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REVIEW PAPER

Harnessing therapeutic potential of vitamins and microelements to mitigate testicular damage caused by drugs or chemical toxins – a review

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ABSTRACT

Introduction and aim. Exposure to drugs and chemical toxins has been a common cause of structural and functional impairment of the male gonad (or testis), often leading to male reproductive disorder and infertility. Health concerns due to drugs or chemical-induced testicular damage have increased the exploration of potential therapeutic agents including vitamins and microelements. This review summarizes therapeutic role of vitamins and microelements against drugs or chemical toxins in preclinical studies.

Material and methods. Relevant articles published on scientific databases like PubMed, Google Scholar, Scopus, and Web of Science were retrieved and critically reviewed for this study.

Analysis of the literature. The mitigating effect of essential vitamins (such as vitamin B2, vitamin B9, vitamin B12, vitamin B17, vitamin C, vitamin E) and microelements (such as zinc and selenium) has been demonstrated on testicular damage caused by exposure to drugs and chemical toxins in preclinical studies and associated with their antioxidant, anti-inflammatory and anti-apoptotic properties. This was further characterized with reparation of testicular histopathology, suppression of testicular oxidative damage, improved sperm parameters, elevated testicular antioxidants and testosterone level, upregulation of steroidogenic gene, inhibition of sperm DNA damage.

Conclusion. Vitamins and microelements exert therapeutic effect against drugs and chemical-induced testicular damage.

Keywords. drugs and chemical toxins, testicular damage, vitamins and microelements

Introduction

The testes are primary reproductive organs (or gonads) in males which are responsible for the gametogenic and endocrine functions.[1] Structurally, the testes are composed of seminiferous tubules and interstitial tissue (containing Leydig cells) that perform the spermatogenic and endocrine functions respectively.[2] The testes are covered by protective fibrous tissue (tunica albuginea) and suspended by the spermatic cords within a pouch (tunica vaginalis of the scrotum) outside the body, thereby enabling the surrounding temperature to be lower than the core body temperature.[3]

Essentially, the development of secondary sexual characteristics and male reproductive function are achieved under normal morphological, physiological and hormonal profile of the testicular tissue.[4] Meanwhile, the exposure of testicular tissue to toxic chemical agents, including chemotherapeutic agents such as an-

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tibiotics, anti-cancer, non-steroidal anti-inflammatory drugs (NSAIDs) and anabolic steroids, has been reported to cause damage of the testicular tissue morphology and impairment of testicular functions, leading to infertility.[5-7]

Testicular damage caused by drugs and chemical toxins is further linked with the interruption of testosterone synthesis, disruption of spermatogenesis process, testicular atrophy and when prolonged, reproductive dysfunction and infertility could happen.[8,9] The mechanisms of drugs and chemical toxins-induced testicular damage essentially involve reproductive hormonal disruption, activation of inflammatory and apoptotic signaling and induction of oxidative stress.[10] The application of potent therapeutic intervention could reverse testicular damage after acute exposure to drugs or chemical toxins while prolonged exposure leads to irreversible testicular damage, reproductive dysfunction and infertility.[11]

Furthermore, preclinical studies using experimental model of drugs and chemical toxins-induced testicular damage have been conducted to harness the efficacy of potential therapeutic agents such as vitamins and microelements. The therapeutic effects have been characterized by the modulation of associated mechanisms including the induction of oxidative stress, activation of inflammatory and apoptotic signaling, and disruption of genetic regulation of gametogenic and endocrine functions of the testes.

Aim

This review was aimed at summarizing the current information about the therapeutic potential of selected vitamins (including vitamin B_2, vitamin B_9, vitamin B_{12}, vitamin B_{17}, vitamin C, vitamin E) and microelements (including zinc and selenium) in mitigating drugs and chemical toxins-induced testicular damage in preclinical studies. The review further highlighted the mechanisms of therapeutic activity of selected vitamins and microelements.

Material and methods

The scientific publications that are relevant to the current review study were searched across databases including Google scholar, PubMed, Scopus and Web of Science. The keywords employed in the search included: 'male gonadoprotective effect of vitamins', 'male gonadoprotective effect of microelements', 'antioxidant effect of vitamins', 'anti-inflammatory effect of vitamins', 'anti-apoptotic effect of vitamins', 'antioxidant effect of microelements', 'anti-inflammatory effect of microelements', and 'anti-apoptotic effect of microelements'. Further in-depth assessment of the identified articles was conducted to extract relevant information regarding the therapeutic activity of selected vitamins and microelements against testicular damage induced by exposure to drugs or chemical toxins in experimental model. Articles containing findings that are relevant to the review study, published in peer-reviewed journals and in English language were regarded as eligible and included in the review. Conversely, duplicated articles and those containing irrelevant information were excluded from the review.

Analysis of the literature

Selected therapeutic agents possess distinct structural formula (Fig. 1) and exhibit different pharmacodynamics and pharmacokinetics which culminate into deleterious effect on the testicular tissue. Similarly, chemical toxins with diverse structural conformation (Fig. 2) exert toxic effects that lead to the morphological and functional impairment of the testes. However, some essential vitamins and microelements have demonstrated therapeutic activity against drugs and chemical toxins-induced testicular primarily based on their antioxidant, anti-inflammatory and anti-apoptotic effects.

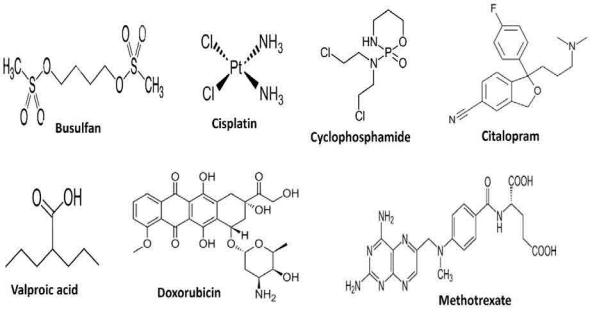

Fig. 1. Structural formula of selected drugs with testicular toxic effect

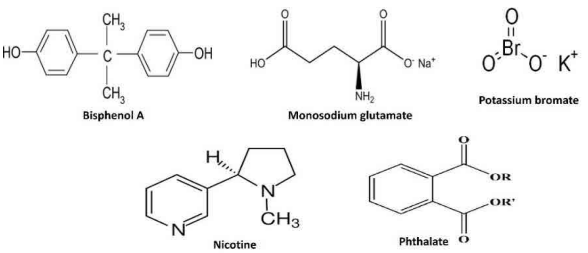

Fig. 2. Structural formula of selected chemicals with testicular toxic effect

Busulfan-induced testicular damage

Busulfan is a chemotherapeutic agent used to treat cancers with characteristic adverse effects such as testicular damage and possibly leading to reproductive dysfunction. The deleterious effect of busulfan on testicular tissue has been characterized with the induction of oxidative stress and inflammation in the testicular tissue, elevated level nitric oxide (NO) and increased myeloperoxidase activity.[12] Other features of busulfan-induced

testicular damage included decreased level of testicular glutathione (GSH), increased level of testicular malondialdehyde (MDA), reduced sperm parameters, destruction of seminiferous tubules and degenerated spermatogenic epithelium, Sertoli cells, and Leydig cells.[13-15] Busulfan-induced testicular toxicity involved reduced activities of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and increased level of tumor necrosis factor alpha (TNF-α).[16,17]

Cisplatin-induced testicular damage

The application of cisplatin, a common antineoplastic agent used to treat different types of cancer, often causes side effect such as testicular damage. The deleterious effect of cisplatin on the testes has been characterized with oxidative damage and upregulation of inflammatory and apoptotic signaling leading to reproductive dysfunction.[5,18] Cisplatin-induced testicular damage has been characterized with increased level of oxidative stress marker (MDA) and reduction in sperm parameters (such as count, motility, and morphology), and levels of testicular testosterone and antioxidants (SOD, GSH, CAT) as well as distortion of testicular histoarchitecture.[19,20] Other associated mechanisms of cisplatin-induced testicular damage included upregulated expressions of TNF-α, NF-κB and caspase-3 factors.[19-21]

Citalopram-induced testicular damage

Citalopram is a selective serotonin reuptake inhibitor widely prescribed to act as a serotonergic antidepressant, with characteristic toxic effects of different body tissues including the testes via induction of oxidative stress.[22,23] Citalopram-induced testicular damage is characterized with diminished sperm parameters (count, motility, viability, morphology and chromatin integrity), significantly increased NO and MDA levels and apoptotic markers.[23] Other associated mechanisms associated with citalopram-induced testicular damage included decreased GSH, increased sperm DNA damage disruption of reproductive hormones.[24,25]

Cyclophosphamide-induced testicular damage

Cyclophosphamide is an alkylating drug that function as anti-cancer agent for treatment of cancer and as immunosuppressive agent for treatment of autoimmune and immune-mediated diseases.[26] It has been reported to exhibit testicular damage mainly through the induction of oxidative damage within testicular tissue and interference with the genetic expression associated with testicular functions.[27] Cyclophosphamide-induced testicular damage has been characterized in experimental model to involve shrinkage of seminiferous tubules, decline in cellular components (Leydig and Sertoli cells) of testes, marked reduction of sperm parameters, testosterone level, tissue antioxidants while MDA level was significantly elevated.[27,28] Moreover, testicular damage due to cyclophosphamide exposure showed deleterious effect on testicular histomorphology and leads to impairment of testicular structural and functional integrity.[29]

Doxorubicin-induced testicular damage

Doxorubicin is a potent anti-neoplastic agent which constitutes the major component of anti-cancer treatment regimens.[30] It has been indicated to cause testicular damage mainly through the induction of oxidative stress, inflammation and apoptosis.[31] Doxorubicin-induced testicular damage has been characterized with prominent distortion of testicular histoarchitecture, testicular atrophy, Leydig cell degeneration, oligospermia, dysregulation of 3β-hydroxysteroid dehydrogenase (3β-HSD) and 17β- hydroxysteroid dehydrogenase (17β-HSD).[32-34] Moreover, other associated mechanisms of doxorubicin-induced testicular damage included reduced testicular antioxidants (SOD, CAT, GPx), elevated level of inflammatory and apoptotic markers (IL-1β, IL-6, TNF-α, Bax, caspase-3); elevated level of MDA, reactive oxygen species, 8-Hydroxy-deoxyguanosine (8-OHdG), 4-Hydroxynonenal (4-HNE).[31,35,36]

Methotrexate-induced testicular damage

Methotrexate is a drug commonly used for treating diverse kinds of cancer and as an immunosuppressant to treat autoimmune diseases.[37] It has been reported to severe adverse including testicular damage. In preclinical studies, methotrexate-induced testicular damage has been characterized with marked decline of sperm parameters (count and motility), testicular antioxidants (SOD, GSH, CAT, GPx), and testosterone level and prominent testicular histopathological changes.[38,39] Other mechanisms of methotrexate-induced testicular damage included increased levels of MDA, protein carbonyl, and inflammo-apoptotic factors including NO, TNF-α, NF-kB, IL-6, IL-1β, caspase-3 and p53, reduced expressions of Bcl-2, IL-10, HO-1, EGF, ERK1/2 factors and steroidogenic genes in the testes.[39-41]

Valproic acid-induced testicular damage

Valproic acid is an anticonvulsant drug used to treat epilepsy. However, it has been indicated to cause tissue toxicities (including the testes) mainly on the basis of induction of oxidative stress and tissue damage. Valproic acid-induced testicular damage has been characterized with marked decline in testosterone levels, sperm parameters (count and normal morphology) and steroidogenic gene expression, as well as prominent testicular histopathological changes.[42,43] Moreover, valproic acid exposure to testicular tissue further caused abrogation of autophagy, increased inflammatory (NF-kB) and apoptotic (caspase-3) signaling and downregulation of AMPK factor.[43,44]

Table 1. Profile of selected drugs and mechanisms of testicular damaging effect

Drug	Molecular formula (molecular weight)	Therapeutic applications	Major mechanisms of testicular damage	References
Busulfan	$C_6H_{14}O_6S_2$ (246.30 g/mol)	Anti-cancer drug	- reduced sperm parameters - testicular histopathological changes - reduced SOD, CAT, GSH levels - increased levels of MDA, NO, and myeloperoxidase activity - upregulated TNF-α expression	Abarikwu et al.[12] Abarikwu et al.[13] Ezim and Abarikwu[14] Abd El-Hay et al.[15] Moghadam et al.[16] Abarikwu et al.[17]
Cisplatin	$Pt(NH_3)_2Cl_2$ (300.10 g/mol)	Anti-cancer drug	- increased level of MDA - reduced sperm parameters - reduced levels of testosterone, testicular antioxidants (SOD, GSH, CAT) - distortion of testicular histoarchitecture - upregulation of TNF-α, NF-κB, caspase-3	Abdel-Latif et al.[5] Soni et al.[18] Elsayed et al.[19] Nofal et al.[20] Othman et al.[21]
Citalopram	$C_{20}H_{21}FN_{20}$ (405.35 g/mol)	Anti-depressant drug	- diminished sperm parameters - increased NO, MDA levels - decreased testicular GSH level - increased sperm DNA damage - disruption of reproductive hormones	Kraai and Seifert[22] Moradi et al.[23] Ilgin et al.[24] Moradi et al.[25]
Cyclophosphamide	$C_7H_{15}Cl_2N_2O_2P$ (261.08 g/mol)	Anti-cancer and treatment of autoimmune diseases	- marked testicular histopathology - reduction of sperm parameters - reduced testosterone level - decreased testicular antioxidants - increased MDA level	Ahlmann and Hempel[26] Ghobadi et al.[27] Shaker Kordedeh et al.[28] Adana et al.[29]
Doxorubicin	$C_{27}H_{29}NO_{11}$ (543.52 g/mol)	Anti-cancer drug	- distortion of testicular histoarchitecture - dysregulation of testicular hormones - reduced testicular SOD, CAT, GPx - elevated levels of IL-1β, IL-6, TNF-α - upregulation of Bax, caspase-3 - elevated MDA, 8-OHdG, 4-HNE levels	Mohan et al.[32] Alafifi et al.[33] Sarman and Koca[34] Tektemur et al.[35] Ijaz et al.[36]
Methotrexate	$C_{20}H_{22}N_8O_5$ (454.40 g/mol)	Anti-cancer or anti-rheumatic drug	- decline of sperm parameters - reduced SOD, GSH, CAT, GPx, - reduced testosterone levels - testicular histopathological changes - increased levels of MDA, PC NO, TNF-α, NF-kB, IL-6, IL-1β, - upregulated caspase-3, p53 expressions - reduced expressions of Bcl-2, IL-10, HO-1, and steroidogenic genes	Akacha et al.[38] Hassanein et al.[39] Rofaeil et al.[40] Sarman et al.[41]
Valproic acid	$C_8H_{16}O_2$ (144.21 g/mol)	Anticonvulsant drug	- reduced sperm parameters - decline in testosterone level and steroidogenic gene expression - testicular histopathological changes - increased NF-kB, caspase-3 levels - downregulation of AMPK and autophagy	Conei et al.[42] Alsemeh et al.[43] Savran et al.[44]

Selected chemical toxin-induced testicular damage in preclinical studies

Bisphenol A-induced testicular damage

Bisphenol A is a synthetic compound used to manufacture polycarbonate plastics and epoxy resins. As an endocrine disruptor, it has been implicated in preclinical studies as a potent cause of chemical toxin-induced testicular damage whereby the impairment of reproductive function occurs through the characteristic anti-androgenic effect.[45] Bisphenol A-induced testicular damage was characterized with marked distortion of testicular morphology, elevated levels of oxidative stress and inflammatory markers and increased TUNEL positive cells indicating apoptosis in testis.[45-47] Moreover, bisphenol A-induced testicular damage caused significant decline of sperm parameters (viability, motility and normal morphology) and testicular antioxidants (SOD, CAT, GSH) while MDA, MMP, ROS levels were increased.[48,49]

Fluoride-induced testicular damage

Fluoride is a common environmental contaminant which causes prominent detrimental effect on body tissues such as the testes leading to male reproductive impairment and thereby constitute public health concern.[50] Fluoride-induced testicular damage and male reproductive impairment was described to involve molecular pathways including apoptosis, DNA damage, hormonal imbalance, inflammatory response, mitochondrial dysfunction.[51] Fluoride exposure caused prominent histopathological and biochemical changes characterized with poor semen quality, reduced testosterone level due

to degeneration of Leydig cells, regression of testicular tissue leading to impaired spermatogenesis and infertility.[52] Other indications of fluoride-induced testicular damage included reduced testicular weight and sperm parameters (count, motility, and viability), increased abnormal sperm morphology, induction of oxidative stress and activation of IL-17A pathway.[53,54]

Monosodium glutamate-induced testicular damage

Monosodium glutamate, chemical commonly used to enhance food flavor, has been reported to cause damaging effects on body tissue (including testes) especially after prolonged exposure via induction of oxidative stress and cell death. Monosodium glutamate-induced testicular damage has been characterized with significant reduction of testosterone level, elevated MDA level, marked testicular histopathological changes.[55] Other associated mechanisms of monosodium glutamate-induced testicular damage included decreased testicular antioxidants (SOD) and PCNA, Bcl-2 and Beclin 1 expressions; elevated levels of apoptotic and inflammatory markers (TNF-α, Bax, caspase-3) which in turn inhibited the AMPK/mTOR pathway and autophagy in the testes.[56,57]

Nicotine-induced testicular damage

Nicotine, a naturally occurring alkaloid commonly used in tobacco production and to stimulate pleasure feeling, exhibits potent adverse effect on body tissues including the testes leading to male reproductive dysfunction and infertility. In preclinical studies, nicotine-induced testicular damage was characterized with significant reduction in testosterone level, testicular sperm parameters (count, viability, normal morphology, motility), marked testicular histopathological changes.[58,59] Other mechanisms of nicotine-induced testicular damage included marked reduction in SOD and GSH, significantly increased levels of testicular MDA, NO, TBARS.[59,60] Furthermore, the exposure to nicotine caused reduction of Nrf-2 expression and destruction of blood-testis barrier (BTB) via induction of ferroptosis in testicular cells.[61]

Potassium bromate-induced testicular damage

Potassium bromate, a food additive used in production of dough, fish paste, beer, cheese or fermented beverages, has been reported to cause deleterious effects on body tissues including testes via induction of oxidative damage due to accumulation of free radicals.[62] Potassium bromate-induced testicular damage has been characterized with increased levels of MDA, ROS and RNS, reduced levels of SOD, CAT and TAC, marked distortion of testicular histomorphology.[63-65] Other mechanisms of potassium bromate-induced testicular damage included significant decline of sperm parameters (count, motility, viability, normal morphology) and reproductive hormones including testosterone, LH, FSH, 3HSD, 17HSD.[63,65,66]

Phthalate-induced testicular damage

Phthalates such as di-(2-ethylhexyl) phthalate (DEHP), Dibutyl phthalate (DBP), and butyl benzyl phthalate (BBP) which are used in making consumer products and plastics, are known environmental toxicants (endocrine disruptors) that cause testicular toxicity through induction of oxidative stress, endocrine disruption, inflammation, and apoptosis.[67] Phthalates-induced testicular toxicity has been characterized with prominent testicular histopathological changes, decreased testosterone level, reduced sperm parameters, disrupted expression of steroidogenic genes (StAR, CYP11A1, CYP17A1, 17β-HSD, CYP19A1).[68,69]

Application of vitamins as mitigants of testicular damage in preclinical studies

Vitamin B2 (or riboflavin) – therapeutic effect against testicular damage

Vitamin B_2 is a member of the vitamin B family (water-soluble vitamins) which plays essential role in various biological activities and acts as a precursor to flavin mononucleotide and flavin adenine dinucleotide which perform vital roles in enzymatic reactions.[70-72] It is an essential nutrient for human health derived from dietary sources (such as egg, fish, nuts, milk, fruits, vegetables and so on) and function as antioxidant that mitigate lipid peroxidation and reperfusion oxidative injury.[71,73,74] The therapeutic effect of Vitamin B2 against fluoride-induced testicular damage has been demonstrated and characterized with reparation of testicular histopathological changes, reduction of testicular ROS and SLC3A2 levels, improved sperm parameters, and inhibition of fluoride-induced ferroptosis in testicular Leydig cells which would result into improved testosterone.[53]

Vitamin B9 (or folic acid) - therapeutic effect against testicular damage

Vitamin B_9, a water-soluble vitamin which is the synthetic form of folate that are derived from dietary sources. It has been reported to exhibit antioxidant property (comparable to vitamins C and E) and could protect tissues against some diseases caused by harmful oxidation.[75,76] In a preclinical study, vitamin B_9 had demonstrated therapeutic effect against nicotine-induced testicular damage and characterized its therapeutic activity with reparation of testicular degenerative changes, elevated testosterone level as well as suppression of inflammatory cytokines (TNF- α, IL-6) and oxidative stress markers.[77] Moreover, the therapeutic effect of vitamin B_9 against bisphenol A-induced testicular damage has been demonstrated in preclinical study and

Table 2. Profile of selected chemicals and mechanisms of testicular damaging effect

Chemicals	Molecular/Atomic formula (Molecular/atomic mass)	Common applications	Major mechanisms of testicular damage	References
Bisphenol A	$C_{15}H_{16}O_2$ (228.29 g/mol)	- used to produce polycarbonate plastics and epoxy resins	- impairment of reproductive function - marked distortion of testicular morphology - increased TUNEL positive apoptotic cells - decline of sperm parameters - reduced testicular SOD, CAT, GSH - increased MDA, MMP, ROS levels	Bordbar et al.[45] Gules et al.[46] Tekin and Celebi[47] Rezaee-Tazangi et al.[48] Asadi-Fard et al.[49]
Fluoride	F[-1] (18.99 g/mol)	- used to build healthy teeth, gums, bones	- prominent testicular histopathology - reduced sperm parameters, testosterone level - regression of testicular tissue leading to impaired spermatogenesis - activation of IL-17A pathway	Chhabra et al.[51] Patial et al.[52] Li et al.[53] Talebi et al.[54]
Monosodium glutamate	$C_5H_8NNa_2O_4$ (169.11 g/mol)	- used as food flavor enhancer	- reduction of testosterone level, - elevated MDA level - testicular histopathological changes - decreased testicular antioxidants (SOD) - downregulation of PCNA, Bcl-2, Beclin-1 - upregulation of TNF-α, Bax, caspase-3 - inhibition of AMPK/mTOR pathway	Luqman et al.[55] Gad et al.[56] Morsy et al.[57]
Nicotine	$C_{10}H_{14}N_2$ (162.23 g/mol)	- used to stimulate pleasure feeling	- reduced testosterone level, sperm parameters - testicular histopathological changes - reduced levels of SOD and GSH - increased levels of MDA, NO, TBARS and ferroptosis - downregulated Nrf-2 expression	Ikwuka et al.[58] Jalili et al.[59] Ashoub et al.[60] Zhang et al.[61]
Potassium bromate	$KBrO_3$ (167.00 g/mol)	- used as flour additive, for production of malt barley	- increased levels of MDA, ROS, RNS - reduced levels of SOD, CAT, TAC - marked testicular histopathology - decline of sperm parameters - reduced level of testosterone, LH, FSH, 3HSD, 17HSD	El-Deeb et al.[62] Mohamed et al.[63] Akinola et al.[64] Nwonuma et al.[65] Akinola et al.[66]
Phthalates	$C_8H_4O_4^{-2}$ (164.11 g/mol)	- used to increase the flexibility and softness of plastics	- testicular histopathological changes - decreased testosterone level - reduced sperm parameters - disrupted expression of steroidogenic genes	Mondal et al.[67] Tang et al.[68] Liu et al.[69]

characterized with improved sperm parameters (sperm count, motility, morphology), increased serum testosterone level, amelioration of testicular histopathological changes, as well as decreased TUNEL-positive apoptotic cells.[46]

Vitamin B12 (or cobalamin) – therapeutic effect against testicular damage

Vitamin B_{12} is a water-soluble vitamin, one of the eight vitamin B family, which participate in metabolism and function as co-factor for two critical biochemical reactions (conversion of l-methylmalonyl coenzyme A to succinyl coenzyme A, and the formation of methionine by methylation of homocysteine).[78,79] It is totally derived from dietary sources (such as fish, meat, poultry, eggs, milk) and exists in four isoforms cyanocobalamin, hydroxocobalamin, 5′-deoxyadenosylcobalamin, and methylcobalamin.[80] It has been suggested that Vitamin B_{12} exhibit antioxidant effect and may protect against induction of oxidative stress and inflammation.[81] In a preclinical study, the therapeutic effect of vitamin B12 against nicotine-induced testicular damage has been assessed and reportedly characterized with amelioration of testicular degenerative changes and increased testosterone level. Other characteristic mechanisms included suppression of inflammatory markers such as TNF- α, IL-6 and markers of oxidative stress.[77]

Vitamin B17 (or amygdalin) – therapeutic effect against testicular damage

Vitamin B_{17} is a glycoside nutrient derived from dietary sources such as apples and apricots and reported to exhibit certain therapeutic properties especially anti-tumor effect.[82] Furthermore, the therapeutic effect of vitamin B_{17} has also been demonstrated in preclinical study against methotrexate-induced testicular damage and characterized with amelioration of testicular histopathology (atrophy and lesions), improved sperm parameters (sperm count, viability, morphology index, total motility, and progressive motility), increased testosterone level, improved level of testicular antioxidants (SOD, CAT, GSH).[83]

Vitamin C (or ascorbic acid) – therapeutic effect against testicular damage

Vitamin C is a water-soluble which is abundantly derived from natural sources such as fresh fruits like oranges, lemons, grape, leafy green vegetables and exists

Table 3. Profile and therapeutic role of selected vitamins against drug or chemical-induced testicular damage

Vitamins (other name)	Molecular formula (molecular weight)	Dietary sources	Therapeutic mechanisms against drug or chemical testicular damage	References
Vitamin B_2 (riboflavin)	$C_{17}H_{20}N_4O_6$ (376.37 g/mol)	meat, eggs, almonds, nuts, spinach, apple, kidney bean, spinach, banana, potato, avocado, tomato, oatmeal	- amelioration of testicular histopathology - reduction of testicular ROS - improved sperm parameters - inhibition of ferroptosis in Leydig cells - increased testosterone level	Li et al.[53]
Vitamin B_9 (folic acid)	$C_{19}H_{19}N_7O_6$ (176.124 g/mol)	banana, papaya, orange, green peas, kidney bean, crab, tomato juice, avocado, black-eyed pea, peanuts, spinach, beef liver	- reparation of testicular degeneration - elevated testosterone level - suppression of TNF- α, IL-6 - reduced oxidative stress, apoptotic markers - improved sperm parameters - increased testosterone level	Gules et al.[46] Ray et al.[77]
Vitamin B_{12} (cobalamin)	$C_{19}H_{19}N_7O_6$ (176.124 g/mol)	liver, oyster, mussel, clam, mackerel, crab, sardines, catfish, cod, low-fat beef, skimmed milk, soy milk, salmon, cheese, eggs	- reparation of testicular histopathology - increased testosterone level - suppression of TNF- α, IL-6 - suppression oxidative stress	Ray et al.[77]
Vitamin B_{17} (amygdalin)	$C_{19}H_{19}N_7O_6$ (176.124 g/mol)	millet, apple seed oil, strawberry, raspberry, spinach, cassava, barley, almonds, yam, cashew, sweet potatoes	- amelioration of testicular histopathology - improved sperm parameters - increased testosterone level - increased level of SOD, CAT, GSH	Felemban et al.[83]
Vitamin C (ascorbic acid)	$C_6H_8O_6$ (441.4 g/mol)	oranges, tomatoes, guava, potato, tomato juice, broccoli, mango, lemon, pepper, grape fruits, strawberries	- increased testosterone level - improved sperm parameters - reparation of testicular histopathology - reduced levels of MDA, NO, - reduced TUNEL-positive apoptotic cells	Moradi et al.[25] Hajjar et al.[89] Rauf et al.[90]
Vitamin E (alpha-Tocopherol)	$C_{29}H_{50}O_2$ (430.71 g/mol)	almonds, nuts, butter, spinach, vegetable oils, olive oil, cereals, meat, egg, avocado, fruits, wheat, cottonseed oil, palm oil, potato, sunflower seeds	- improved sperm parameters - increased testosterone level - improved testicular histology - upregulation of steroidogenic gene - diminished levels of ROS, RNS - increased levels of SOD, CAT, TAC	Alsemeh et al.[43] Akinola et al.[64] Rauf et al.[90]

in the body in ascorbate form.[84,85] It is a natural antioxidant with ability to inhibit ROS production and scavenge free radicals thereby abrogating oxidative stress that follows exposure to tissue toxins.[82-84] Accordingly, preclinical studies have explored the therapeutic potential of vitamin C to combat testicular pathologies due to exposure to drugs and chemical toxins.

Therapeutic role of vitamin C, based on its potent antioxidant activity, has been demonstrated against cyclophosphamide-induced testicular damage with satisfactory outcomes. This was characterized with restoration of testosterone level, improved sperm parameters and reparation of testicular histopathological changes.[89] Similarly, preclinical studies involving experimental models of citalopram-induced testicular damage and cisplatin-induced testicular damage have demonstrated therapeutic effect of vitamin C and characterized with improvement of sperm parameters (count, motility, viability, morphology, and chromatin integrity), testosterone level, amelioration of testicular histopathology, reduced levels of MDA, NO, and TUNEL-positive apoptotic cells.[25,90]

Vitamin E (or alpha-tocopherol) – therapeutic effect against testicular damage

Vitamin E is a fat-soluble vitamin composed of eight essential compounds including four tocopherols and four tocotrienols which are all made up of a chromane ring with a hydroxyl group and side chain.[91] Alpha-tocopherol is a common component which function as an antioxidant that protects the cellular membranes and lipoproteins from peroxidation activity of free radicals.[66,92,93] As an antioxidant, the therapeutic potential of vitamin E has been explored in preclinical studies using the experimental model of tissue pathologies including the testes. The therapeutic activity of Vitamin E against cisplatin-induced testicular damage has been demonstrated in a preclinical study and characterized with amelioration of testicular histopathology (atrophy and lesions), improvement of sperm parameters (sperm count, motility, viability) testosterone level, testicular weight and lipid profile.[90]

Furthermore, vitamin E mitigated valproic acid-induced testicular damage, characterized with increased testicular weight, improved testicular histology, elevated sperm parameters and testosterone level, upregulation of steroidogenic gene and induction of autophagy through upregulation of LC3, beclin1 and downregulation of p62 factors.[43] The study by Akinola et al.[64] further demonstrated that vitamin E ameliorated potassium bromate-induced testicular damage with the ameliorative activity characterized by improved sperm parameters (count, motility, viability and normal morphology),

Table 4. Profile and therapeutic role of selected microelements against drug or chemical-induced testicular damage

Trace element (symbol)	Atomic number (mass)	Sources	Therapeutic mechanisms against drug or chemical testicular damage	References
Zinc (Zn)	30 (65.41 u)	oysters, pork, fishes, liver, meat, wheat, mollusks, dairy products, oats, dried peas, nuts, cheese	- increased testosterone level - improved sperm parameters - reparation of testicular histopathology - reduced oxidative stress markers - inhibition of sperm DNA damage - upregulation of Nrf2 factor	Hajjar et al.[89] Maremanda et al.[97]
Selenium (Se)	34 (76.96 u)	garlic, nuts, cabbage, rice, potatoes, oats, fishes, eggs, meats, lentils	- amelioration of testicular histopathology - elevated testosterone level - improved sperm parameters - reduced MDA level - increased levels of SOD, CAT, GPx, GSH, CAT	Huang et al.[100] Hamza et al.[101] Keshta et al.[102]

diminished levels of ROS, RNS, increased levels of testicular antioxidants (SOD, CAT, TAC) and hormones (testosterone, FSH and LH, 17HSD).

Application of microelements as mitigants of testicular damage in preclinical studies

Zinc – therapeutic effect against testicular damage

Zinc (Zn) is an essential microelement which participates in several body functions and physiological processes including reproduction. Aside its role in enhancing the body antioxidant system, it also acts to promote the activity of vitamin D, suppress prostaglandin synthesis and participate in immune responses and tissue homeostasis.[94,95] Zn exhibits antioxidant and anti-inflammatory properties which underscore its role in oxidative metabolism of spermatozoa. In addition, it plays vital role in maintenance of epithelial lining of reproductive tracts and exerts regulatory role during the process of capacitation and acrosome reaction.[96] Hence, Zn deficiency disrupts spermatogenesis and could result into sperm anomalies and reduced testosterone concentration.[96] The therapeutic role of Zn, based on its potent antioxidant activity, has been demonstrated against cyclophosphamide-induced testicular damage with satisfactory outcomes. This was characterized with restoration of testosterone level, improved sperm parameters, reparation of testicular histopathological changes, reduced oxidative stress markers, and inhibition of sperm DNA damage.[89,97] The mechanisms of therapeutic role Zn included the modulation of metallothionein (MT), tesmin and Nrf2 pathways.[97]

Selenium – therapeutic effect against testicular damage

Selenium (Se) is a metalloid which is essential to human health in trace amounts but could be harmful in excessive amount.[98] As an essential microelement involved in improving antioxidant defense, immune functions, and metabolic homeostasis, its deficiency increased susceptibility to various disorders and accelerate aging process leading to reduction of life expectancy.[95] Se demonstrated protective effect against testicular toxicity primarily based on its antioxidant and anti-inflammatory properties.[100] Accordingly, Se has been explored as potent therapeutic agent in mitigating testicular damage that results from exposure to drugs and chemicals in preclinical studies. The therapeutic activity of Se, through its nanoparticles, has been further demonstrated against monosodium glutamate-induced testicular damage and characterized with reparation of testicular histopathology, elevated testosterone level, reduced MDA level, increased levels of testicular antioxidants (SOD, CAT and GPx).[101] Moreover, Se nanoparticles have exhibited ameliorative effect against cisplatin-induced testicular damage. The antioxidant property of Se underscored the therapeutic role of Se which was characterized with increased levels of testicular antioxidants (SOD, GSH, GPx, CAT), decline of MDA level, improvement of sperm parameters (count, motility and abnormal morphology), amelioration of testicular degenerative changes.[102]

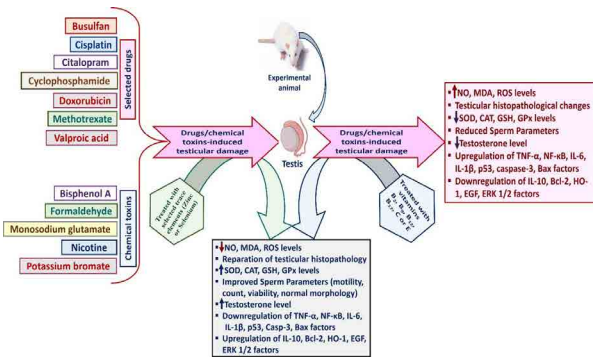

Fig. 3. Schematic summary of mechanisms of drugs and chemical toxins-induced testicular damage and therapeutic effect of selected vitamins and microelements

Conclusion

The damaging effect of drugs and chemical toxins exposure on testicular tissue has been demonstrated to result from the induction of oxidative stress, activation of inflammatory and apoptotic signaling, and characterized with disruption of genetic regulation of gametogenic and endocrine functions of the testes. Hence, potential therapeutic agents with antioxidant, anti-inflammato-

ry and anti-apoptotic properties such as essential vitamins (like Vitamin B_2, Vitamin B_9, Vitamin B_{12}, Vitamin B_{17}, Vitamin C, and Vitamin E) and microelements (like Zinc and Selenium) have demonstrated therapeutic efficacy against testicular damage caused by exposure to drugs and chemical toxins in preclinical studies.

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Conflicts of interest
The authors declare no conflicts of interest.

Data availability
The data that support the relevant findings to the review have been included in the article.

Ethics approval
Not applicable.

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