSD, and 17β-HSD activities, and testosterone concentration. Treatment with QE could attenuate the adverse effects of Cd on steroidogenesis, penile erection, and sexual behavior	Ujah (2018)
Cd, Hibiscus sabdarrifa L (HSA)	3 mg/kg (Cd), daily, for 5 days, 3 g/kg (HSA), daily, for 10 days	Orally	Rat	-	Cd reduced serum testosterone level, while increased FSH and LH levels. Treatment with HSA could attenuate the reproductive toxicity of Cd	Orororo et al. (2018)
Cd, Zinc (Zn), Magnesium (Mg)	1 mg/kg (Cd), 0.5 and 1.5 mg/kg (Zn), 0.5 and 1.5 mg/kg (Mg), daily, 3 for weeks	IP	Rat	MDA	Cd reduced sperm parameters and led to histological damage in testis, while increased testis MDA. Treatment with Zn and/or Mg could improve Cd testicular toxicity in rats	Babaknejad (2018)

Table 8 continued

Metal/antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
CdCl2	1.2 mg/kg, once every 5 days, from postnatal day 5 to 60	IP	Mouse	GAPDH, ATP, cAMP, H3, H3K14/48/27ac, H4K5/12ac	Cd by restricting GAPDH activity, ATP, and cAMP levels of germ cells could inhibit lysine acetylation and succinylation in the testes. Cd also could disrupt spermiogenesis by restricting acetylation of histone H4K5 and H4K12	Yang (2018)
Cd, aqueous extract of Moringa seeds (AEMS)	2 mg/kg (Cd), single-dose, 100 and 500 mg/kg (AEMS), daily, for 6 weeks	IP, Orally	Rat	SOD, MDA, CAT	Cd decreased sperm parameters. AEMS dose-dependently decreased sperm motility, count, and testosterone. Cd and AEMS increased MDA levels, while decreased SOD and CAT levels. Therefore, Moringa seeds exhibit male reproductive toxicity	Obembe and Raji, (2018)
CdCl2	Acute Cd exposure: 2 mg/kg, single-dose, Chronic Cd exposure: 20 mg/kg, 5 days/week for 5, 10, and 15 weeks	IP, Orally	Rat	GSH, GST, MT-I/II/III, MTLCdBP, HO1, OGG, iNOS, COX2, p53	The concentration of MTLCdBP increased with increasing Cd accumulation. In the chronic oral administration group, the expression of COX2, HO1, MT-I/II/III did not change compared to the acute group. MTLCdBP could be involved in protecting the testis against Cd toxicity	Ohta et al. (2018)
CdCl2, Vit C, Origanum vulgar aqueous extract (OV)	2 mg/kg (Cd), single-dose, 250 mg/kg (vit C), 125, 250 and 500 mg/kg (OV), daily, for 10 days	IP	Rat	MDA, TCA	Cd reduced the mean of testicular tissue cells (Sertoli, spermatogonia, spermatocytes, and Leydig cells), and antioxidant capacity, while treatment with OV and Vit C could attenuate the adverse effects of Cd. However, OV extract in the same dose 250 mg/kg has a better performance than vitamin C, in controlling oxidative stress damage	Raeeszadeh and Fallah (2018)
Cd, Sulforaphane (SFN)	0, 0.0975, 0.195, 0.39, 0.78, 1.56, 3.125, 6.25, 12.5, 25, 50, 75, 100, 125, 150, 200, and 400 µmol/L of cadmium and 0, 2.5, 5, 10, 20, 40, 80, and 160 µmol/L of SFN were added to the TM4 cells culture media	Cell culture	Mouse	Nrf2, NQO1, γ-GCS, HO-1, GSH-Px, ARE, T-SOD, MDA	CdCl2 (12.5 µmo/L) + SFN (2.5 µmo/L) group showed lowest apoptosis rate. Cd led to the oxidative damage and apoptosis of TM4 cells, while SFN by activating the Nrf2/ARE signaling pathway could weaken the Cd-induced cell injury	Yang (2018)

Table 8 continued

Metal/antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
CdCl2, Lycium barbarum polysaccharides (LBP)	5 mg/kg (CdCl2), daily, for 5 weeks, 0, 10, 33.3 or 100 mg/kg (LBP), daily, for 6 weeks	Orally	Mouse	SOD, GSH-Px, MDA	Pretreatment with LBP could ameliorate the Cd-induced reduction in serum testosterone level, sperm motility, body weight, GSH-Px, and SOD. LBP was able to attenuate Cd-induced degeneration of seminiferous tubules	Zhang (2017)
CdCl2, Methanolic extract of Phoenix dactylifera (MEPD)	3 mg/kg (CdCl2), daily, for 7 days, 300,600,and 900 mg/kg (MEPD), daily, for 56 days	Orally	Rabbit	-	Cd reduced semen parameters including semen volume, motility, libido, concentration, total ejaculate, viability, and morphology, and also led to severe testicular damage. MEPD administration could reverse the deleterious reproductive effects induced by Cd	Ansa et al. (2017)
CdCl2, Lycium barbarum polysaccharides (LBP)	4 mg/kg (CdCl2), single-dose, 300 mg/kg (LBP) daily, for 30 days	IP, Orally	Rat	GSH, TEAC, 3NT,	Cd decreased of GSH and TEAC in testis, while increased MDA and 3-nitro-l-tyrosine. Pretreatment with LBP by ameliorating oxidative stress could improve the morphology of the seminiferous tubules	Varoni (2017)
Cd, Grape juice concentrate (GJC)	1.2 mg/kg (Cd), single-dose, 2 g/kg (GJC), daily, for 86 days	IP, Orally	Rat	MDA, CAT, SOD, GSH	GJC could lead to an improvement in testis and epididymis sperm count, normal sperm structure, and sperm transit time. It could also decrease tissue Cd and MDA concentrations	Lamas (2017)
CdCl2, Sclerocaryabirrea fruit pulp (S)	1 mg/kg (CdCl2), daily, for 3 days, 200 mg/kg (S), daily, for 10 days	IP	Rat	SOD, TNF-α, MDA	Cd reduced sperm count, serum reproductive hormones (T, FSH, and LH), SOD, led to a disruption in blood-testis-barrier function and severe damage of seminiferous tubules, increased MDA, and TNF-α levels. Treatment with S. birrea fruit pulp could attenuate the deleterious effects of Cd in rats	Sewani-Rusike (2017)

Table 8 continued

Metal/antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
CdCl2, Mistletoe leaf (ML)	50 mg/kg (CdCl2), 100 mg/kg (ML), daily, for 14 days	–	Rat	–	Cd reduced sperm parameters (count, motility, and viability) and hormones (T, LH, and FSH), and led to severe degeneration in spermatogenic cells and seminiferous tubule. Treatment with ML extract could protect testicles against Cd toxicity	Oyewopo and Olaniyi, (2017)
CdCl2, Eruca sativa seeds (ESS)	30 ppm/L (CdCl2), 250 mg/kg (ESS), daily, for 8 weeks	Orally	Rat	–	Testes shrinkage, irregular arrangement of seminiferous tubules, and enhancement of intertubular spaces were observed in rats exposed to Cd. Treatment with ESS could ameliorate the adverse effects of Cd on testicular tissue	Al-Okaily (2017)
CdCl2, Date palm pollen (DPP), Date palm seed extract (DPS)	5 mg/kg (CdCl2), every other day, 240 mg/kg (DPP), 100 mg/kg (DPS), daily, for 30 days	Orally	Rat	TAC, GSH, SOD, CAT, MDA, XO	Cd reduced sperm quality, hormones (T, E2, FSH, LH), and antioxidant enzymes (TAC, GSH, SOD, and CAT). Treatment with DPP and DPS decreased MDA and XO levels and improved testicular histoarchitecture	El-Komy and Saad (2017)
CdCl2, Curcumin (CMN)	0.67 mg/kg (CdCl2), daily, for 96 h, 50 mg/kg (CMN), daily, for 8 days	IP	Mouse	-	Cd enhanced sperm amorphous abnormality (sperm hummer, without hook), and led to a higher frequency of chromosomal aberrations as fragments, stickiness, gaps, centric fusion, and aneuploidy. CMN administration after Cd exposure could enhance normal sperm values. However, treatment with CMN before Cd injection did not improve the Cd effects	Zowail et al.
CdCl2, proanthocyanidins (PAs)	5 mg/kg (CdCl2), 100 mg/kg (PAs), daily, for 4 weeks	Orally	Mouse	MDA, H2O2, GSH, T-SOD, CAT, GSH-Px, Nrf2, HO-1, γ-GCS, NQO1, Keap1	Cd reduced sperm parameters, the antioxidant enzymes, serum testosterone, and the expression of some genes including, Nrf2, HO-1, γ-GCS, NQO1, increased the expression of Keap1, and also let to severe degeneration in seminiferous tubules. PAs via the modification of the Nrf2-Keap1 pathway could protect the testes against Cd toxicity	Wang (2018)

Table 9 The impact of other agents on male fertility

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
Tributyltin (TBT)	100 and 500 ng/L (TBT), daily, for 28 days	Water	Zebrafish	Bax, Bcl2, Cyclin D1, PCNA	Treatment with TBT reduced the number of spermatogonia and spermatozoa and increased the number of apoptotic-positive spermatocytes	Lan et al. (2020)
TBT	10, 20, and 30 mg/kg (TBT), daily, 3 and 7 days	Orally	Rat	ROS GSH/GSSG	Treatment with TBT led to blood-testicular barrier (BTB) disruption	Mitra et al. (2017)
TBT	50, 100 and 150 ppm/kg (TBT), daily, for 65 days	Orally	Syrian hamsters	SR-B1, LXR, PPARs α/β/γ, SCAP, SREBP 1/2, 3β-HSD, 17β-HSD, CYP17A1, $P450_{SCC}$	Exposure to TBT hindered intracellular cholesterol transport resulting in abnormal sex steroid biosynthesis, then altered the steroidogenic enzyme activities	Kanimozhi et al. (2018)
TBT	0.1, 1.0, or 10.0 mg/ kg/day (TBT), daily, for 10 days	Orally	Rat	LHCGR, Cyp11a1, Hsd3b1, Cyp17a1, Hsd17b3, FSHR, Dhh, Sox9	TBT significantly reduced serum testosterone levels and increased serum LH and FSH levels. Damage in Leydig cells and Sertoli cells was observed	Wu (2017)
TBT	50, 100 and 150 ppm (TBT), daily, for 65 days	Orally	Syrian hamsters	MDA GPx CAT SOD	Treatment with TBT led to a change in the activity of antioxidant enzymes	Kanimozhi et al. (2016)
TBT	0.4, 0.6, and 0.8 µg/L (TBT), daily, for 36 weeks,	Orally	(Gomphina veneriformis)	–	Marine pollution by TBT compounds could alter reproductive indicators, such as sex ratio, gonadal development, and intersexuality	Park (2015)
TBT	1, 2, and 4 mg/L TBT, daily, for 90 days	Water	Macrobrachim rosenbergii	–	A significant decrease of antioxidant contents and an increase of DNA damage levels were seen at higher doses of 2 and 4 mg/L	Rani (2015)
TBT	5, 50, and 500 ng/L, daily, for 28 days	Water	Fish Poecilia reticulata		TBT could cause abnormalities of secondary sexual characteristics in teleosts. Suppression of reproductive behavior in teleosts by TBT is due to its endocrine-disrupting action as an aromatase inhibitor targeting the nervous system	Tian et al. (2015)

Table 9 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
Lithium carbonate (LC), Malva sylvestris (MS)	25 mg/kg (LC), twice daily for 30 days, 0.2 g/kg (MS), daily, for 60 days	IP	Rat	MDA, SOD, CAT, GPx	Exposure to LC decreased the weight of testes, accessory sex organs, sperm count and motility, and serum testosterone level. Treatment with MS could ameliorate the deleterious effects of LC in testis and increased the activity of antioxidant enzymes	Saad (2017)
LC, Ficus carica (FC), Ubiquinone (CoQ10)	25 mg/kg (LC), 200 mg/kg (FC), 20 mg/kg (CoQ10), daily, for 60 days	Orally	Rat	8OHdG, GSSG, NO, MDA, SOD, CAT, Caspase-3	Exposure to LC decreased testicular GSH, endogenous antioxidant enzymes, cell energy (ATP), testosterone level, and semen quality, while treatment with FC and CoQ10 could ameliorate negative impacts exhibited by LC	Haredy et al. (2017)
LC, Rosemary (Rosmarinus officinalis)	100 mg/kg (LC), 220 mg/kg (RO), daily, for 4 weeks	Orally	Rat	HCG GSH MDA	Exposure to LC could decrease plasma free and total testosterone levels, while treatment with rosemary could improve it	Mwaheb et al. (2016)
LC	0.1, 0.01, and 0.001 mg/dL (LC)	In Vitro	Human	–	LC exposure could decrease the motility of sperms with a dose-dependent pattern	Ahmadi and Faraji
LC, Melatonin (Mel)	1–2 mg kg (LC), 5 mg/kg (Mel), daily, for 60 days	IP	Rat	TAT, SOD, CAT, MDA, GSH-px	Melatonin administration improved sperm motility by increasing the total antioxidant level and decreased the rate of apoptosis in the spermatogenic cells, which was induced by LC	Shokri (2015)
LC, Cilybum marianum (SM)	0.2, 0.5, 1 mM (LC), 0.01, 0.1, 0.15 mM (SM)	In vitro	*Farahani's Ram*	-	LC had a negative influence on sperm viability and motility. Silymarin was able to compensate for the adverse effects of LC on these parameters	Choobineh et al. (2018)
Manganese (Mn)	50 mg/kg (Mn), daily, for 3 days	IP	Mouse	PGE2	Mn exposure reduced sperm count and sperm shape deformities. These findings suggest that EP1 and EP2, the receptors of PGE2, may be the key to abnormal GnRH secretion caused by Mn exposure	Wu (2020)
Mn, Coridius chinensis (Cc)	30 mg/kg (Mn), daily for 14 days, 50, 100, 200 mg/kg (Cc), daily, for 28 days	IP, Orally	Rat	Caspase-3, SOD, CAT, GPx, MDA, Cytochrome C, SOX9	Exposure to Mn increased the number of apoptotic cells. Treatment with Cc by improving the activity of antioxidant enzymes could ameliorate the adverse effects of Mn	Liu (2019)

Table 9 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
(MnO_2)	100 mg/kg (MnO_2) once a week for 4 week	IP	Rat	–	Chronic injection of MnO2 nanoparticles decreased the number of sperms, spermatogonia, spermatocytes, the diameter of seminiferous tubes, and the motility of sperms. Also, no significant difference was observed in the weights of the epididymis, prostate, left testicle, testosterone, and estradiol hormone	Yousefalizadegan et al. (2019)
Mn, Molasses	100 mg/kg (Mn), 200 mg/100 g, daily, for 7 days	IP, Orally	Rat	NOx, MDA, TAC, COX	Treatment with molasses improved the level of serum testosterone, LH, and FSH, and also increased the epididymal sperm count as well as motility	Abdelmagid et al. (2019)
Mn, Gallic acid (GA), Omega-3 fatty acids (ω-3)	15 mg/kg (Mn), 30 mg/kg (GA), 20 mg/kg (ω-3), daily, for 14 days	Orally	Rat	–	GA or ω-3-FA could prevent the manganese-mediated increase in lipid peroxidation, myeloperoxidase activity, reactive oxygen, and nitrogen species production in epididymis and testes of rats. They could also enhance the activities of testicular function marker enzymes such as ACP, LDH, ALP, and G6PD, and also increased the concentrations of LH, FSH, and testosterone	Owumi et al. (2020)
Mn	Ranged from 0.56 to 34.25 mg/L, and the average level was 15.92 + 8.49 mg/L	In vitro	Human	–	Exposure of Mn decreased sperm progressive motility and total motility	Yang (2019)
$MnCl_2$, Ebselen (EBS)	50 mg/kg (MnC_{l2}), 15 mg/kg (EBS), daily, for 30 days	Orally, IP	Rat	GSI, NO, 8-OhdG, TAC	Exposure to $MnCl_2$ increased sperm abnormalities, decreased gonadosomatic index, sperm motility, sperm count, and serum levels of testosterone and LH. Also, it could decrease the height of germinal epithelium, the diameter of seminiferous tubules, the numbers of spermatogenic cells, including spermatogonia, spermatocytes, and spermatids, and Leydig cells	Mohammed et al. (2018)
Mn, Ethanol (EtOH)	30 mg/kg (Mn), 1.25 and 5 g/kg (EtOH), daily, for 35 days	Orally	Rat	SOD, CAT, GST, GSH, MDA, NO, MPO	EtOH exposure exacerbated Mn-induced decrease in antioxidant enzyme activities, glutathione level, and increased oxidative stress biomarkers in the testes	Nkpaa et al. (2018)
Mn	50,100 ppm (Mn), daily, for 30 days	Orally	Mouse	–	Exposure to Mn decreased the diameter of the seminiferous tubules, the number of cells such as spermatogonia, spermatocytes, spermatids, and Sertoli cells	Abd-Allh and ahmed Rahim (2017)

Table 9 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
Mn	0.5 mg L^{-1} (Mn), 24 h	Water	Fish (Astyanax altiparanae)	–	Manganese increased the 17β-estradiol levels after 24 h of exposure	Kida, Abdalla and Moreira (2016)
Mn	30 mg/L, (Mn), daily, for 15 days	Orally	Rat	–	Exposure to Mn decreased the antioxidant status in testes as well as epididymis, and also decreased the concentrations of FSH, LH, and testosterone	Adedara et al. (2017)
Mn	600, 900, and 1800 mg/kg (Mn), daily, for 30, 60, and 90 days	Orally	Chicken	iNOS, NO, NF-κB, COX-2, TNF-α	Mn exposure induced chicken testis histological changes in a dose- and time-dependent manner. It could upregulate the mRNA expression of NF-κB, COX-2, and TNF-α, and iNOS, NO content, and iNOS activity in the 60th and 90th days, and also affect NF-κB and TNF-α mRNA expression, time-dependently	Du (2015)

through counteracting oxidative processes (Adewoyin et al. 2017). Other beneficial antioxidants in this field are vitamins C and E, Coenzyme Q, and glutathione (Crha et al. 2003). Besides, herbal agents such as those extracted from *Eurycoma longifolia*, *Cardiospermum halicacabum*, *Syzygium aromaticum,* and grape seed have been shown to improve sperm parameters through diverse mechanisms among them is the modulation of testosterone levels and antioxidant effects (reviewed in (Adewoyin et al. 2017)). Among the assessed herbal extracts is *Lycium barbarum* extract which has been shown to protect mouse testicular cells against H_2O_2-associated DNA damage (Luo et al. 2006). Cerium dioxide nanoparticles have been shown to increase the regeneration of seminiferous tubules, enhance quantity and activity of Leydig cells, and surge serum testosterone levels. Moreover, these nanoparticles have increased linear dimension and size of rat testes conteracting the age-related changes in the testes (Kobyliak et al. 2015). Finally, resveratrol can counteract with the heavy metal-associated oxidative stress ameliorating the oxidative stress produced by As, Cd, Cu, Cr and Fe heavy metals (Nicolás-Méndez et al. 2020).

Discussion

The toxic effects of several environmental factors have been verified in animal models. These studies also demonstrated the beneficial effects of a number of antioxidants in the attenuation of such effects with various degrees. For instance, while Aluminum has been regarded as a toxic agent in this regard, garlic, vitamin E and tyrosol have been shown to at least partially compensate for Aluminum-induced detrimental effects on sperm activity and testis architecture. The toxic effects of Pb are completely reversed by vitamin E and TQ in animal models. In addition, each antioxidant might amend a certain pathological feature in the testis. For instance, vitamin C has been shown to ameliorate Hg effects on the spermatozoa speed and motility, while date palm exerted beneficial effects on the testosterone and spermatozoa speed. Yet, the combined administration of these two agents has only amended the testosterone level and spermatozoa speed (Moumen et al. 2011). Therefore, the effects of combinations of antioxidants on metal-induced changes in the testis should be assessed in

Table 10 Summary of studies which assessed the antioxidant effects of Se

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
Selenium (Se)	0.5, 1, and 2 mg/kg (Se), daily, for 45 days	Basal diet	Rooster	CDC2, Caspase-3/9, Bcl-2	The lower dose of Se (0.5) could decrease the mRNA expression of related-apoptotic genes, while a higher dose (2) increased mentioned apoptotic genes	Song et al. (2015)
Se	2 mg/mL solution of Na2SeO3	–	Mouse	–	Adding Se to the media could reduce seminiferous tubules injury at the slow freezing–thawing procedure	Kushki et al. (2015)
Se	0, 0.25, 0.50, 0.75, and 1 mg/L of sodium selenite	In vitro	Bovine	IL-4, IL-10, TGFβ1, TNF-α, IL-1β, IFN-γ, Occludin, ZO-1, Connexin-43, E-cadherin, TLR4	Adding Se (0.50 mg/L) to the culture media enhanced Sertoli cell viability and upregulate blood-testis barrier proteins and anti-inflammatory cytokines	Adegoke (2018)
Selenium (Se), L-carnitine (LC)	0.35 mg/kg (Cd), 0.87 mg/kg (Se), 10 mg/kg (LC), daily, for 30 days	IP	Mouse	CAT, SOD, GR, GST	Treatment with Se and LC could ameliorate the damaging impact of Cd on the testis via elevating the enzymatic antioxidants	Alharthi et al. (2019)
Se	10 µg sodium selenite/100 g body weight, daily, for 21 days	Orally	Rat	3β-HSDH, 17β-HSDH, VEGF, NGF-β	Treatment with Se could increase the numbers of different types of spermatogenic cells, such as Sertoli cells, and Leydig cells, growth factors expression, and testicular steroidogenesis in STZ-induced diabetic rats	Moghazy et al. (2016)
Se	350 mg/L (Pb), 1 mg/kg (Se), daily, for 90 days	Drinking water (DW) and basic diet (BD)	Chicken	CHOP, ATF4, Caspase-3/12, SOD, GPx, MDA, CAT, GSH, GST, eIF2α, GRP78, PERK	Treatment with Se decreased MDA content, increased GPx, GST, and SOD activities increased GSH content, decreased mRNA expressions of GRP78, PERK, eIF2α, ATF4, CHOP, caspase-3/12, and decreased the index of apoptosis in the chicken testes exposed to lead	Huang (2018)
Se	0.5 ppm/kg, daily, for 8 weeks	Basic diet	Mouse	HMOX-1, Bcl-2, Caspase-3/8/9, Bid, AKT, GSH-Px	Treatment with Se enhanced sperm motility, increased GSH-Px content, decreased the expression of caspase-3/8/9, and Bid. Hence, Se could protect testicles from apoptosis and oxidative stress induced by heat stress	Kaur and Bansal (2015)
Se	0.5 ppm/kg, daily, for 12 weeks	Basic diet	Mouse	ROS, GSH-Px, LPO, MDA	Treatment with Se could ameliorate oxidative stress and rate of apoptosis, and improve sperm parameters in mice testes exposed to Bisphenol-A	Kaur et al. (2018)

Table 10 continued

Metal/ antioxidant	Doses/duration	Route administration	Species	Targets, pathways, biochemical factors	Observations	References
Se, Nano-selenium (NSe)	3 mg/kg (Se), 2 mg/kg (NSe), daily, for 70 days	Orally	Rat	COX-2, ER-2, CAT, GSH, MDA, PAP, CAT, LPO	Treatment with Se and NSe could protect testicular tissue against bisphenol-induced toxicity	Khalaf et al. (2019)
Se, Inorganic selenium	0.3 mg/kg (Se), 0.3 mg/kg (inorganic selenium), daily, for 6, 9, and 12 weeks	Basic diet	Chicken	SelW, GPx4, LHCGR, ACE	Treatment with Se could improve the development of the seminiferous tubules at the cellular level by targeting SelW, GPx4, LHCGR, and ACE. Also, Se could promote Sertoli cell viability	Khalid (2016)

future studies to propose the best combinatory formula.

The detrimental effects of heavy metals on human fertility have also been assessed. For instance, Telisman et al. have reported the effects of even moderate exposures to Pb and Cd on the reduction of human semen quality. Yet, they did not find convincing evidence of diminishing male reproductive endocrine function (Telisman et al. 2000). Moreover, Cd levels have been negatively correlated with sperm motility and sperm quantity in infertile men with few motile sperm. Nevertheless, after adjustment of the effects of smoking, Cd was not associated with sperm quantity or motility (Pant et al. 2003). Others have reported a significant correlation between abnormal Pb and Sb levels and abnormal semen quality. Moreover, Hg and Zn levels have been correlated with these parameters (Giaccio et al. 2012). Also, traces of heavy metals have been found in seminal plasma of infertile males in an Italian cohort (Rispoli et al. 2018). Based on the unavailability of appropriate tissue samples, mechanistical effects of heavy metals have not been fully assessed in human subjects. Moreover, the results of human studies are not always consistent (Wirth and Mijal 2010).

Some natural products can amend the metal-induced abnormalities in the testis. Most of these natural products have beneficial effects on antioxidant activity in this tissue. However, certain products can also exert anti-inflammatory effects (Bashandy et al. 2019). Several antioxidants might reverse the abnormal changes induced by several metals. For instance, toxic effects of a mixture of six metals including Pb, As, Cd, Hg, iron (Fe), and copper (Cu) on testis function could be reversed by curcumin (Zoheb et al. 2014). The beneficial effects of many probiotics in the amendment of tissue injury and sperm abnormalities induced by metals have also been assessed in a few studies (Fadda et al. 2020). Although the molecular mechanism of such effects has not been elucidated yet, studies in other tissues indicate that they can modulate both inflammatory responses and oxidative stress (Jiang et al. 2018).

The beneficial effects of antioxidants have been appraised in other conditions such as aging and atherosclerosis (Fusco et al. 2007). Vitamins C and E and carotenoids have been reported to have synergic effects against lipid peroxidation (Niki et al. 1995). The mammalian hormone melatonin has also antioxidant effects through inducing expression and activity of glutathione peroxidase, superoxide dismutase, and NO synthetase (Nishida 2005). Therefore, antioxidants with beneficial influences in other human disorders can be tested for their effects on human fertility.

Taken together, based on the vast body of evidence obtained from animal studies, several antioxidants including selenium and vitamins as well as natural products can amend the metal-induced abnormalities in the testis tissue and sex hormones. Although the results of these animal studies have not been completely verified in human subjects, it seems rational to administer appropriate antioxidants in persons who suffer from abnormal sperm parameters and infertility due to exposure to toxic elements. Conduction of large-scale clinical trials would help in the

identification of the appropriate dose of administration of antioxidants in human subjects.

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Declarations

Conflict of interest The authors declare they have no conflict of interest.

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