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Review of the therapeutic effect of alpha-tocopherol, ascorbic acid, and folic acid against ovarian toxicity induced by drugs and heavy metals

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ABSTRACT

Introduction and aim. The ovaries are almond-shaped organs that produce the female gametes and reproductive hormones. They also play a critical role of ovulation under well-coordinated hormonal regulation. However, chemotherapy involving the application of drugs to combat chronic diseases (like cancer) results in toxicity to tissues like ovaries. Similarly, exposure to heavy metals has a toxic effect on the ovaries. Hence, potential therapeutic agents including vitamin antioxidants have been explored to combat ovarian toxicity caused by drugs or heavy metals.

Material and methods. This review was based on previous articles archived on Web of Science, PubMed, Scopus and Google Scholar databases. After initial assessment, the relevant articles were selected for further critical assessment.

Analysis of the literature. Induction of oxidative stress and activation of inflammo-apoptotic signaling were indicated as the major mechanisms of ovarian toxicity due to exposure to drugs and heavy metals. Moreover, vitamins such as alpha-tocopherol, ascorbic acid and folic acid demonstrated therapeutic effects against drug and heavy metal-induced ovarian toxicity based on their modulatory effect on the downstream mechanisms of the toxicity.

Conclusion. Vitamins exert a therapeutic effect against ovarian toxicity caused by drugs or heavy metal exposure due to their antioxidant, anti-inflammatory and anti-apoptotic properties.

Keywords. experimental animal model, ovarian toxicity, vitamins

Introduction

The ovaries (or gonads) of female humans are almond-shaped organs which perform the function of production of female gametes (oocytes) and reproductive hormones.[1] The basic functional unit of the ovary, regarded as the ovarian follicle is comprised of the oocyte surrounded by granulosa and thecal cells.[2] However, the interaction of all the morphological components of the ovaries, which include the germ cells (oocytes), granulosa cells (GCs), theca cells and ovarian stroma, determines the normal physiology of the female gonads and fertility.[3] Moreover, follicular development spans through several stages including primordial primary, secondary, preantral, and graafian stages and culminate into ovulation during each monthly reproductive cycle.[2,4]

As a pivotal function of the ovaries, follicular development is highly regulated by hormones (gonadotropins) such as follicle stimulating hormone (FSH) and luteinizing hormone (LH), secreted by the anterior pituitary gland under the control of gonadotropin-releasing hormone (GnRH) secreted by the hypothalamus.[2,3] Essentially, human ovaries achieve the critical role of oocyte release (ovulation) under well-coordinated hormonal regulation. Hence, the exposure to agents (such as chemotherapeutic agents or heavy metals) with ability to disrupt the highly-connected hormonal regulation of the ovarian function, could cause ovarian toxicity and dysfunction that may culminate into female infertility.[5,6]

Chemotherapy, which involves application of drugs to combat chronic diseases (like cancer), has resulted in adverse effects and toxicity of non-target tissues including the ovaries. Drug-induced ovarian toxicity has been characterized with ovarian atrophy, depletion of ovarian follicles leading to iatrogenic premature ovarian insufficiency (POI) and infertility.[7,8] The mechanisms of drug-induced ovarian toxicity included impairment of ovarian anti-oxidative capacity and oxidative damage of ovaries characterized with apoptosis of GCs due to accumulation of reactive oxygen species (ROS).[7,9] Other associated mechanisms included mitochondrial dysfunction due to excess production of superoxide leading to ROS-induced lipid peroxidation and ferroptosis.[7,10]

Furthermore, exposure to heavy metals has been reported to exhibit a significant toxic effect on body tissues including the ovaries. Heavy metal-induced ovarian toxicity primarily occurs through the induction of oxidative stress due to accumulation of ROS within the ovarian tissue. Moreover, the ROS accumulation induced DNA damage in the oocytes can activate cascades of apoptotic signaling.[11] In addition, the heavy metal-induced ovarian toxicity has been characterized with follicular atresia, reduced estrogen secretion and culminate into ovarian insufficiency and infertility.[12]

The understanding of the aforementioned mechanisms of ovarian toxicity induced by drugs or heavy metals constitute the pivotal rationale for the discovery and development of effective therapeutic intervention in order to protect the morphology and function of ovaries and preserve female fertility. In this regard, the therapeutic potential of essential vitamins has been harnessed to mitigate drug or heavy metal-induced

ovarian toxicity. Accordingly, preclinical studies have demonstrated the therapeutic effect of vitamins (such as alpha-tocopherol, ascorbic acid and folic acid) via modulation of the downstream mechanisms of drug-induced or heavy metal-induced ovarian toxicity.

Aim

This narrative review was thereby aimed at presenting the current findings on therapeutic effect of the selected vitamins against ovarian toxicity induced by drugs or heavy metals in experimental animal models. The review further highlights the associated mechanisms and signaling factors that culminate into the therapeutic effect of the selected vitamins.

Material and methods

Relevant research articles were searched across the different scientific databases which include Web of Science, PubMed, Scopus and Google Scholar. The keywords used for the search included 'antioxidant activity of vitamins', 'anti-inflammatory activity of vitamins', 'anti-apoptotic activity of vitamins', 'vitamins mitigate ovarian toxicity', 'vitamins mitigate drug-induced ovarian toxicity', and 'vitamins mitigate heavy metal-induced ovarian toxicity.' The search results were critically assessed to select articles which contain relevant findings about the therapeutic role of vitamins against drug-induced and heavy metal-induced ovarian toxicity in experimental animal models. The criteria for the eligibility of articles in this review included: articles published in English language, articles which contain findings that are relevant to the scope of the review, and articles published in peer-reviewed journals. Conversely, the criteria for exclusion included duplicate articles and articles published in predatory journals.

Analysis of the literature

The induction of oxidative stress and activation of inflammatory and apoptotic signaling pathways in the ovarian tissue have been demonstrated as the major cellular mechanisms that triggers ovarian toxicity following exposure to drugs and heavy metals in experimental animal models. Hence, potential therapeutic agents such as essential vitamins like alpha-tocopherol, ascorbic acid and folic acid, with antioxidant, anti-inflammatory and antiapoptotic properties, have been explored in preclinical studies to demonstrate their therapeutic effect against drug-induced and heavy metal-induced ovarian toxicity.

Drug-induced ovarian toxicity and associated mechanisms

The selected chemotherapeutic agents in the current narrative review (including busulfan, cyclophosphamide, cisplatin and doxorubicin) possess unique structural formulas (Fig. 1) and exhibit

characteristic pharmacological (anti-cancer) effects. However, they also exhibit toxic effects on the morphology and function of the ovaries (female gonads) outlined in Table 1.

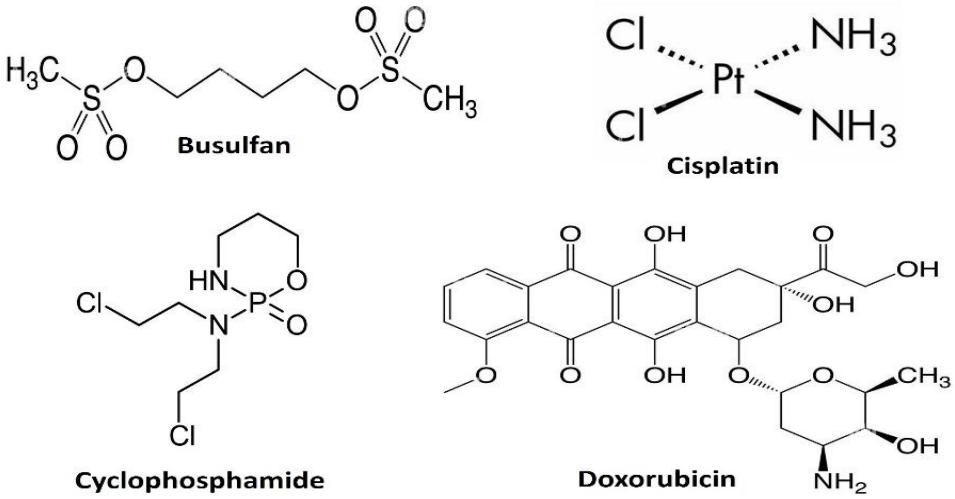

Fig. 1. Molecular structures of selected drugs with female gonadotoxic effects

Busulfan is an alkylating agent commonly used as anti-cancer drug, in combination with cyclophosphamide. Experimental animal studies have reported that the chemotherapeutic agents individually cause female gonadotoxicity and both demonstrate a synergistic toxic effect during combined exposure resulting into POI and infertility.[13] Busulfan-induced ovarian toxicity in experimental animal models is characterized with ovarian atrophy, weight loss, dysregulation of hormones, and significant depletion of primordial and primary ovarian follicles.[14,15] Other associated mechanisms of busulfan-induced ovarian toxicity included an increase in DNA-damage in oocytes and induction of apoptosis in GCs.[16] Aside from the significant loss of ovarian follicles at all developmental stages, busulfan exposure further caused a decrease in serum levels of oestradiol, progesterone, and anti-mullerian hormone (AMH) leading to toxic effect on GCs and ovarian reserve.[13,17]

Cyclophosphamide is an alkylating therapeutic agent used in the management and treatment of neoplasms which has been indicated to exhibit a female gonadotoxic effect primarily through the induction of oxidative stress and activation of inflammatory and apoptotic signaling. Cyclophosphamide-induced ovarian toxicity has been characterized with atrophy of ovarian tissue, reproductive hormone dysregulation, and marked reduction of ovarian follicles in experimental animal models.[15,18] Cyclophosphamide exposure also caused adverse morphological alterations of ovaries such as GCs derangement, ovarian stroma vacuolization, and formation of edema and fibrosis within the ovarian interstitium.[18,19] Other associated mechanisms of cyclophosphamide-induced ovarian toxicity included decreased levels of AMH, increased levels of MDA,

TNF-α, IL-6 factors, downregulation of estradiol, Bcl-2, VEGF-A and SIRT1 expression while Bax, caspase-3, P13k-AKT, HIF-1, Ac-Foxo3a, and p-Foxo3a expressions were upregulated. [19,20,21]

Another chemotherapeutic agent – cisplatin, used for treatment of different forms of cancer, has been reported to cause female gonadotoxicity through induction of oxidative stress and activation of inflammatory and apoptotic signaling resulting in impairment of ovarian function. Cisplatin exposure in experimental models causes ovarian histopathological changes and decreased serum AMH levels.[22] Moreover, the cellular mechanisms associated with cisplatin-induced ovarian toxicity in experimental models included elevated levels of ROS, MDA, IL-6, TNF-α, NF-κB, and upregulation of Bax, cytochrome-c, caspase-3, PARP-1, PTEN, P-AKT, P-mTOR, and P-AMPKα expressions.[22-24] In addition, cisplatin exposure caused reduced levels of GSH, SOD, CAT, and Bcl-2 expression in ovarian tissues in experimental animal models.[22,25]

Doxorubicin, a common anti-cancer drug, is widely known for its adverse effects on multiple body tissues including ovarian tissue through induction of oxidative stress and apoptotic signaling. Previous studies in experimental animal models have reported that exposure to doxorubicin caused a reduction in ovarian size and weight which could be attributed to a significant decline in the population of different stages of ovarian follicles.[26] Doxorubicin-induced ovarian toxicity also caused induction of GCs apoptosis, increased ROS levels, and reduced MMPs levels.[27] Other mechanisms of doxorubicin-induced ovarian toxicity included upregulation of Bax, p53, StAR expressions, and oocyte mitochondrial dysfunction characterized with impaired calcium signaling and ER stress.[27,28] In essence, doxorubicin impairs folliculogenesis and oogenesis leading to dysfunctional ovarian and endometrial cycles.[28] Moreover, the toxic effect of doxorubicin on the three pivotal ovarian functions (development of ovarian follicles, hormone secretion and oocyte maturation) has been demonstrated to exhibit dose-dependency.[29]

Table 1. Profile of selected drugs and mechanisms of ovarian toxicity

Selected drugs	Molecular formula (Molecular weight)	Properties and uses	Mechanisms of ovarian toxicity	References
Busulfan	$C_6H_{14}O_6S_2$ (246.30 g/mol)	- white crystalline powder - slightly soluble in water or ethanol - used as chemotherapeutic drug for treating cancer	- ovarian atrophy and weight loss - dysregulation of reproductive hormones - depletion of ovarian follicles - increased DNA-damage in oocytes - induction of apoptosis in GCs - reduced levels of reproductive hormones	Thonen et al.[13] Sakurada et al.[14] Peng et al.[15] Del Castillo et al.[16] Jiang et al.[17]
Cyclophosphamide	$C_7H_{15}Cl_2N_2O_2P$ (261.08 g/mol)	- white crystalline powder - used for treating cancer and autoimmune diseases	- distortion of ovarian histoarchitecture - decreased level of AMH - increased levels of MDA, TNF-α, IL-6 factors - reduced estradiol, Bcl-2, VEGF-A, SIRT1 levels - upregulation of Bax, caspase-3, P13k-AKT, HIF-1, Ac-Foxo3a, and p-Foxo3a expressions	Peng et al.[15] Pascuali et al.[18] Nan et al.[19] Xiu et al.[20] Notghi et al.[21]
Cisplatin	$Pt(NH_3)_2Cl_2$ (300.10 g/mol)	- yellow or orange crystalline powder, - used as anti-cancer drug	- ovarian histopathological changes - elevated MDA, IL-6, TNF-α, NF-κB levels - upregulation of Bax, caspase-3, PARP-1, PTEN, P-AKT, P-mTOR, P-AMPKα - reduced levels of GSH, SOD, CAT, and Bcl-2 - reduced AMH level	Eid et al.[22] Said et al.[23] Li et al.[24] Soyman et al.[25]
Doxorubicin	$C_{27}H_{29}NO_{11}$ (543.52 g/mol)	- orange-red lyophilized, water-soluble powder - used to treat cancer	- increased ROS level - reduced MMPs level - upregulation of Bax, Bcl-2, p53, StAR expressions - impairment of folliculogenesis and oogenesis	Ben-Aharon et al.[26] Zhang et al.[27] Mohan et al.[28] Xiao et al.[29]

	- dysfunctional ovulatory and endometrial cycle

Heavy metal-induced ovarian toxicity and associated mechanisms

Heavy metals are metallic elements which possess high densities and atomic weight, derived from different sources (both natural and industrial) and used for various applications as outlined in Table 2. Generally, exposure to different heavy metals potently exhibits a toxic effect on ovarian morphology and function (including reproductive and endocrine) by inducing oxidative stress through direct or indirect mechanisms, thereby culminating into oxidative damage, ovarian dysfunction, and infertility.[30]

The exposure to toxic heavy metals like cadmium (Cd) often leads to its accumulation in body tissues including the ovary, causing severe deleterious effects and female infertility. Cd-induced ovarian toxicity, primarily due to induction of oxidative stress, is characterized by ovarian follicular apoptosis, dysregulation of reproductive hormones and oocyte growth impairment.[31] Exposure to cadmium further caused distorted ovarian histoarchitecture, reduced ovarian follicular growth, ovarian follicular atresia, decreased serum levels of LH and FSH, and an impaired reproductive cycle.[32,33]

Copper (Cu) is a heavy metal which exhibits toxic effects on ovarian tissue. In preclinical studies, exposure to Cu has been reported to cause oxidative stress and inflammation in ovarian tissue which in turn causes impaired ovarian folliculogenesis and disrupted reproductive hormonal signaling thereby causing steroidogenesis disorder.[34,35] Cu-induced ovarian toxicity was further characterized by upregulation of Bax, Fas, Caspase8, and Caspase3 expressions thereby indicating the caspase-dependent apoptosis signaling as a pivotal mechanism.[36]

Arsenic (As) is also a heavy metal that acts as endocrine disruptor and induces oxidative stress to exert toxic effects on the ovarian tissue. As-induced ovarian toxicity has been characterized with decreased levels of gonadotropins, downregulation of StAR, CYP11A1, and HSD3β1 resulting into decline of mature ovarian follicles and an increased population of atretic follicles.[37] Other mechanisms of As-induced ovarian toxicity included induction of mitochondrial dysfunction and autophagy via the upregulation of associated factors such as PDK_1, PI3K, TSC2, AMPK, ULK1, ATG13, Beclin1, LC3, P62, ATG3, ATG7, and p62 and downregulation of mTOR and Bcl-2 factors in the ovaries.[38]

Mercury (Hg) is a heavy metal which exhibits severe toxic effects during body tissue exposure including the ovaries. Hg-induced ovarian toxicity in experimental animal models is characterized by induction of oxidative stress and inflammation which further results in overall depletion of ovarian follicles, increased atretic and cystic ovarian follicles, and ovarian fat or lipid droplet accumulation.[39] Exposure to Hg has also been reported to cause distortion of ovarian histomorphology, decreased follicular growth and serum levels of LH and FSH.[33]

Exposure to lead (Pb), a common heavy toxic metal, has also been indicated as a potential cause of ovarian toxicity. Pb-induced ovarian toxicity resulted primarily from the disruption of antioxidant defense systems and excess production of ROS.[40] It was further characterized by distortion of ovarian cytoarchitecture, and a decreased population of ovarian follicles.[40,41] Pb exposure further caused disruption of the hypothalamic-

pituitary-gonadal (HPG) axis and decreased reproductive hormone (AMH) level leading to dysregulation of folliculogenesis and steroidogenesis.[40,42] Other mechanisms of Pb-induced ovarian toxicity included increased levels of SDHA, mitofilin and MTCO2, OPA1, MFN and FIS1; decreased levels of MFF and MPP, and inhibition of phosphorylation in the P38 pathway.[43]

Table 2. Profile of heavy metals and mechanisms of ovarian toxicity

Heavy metals (symbol)	Molar mass	Sources	Applications	Mechanisms of ovarian toxicity	References
Cadmium (Cd)	112.41 g/mol	contaminated water, food, or beverages, earth's crust, cigarette smoke, welding, mining	production of batteries, paints, plastics, television screens, cosmetics	- ovarian follicular atresia and apoptosis - dysregulation of reproductive hormones and impairment of growth of oocytes - distorted ovarian histoarchitecture - reduced follicular growth - decreased serum levels of LH and FSH	Bhardwaj et al.[31] Oyewopo et al.[32] Massányi et al.[33] Khan et al.[44]
Copper (Cu)	63.55 g/mol	decaying vegetation, volcanic eruptions, forest fires, mining, dietary sources (liver, oysters, avocados, nuts, salmon, potatoes, mushrooms	production of electric wires, cooking utensils, heat sinks, electronics, electric motors, copper alloys, plumbing pipes, jewelry	- impaired ovarian folliculogenesis - disruption of reproductive hormonal signaling - steroidogenesis disorder - upregulation of Bax, Fas, Caspase8, and Caspase3 expressions	Wang et al.[34] Yiqin et al.[35] Chen et al.[36]
Arsenic (As)	74.92 g/mol	contaminated water or groundwater, food, earth's crust, in combined form with other metals, sulphur or oxygen	production of insecticide, alloys, lasers, bronzing, semiconductors (gallium arsenide), pyrotechnics	- mitochondrial dysfunction and autophagy - downregulation of StAR, CYP11A1, HSD3β1, mTOR and Bcl-2 expressions - decreased levels of gonadotropins - upregulation of PDK_1, PI3K, Beclin1, TSC2, AMPK, ULK1, ATG13, LC3, P62, ATG3, ATG7, and p62 factors	Chen et al.[37] Ommati et al.[38]
Mercury (Hg)	200.59 g/mol	weathering of rocks, volcanic eruptions, coal,	production of mirrors, thermometers, batteries,	- overall depletion of ovarian follicles, - increased atretic, cystic ovarian follicles	Massanyi et al.[33] Merlo et al.[39]

		contaminated seafood, water, air or food, industrial wastes	fluorescent lamps, cosmetics,	- elevated ovarian fat accumulation - distortion of ovarian histomorphology - decreased serum levels of LH and FSH	
Lead (Pb)	207.2 g/mol	vehicle exhaust, burning of fossil fuels, volcanic eruptions, weathering of rocks, mining, smelting, landfills	production of pipes, gasoline, roofing sheets, paints, alloys, ammunition, weights, batteries, cosmetics, and gasoline	- distortion of ovarian cytoarchitecture - decline in ovarian follicles population - decreased AMH, MFF and MPP levels - disruption of HPG axis, steroidogenesis - increased levels of SDHA, mitofilin and MTCO2, OPA1, MFN and FIS1	Qu et al.[40] Wassem et al.[41] Fatima et al.[42] Yang et al.[43]

Therapeutic potential of selected vitamins against ovarian toxicity induced by drugs or heavy metals

Vitamins are micronutrients which play an essential role in the physiological and metabolic functions of the body, help to reduce the risk of diseases and deficiencies result in diverse tissue disorders.[45] The two classes of vitamins, namely fat-soluble and water-soluble vitamins, are comprised of different vitamins with diverse properties based on their varying structures. Vitamins such as alpha-tocopherol, ascorbic acid, and folic acid possess variable structural conformations (Fig. 2) and exhibit diverse properties. Previous preclinical studies have demonstrated their therapeutic effect against ovarian toxicity induced by drugs or heavy metals in experimental animal models as outlined in Table 3.

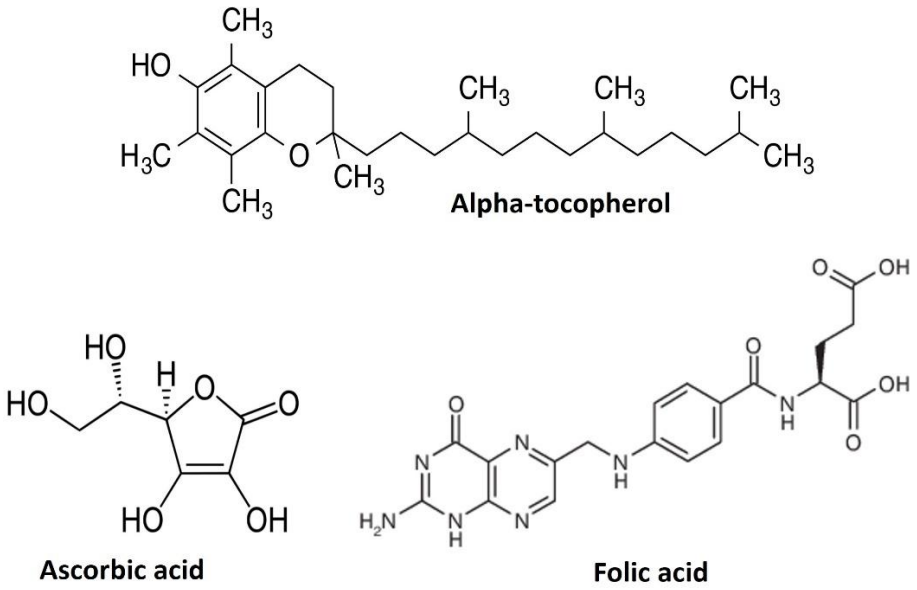

Fig. 2. Molecular structures of vitamins B_9, C and E

Alpha-tocopherol – therapeutic role against ovarian toxicity in experimental model

Alpha-tocopherol is a fat-soluble vitamin which is abundantly derived from cereals, vegetables oils, eggs, fruits, and meats, and one of the eight essential compounds (four tocopherols and four tocotrienols) of the vitamin E family.[46] The vitamin E family possesses a chromane ring with a hydroxyl group and side chain with tocopherol members possessing saturated side chain while tocotrienol members bear an unsaturated isoprenoid side chain with double bonds at third, seventh, and eleventh carbon.[47] Alpha-tocopherol acts as an antioxidant which protects tissue against oxidative damage that results from activities of free radicals.[46,48] Hence, it has demonstrated protective effect against drug-induced ovarian toxicity in preclinical studies.

In a previous study using experimental model, therapeutic activity of alpha-tocopherol against cisplatin-induced ovarian toxicity was characterized with reversal of follicle developmental disorders and ovarian fibrosis, increased level of reproductive hormones, marked inhibition of ferroptosis and abrogation of lipid peroxidation leading to the restoration of ovarian function.[49] In addition, the mitigating effect of alpha-

tocopherol on cyclophosphamide-induced ovarian toxicity was characterized with elevated levels of ovarian tissue antioxidant (GSH), proliferating cell nuclear antigen (PCNA) and growth differentiation factor-9 (GDF-9).[50] Furthermore, as a natural non-enzymatic antioxidant, the ability to scavenge free radicals and inhibit lipid peroxidation highlighted its mitigating potential on heavy metal-induced toxicity of body tissues.[51,52] On this basis, alpha-tocopherol has demonstrated mitigating effect on ovarian toxicity caused by exposure to heavy metals in experimental animal models. The associated mechanisms of amelioration of heavy metal-induced ovarian toxicity by alpha-tocopherol further included the modulation of the NF-kB, Nrf2 and MAPK signaling pathways.[53]

Ascorbic acid – therapeutic role against ovarian toxicity in experimental model

Ascorbic acid (vitamin C) is a water-soluble vitamin which is abundantly derived from natural sources like oranges, lemons, grape, vegetables and is composed of an almost planar five-member ring with two chiral centers that resolves into the four stereoisomers.[54,55] Essentially, ascorbic acid is a natural antioxidant which interacts with other antioxidants (including tocopherol and glutathione) and stimulates the biosynthesis and activation of antioxidant enzymes like SOD, CAT, GPx. It further enhanced the activity of Nrf2, Ref-1, AP-1 which then upregulate genes encoding antioxidant proteins.[56,57] Hence, ascorbic acid possesses ability to scavenge free radicals that follows the exposure of body tissues to potential toxicants (such as drugs or heavy metals) thereby abrogating oxidative damage of tissues due to the exposure.[57-59]

The therapeutic potential and antioxidant properties of ascorbic acid has been explored in experimental animal models to mitigate ovarian toxicity induced by drugs or heavy metals. Previous experimental studies have demonstrated the potency of ascorbic acid in mitigating cyclophosphamide-induced ovarian toxicity characterized with preservation of ovarian morphology, elevated levels of ovarian tissue antioxidant (GSH), proliferating cell nuclear antigen (PCNA) and growth differentiation factor-9 (GDF-9) thereby preserving the growth of ovarian follicles.[50]

Folic acid – therapeutic role against ovarian toxicity in experimental model

Folic acid (or folate or vitamin B_9) is a member of vitamin B family which is abundantly derived from dietary sources such as banana, papaya, orange, green peas, kidney bean, crab, tomato juice, avocado, black-eyed peas, peanuts, and spinach.[60] The chemical structure of folic acid is composed of a methylated pteridine ring attached to *p*-aminobenzoic acid (PABA), and is in turn linked to the α nitrogen of glutamic acid via carboxyl group. It is an essential vitamin that plays a key role in biosynthesis of purine and pyridine bases as well as during prenatal development.[61]

Furthermore, folic acid has been demonstrated to exhibit antioxidant properties comparable to alpha-tocopherol and ascorbic acid *in vivo,* with its supplementation contributing to the role of tissue antioxidant systems in scavenging free radicals and inhibiting lipid peroxidation.[62] The antioxidant role of folic acid was

characterized with significantly increased GSH and TAC levels and reduced MDA level.[63,64] Hence, it has potential to mitigate pathologies of tissues (including ovaries) following exposure to drugs and heavy metals. Moreover, folic acid supplementation has enhanced ovarian function and ensures high ovarian reserve or antral follicle count thereby promoting the overall female reproductive health.[65] Treatment with folic acid has further demonstrated protective effects against methotrexate-induced ovarian toxicity in experimental models characterized by inhibition of ovarian follicle degeneration, preservation of normal ovarian morphology and downregulation of apoptotic factors.[66]

Table 3. Profile and therapeutic role of selected vitamins against ovarian toxicity

Vitamins (other names)	Molecular formula (molecular weight)	Natural sources	Possible mechanisms of therapeutic effect against ovarian toxicity	References
Alpha-tocopherol (vitamin E)	$C_{29}H_{50}O_2$ (430.71 g/mol)	almonds, nuts, butter, spinach, vegetable oils, cereals, meat, egg, avocado, fruits, wheat	- reversal of follicle disorders and ovarian fibrosis - increased levels of reproductive hormones, - inhibition of ferroptosis and lipid peroxidation - elevated levels of GSH, PCNA, GDF-9 factors - modulation of NF-kB, Nrf2 and MAPK signaling	Du et al.[49] Gürgen et al.[50] Zhai et al.[51] Fan et al.[53]
Ascorbic acid (vitamin C)	$C_6H_8O_6$ (441.4 g/mol)	orange, tomato, guava, potato, mango, lemon, pepper, strawberries, grape fruits	- stimulated antioxidant enzymes like SOD, CAT, GPx - enhanced the activity of Nrf2, Ref-1, AP-1 - preservation of ovarian morphology - elevated levels of GSH, PCNA, GDF-9 - preserve ovarian follicular growth	Gürgen et al.[50] Gęgotek et al.[56,] Gęgotek et al.[57]
Folic acid (vitamin B_9)	$C_{19}H_{19}N_7O_6$ (176.124 g/mol)	banana, papaya, orange, green peas, kidney bean, crab, tomato juice, avocado, black-eyed pea, peanuts, spinach, beef liver	- increased GSH and TAC levels - reduced MDA level - increased ovarian reserve or antral follicle count - inhibition of ovarian follicle degeneration - preservation of normal ovarian morphology - downregulation of apoptotic factors	Gliszczyńska-Świgło et al.[62] Asbaghi et al.[63] Liao et al.[64] Kadir et al.[65] Shohda et al.[66]

Conclusion

The exposure of ovarian tissue to potential toxins, including drugs and heavy metals, triggers ovarian toxicity primarily due to the induction of oxidative stress and activation of inflammatory and apoptotic signaling. The resultant ovarian toxicity results in distortion of ovarian morphology and loss reproductive function leading to infertility. This narrative review presents the therapeutic effect of selected vitamins including alpha-tocopherol, ascorbic acid and folic acid against drug or heavy metal-induced ovarian toxicity primarily through suppression of oxidative stress and inhibition of inflammatory and apoptotic signaling pathways. The therapeutic effect of the selected vitamins thereby underscores their efficacy in therapeutic intervention against drug or heavy metal-induced ovarian toxicity.

Declarations

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Author contributions

Conceptualization, D.R.O., O.O.A.; Methodology, D.R.O.; Software, O.O.A. O.A.; Validation, D.R.O., O.O.A., O.A.; Formal Analysis, D.R.O.; Investigation, O.O.A., O.A.; Resources, D.R.O.; Data Curation, D.R.O.; Writing – Original Draft Preparation, O.O.A., O.A.; Writing – Review & Editing, D.R.O; Supervision, D.R.O.

Conflicts of interest

Authors do not declare any conflict of interest.

Data availability

The data that support the findings of this study have been included in the article.

Ethics approval

Not applicable.

References

1. Moore KL, Dalley AF, Agur AMR. *Clinically Oriented Anatomy*. 7th ed. Philadelphia, PA: Wolters Kluwer; 2018:1411-1413.
2. Orisaka M, Miyazaki Y, Shirafuji A, et al. The role of pituitary gonadotropins and intraovarian regulators in follicle development: A mini-review. *Reprod Med Biol*. 2021;20(2):169-175. doi: 10.1002/rmb2.12371

3. Richards JS, Pangas SA. The ovary: basic biology and clinical implications. *J Clin Invest.* 2010;120(4):963-972. doi: 10.1172/JCI41350
4. Li H, Chian RC. Follicular development and oocyte growth. In: Chian RC, Nargund G, Huang J, eds. *Development of In Vitro Maturation for Human Oocytes*. Cham, Switzerland: Springer; 2017. doi: 10.1007/978-3-319-53454-1_2
5. Yilmaz B, Terekeci H, Sandal S, Kelestimur F. Endocrine disrupting chemicals: exposure, effects on human health, mechanism of action, models for testing and strategies for prevention. *Rev Endocr Metab Disord.* 2020;21(1):127-147. doi: 10.1007/s11154-019-09521-z
6. Biswas S, Ghosh S, Das S, Maitra S. Female reproduction: at the crossroads of endocrine disruptors and epigenetics. *Proc Zool Soc.* 2021;74:532-545. doi: 10.1007/s12595-021-00403-4
7. Zhang S, Liu Q, Chang M, et al. Chemotherapy impairs ovarian function through excessive ROS-induced ferroptosis. *Cell Death Dis.* 2023;14(5):340. doi: 10.1038/s41419-023-05859-0
8. Cho HW, Lee S, Min KJ, et al. Advances in the Treatment and Prevention of Chemotherapy-Induced Ovarian Toxicity. *Int J Mol Sci.* 2020;21(20):7792. doi: 10.3390/ijms21207792
9. Melekoglu R, Ciftci O, Eraslan S, Cetin A, Basak N. Beneficial effects of curcumin and capsaicin on cyclophosphamide-induced premature ovarian failure in a rat model. *J Ovarian Res.* 2018;11(1):33. doi: 10.1186/s13048-018-0409-9
10. Spears N, Lopes F, Stefansdottir S, et al. Ovarian damage from chemotherapy and current approaches to its protection. *Human Reprod Update.* 2019;25(6):673-693. doi: 10.1093/humupd/dmz027
11. Wang Y, Li SH, Yang SJ, et al. Exposure to phenanthrene affects oocyte meiosis by inducing mitochondrial dysfunction and endoplasmic reticulum stress. *Cell Pro.* 2023;56(1):e13335. doi: 10.1111/cpr.13335
12. Xiao C, Lai D. Impact of oxidative stress induced by heavy metals on ovarian function. *J Appl Toxicol.* 2025;45(1):107-116. doi: 10.1002/jat.4664
13. Thonen M, Jiang H, Luan Y, Dong R, Wadhwa A, Kim SY. The gonadotoxic effects of cyclophosphamide and busulfan on ovaries in CD-1 mouse model. *J Endocr Soc.* 2023;7(1):bvad114.1575. doi: 10.1210/jendso/bvad114.1575
14. Sakurada Y, Kudo S, Iwasaki S, Miyata Y, Nishi M, Masumoto Y. Collaborative work on evaluation of ovarian toxicity: two- or four-week repeated-dose studies and fertility study of busulfan in female rats. *J Toxicol Sci.* 2009;34(1):SP65-SP72. doi: 10.2131/jts.34.s65
15. Peng Y, Sun L, Guo W, et al. Berberine protects cyclophosphamide and busulfan-induced premature ovarian insufficiency in mouse model. *J Pharmacol Sci.* 2023;153(1):46-54. doi: 10.1016/j.jphs.2023.07.004

16. Del Castillo LM, Buigues A, Rossi V, et al. The cyto-protective effects of LH on ovarian reserve and female fertility during exposure to gonadotoxic alkylating agents in an adult mouse model. *Hum Reprod.* 2021;36(9):2514-2528. doi: 10.1093/humrep/deab165
17. Jiang Y, Zhao J, Qi HJ, et al. Accelerated ovarian aging in mice by treatment of busulfan and cyclophosphamide. *J Zhejiang Univ Sci B.* 2013;14(4):318-324. doi: 10.1631/jzus.B1200181
18. Pascuali N, Scotti L, Di Pietro M, et al. Ceramide-1-phosphate has protective properties against cyclophosphamide-induced ovarian damage in a mice model of premature ovarian failure. *Hum Reprod*. 2018;33(5):844-859. doi: 10.1093/humrep/dey045
19. Nan N, Du XL, Chen M, Luo JQ. Qirong Tablets inhibits apoptosis of ovarian granulosa cells via PI3K/Akt/ HIF-1 signaling pathway. *Zhongguo Zhong Yao Za Zhi.* 2023;48(17):4774-4781. doi: 10.19540/j.cnki.cjcmm.20230424.501
20. Xiu Z, Tang S, Kong P, et al. Zigui-Yichong-Fang protects against cyclophosphamide-induced premature ovarian insufficiency via the SIRT1/Foxo3a pathway. *J Ethnopharmacol.* 2023;314:116608. doi: 10.1016/j.jep.2023.116608
21. Notghi P, Mehranjani MS, Shariatzadeh SMA. Atorvastatin improves ovarian function and follicular reserve in rats with premature ovarian insufficiency. *Reprod Biomed Online.* 2024;49(5):104324. doi: 10.1016/j.rbmo.2024.104324
22. Eid BG, Binmahfouz LS, Shaik RA, Bagher AM, Sirwi A, Abdel-Naim AB. Icariin inhibits cisplatin-induced ovarian toxicity via modulating NF-κB and PTEN/AKT/mTOR/AMPK axis. *Naunyn-Schmiedeberg's Arch Pharmacol.* 2025;398:1949-1959. doi: 10.1007/s00210-024-03395-y
23. Said RS, Mantawy EM, El-Demerdash E. Mechanistic perspective of protective effects of resveratrol against cisplatin-induced ovarian injury in rats: emphasis on anti-inflammatory and anti-apoptotic effects. *Naunyn-Schmiedeberg's Arch Pharmacol.* 2019;392:1225-1238. doi: 10.1007/s00210-019-01662-x
24. Li F, Zhu F, Wang S, et al. Icariin alleviates cisplatin-induced premature ovarian failure by inhibiting ferroptosis through activation of the Nrf2/ARE pathway. *Sci Rep.* 2024;14:17318. doi: 10.1038/s41598-024-67557-x
25. Soyman Z, Uzun H, Bayindir N, Esrefoglu M, Boran B. Can ebselen prevent cisplatin-induced ovarian damage? *Arch Gynecol Obstet.* 2018;297:1549-1555. doi: 10.1007/s00404-018-4750-4
26. Ben-Aharon I, Bar-Joseph H, Tzarfaty G, et al. Doxorubicin-induced ovarian toxicity. *Reprod Biol Endocrinol.* 2010;8:20. doi: 10.1186/1477-7827-8-20
27. Zhang T, He WH, Feng LL, Huang HG. Effect of doxorubicin-induced ovarian toxicity on mouse ovarian granulosa cells. *Regul Toxicol Pharmacol.* 2017:86:1-10. doi: 10.1016/j.yrtph.2017.02.012

28. Mohan UP, Pichiah TPB, Iqbal STA, Arunachalam S. Mechanisms of doxorubicin-mediated reproductive toxicity – A review. *Reprod Toxicol.* 2021;102:80-89. doi: 10.1016/j.reprtox.2021.04.003
29. Xiao S, Zhang J, Liu M, Iwahata H, Rogers HB, Woodruff TK. Doxorubicin Has Dose-Dependent Toxicity on Mouse Ovarian Follicle Development, Hormone Secretion, and Oocyte Maturation. *Toxicol Sci.* 2017;157(2):320-329. doi: 10.1093/toxsci/kfx047
30. Xiao C, Lai D. Impact of oxidative stress induced by heavy metals on ovarian function. *J Appl Toxicol.* 2025;45(1):107-116. doi: 10.1002/jat.4664
31. Bhardwaj JK, Bikal P, Sachdeva SN. Cadmium as an ovarian toxicant: A review. *J Appl Toxicol*. 2024;44(1):129-147. doi: 10.1002/jat.4526
32. Oyewopo AO, Olaniyi KS, Olojede SO, Lawal SK, Amusa OA, Ajadi IO. *Hibiscus sabdariffa* extract protects against cadmium-induced ovarian toxicity in adult Wistar rats. *Int J Physiol Pathophysiol Pharmacol.* 2020;12(4):107-114.
33. Massányi P, Massányi M, Madeddu R, Stawarz R, Lukáč N. Effects of Cadmium, Lead, and Mercury on the Structure and Function of Reproductive Organs. *Toxics.* 2020;8(4):94. doi: 10.3390/toxics8040094
34. Wang Q, Sun Y, Zhao A, et al. High dietary copper intake induces perturbations in the gut microbiota and affects host ovarian follicle development. *Ecotoxicol Environ Saf.* 2023;255:114810. doi: 10.1016/j.ecoenv.2023.114810
35. Yiqin C, Yan S, Peiwen W, et al. Copper exposure disrupts ovarian steroidogenesis in human ovarian granulosa cells via the FSHR/CYP19A1 pathway and alters methylation patterns on the SF-1 gene promoter. *Toxicol Lett.* 2022;356:11-20. doi: 10.1016/j.toxlet.2021
36. Chen Y, Guan F, Wang P, et al. Copper exposure induces ovarian granulosa cell apoptosis by activating the caspase-dependent apoptosis signaling pathway and corresponding changes in microRNA patterns. *Ecotoxicol Environ Saf.* 2023;264:115414. doi: 10.1016/j.ecoenv.2023
37. Chen Y, Sun Y, Zhao A, et al. Arsenic exposure diminishes ovarian follicular reserve and induces abnormal steroidogenesis by DNA methylation. *Ecotoxicol Environ Saf.* 2022;241:113816. doi: 10.1016/j.ecoenv.2022.113816
38. Ommati MM, Shi X, Li H, et al. The mechanisms of arsenic-induced ovotoxicity, ultrastructural alterations, and autophagic related paths: An enduring developmental study in folliculogenesis of mice. *Ecotoxicol Environ Saf.* 2020;204:110973. doi: 10.1016/j.ecoenv.2020.110973
39. Merlo E, Schereider IRG, Simoes MR, Vassallo DV, Graceli JB. Mercury leads to features of polycystic ovary syndrome in rats. *Toxicol Lett.* 2019;312:45-54. doi: 10.1016/j.toxlet.2019.05.006
40. Qu J, Niu H, Wang J, Wang Q, Li Y. Potential mechanism of lead poisoning to growth and development of ovarian follicle. *Toxicol Lett.* 2021;457:152810. doi: 10.1016/j.tox.2021.152810

41. Waseem N, Butt SA, Hamid S. Amelioration of lead induced changes in ovary of mice by garlic extract. *J Pak Med Assoc.* 2014;64:798-801.
42. Fatima P, Hossain MM, Rahman D, et al. Association of blood and semen lead and zinc level with semen parameter in the male partner of infertile couple. *Mymensingh Med J.* 2015;24:537-541.
43. Yang ZN, Du X, Wang A, et al. Melatonin ameliorates Pb-induced mitochondrial homeostasis and ovarian damage through regulating the p38 signaling pathway. *Ecotoxicol Environ Saf.* 2025;292:117937. doi: 10.1016/j.ecoenv.2025.117937
44. Khan Z, Elahi A, Bukhari DA, Rehman A. Cadmium sources, toxicity, resistance, and removal by microorganisms: a potential strategy for cadmium eradication. *J Saud Chem Soc.* 2022;26(6):101569. doi: 10.1016/j.jscs.2022.101569
45. Akram M, Munir N, Daniyal M, et al. Vitamins and minerals: types, sources and their functions. In: Egbuna C, Dable Tupas G, eds. *Functional Foods and Nutraceuticals*. Cham, Switzerland: Springer; 2020. doi: 10.1007/978-3-030-42319-3_9
46. Akinola AO, Omotoso DR, Oyeyemi AW, Daramola OO, Emojevwe V. α-Tocopherol mitigates adverse effects of potassium bromate on hematological parameters and markers of hepatic function in rat model. *J Morphol Sci.* 2023;40:89-94.
47. Niki E, Abe K. Vitamin E: chemistry and nutritional benefits. In: Niki E, ed. *Vitamin E*. Cambridge, UK: The Royal Society of Chemistry; 2019:1-11. doi: 10.1039/9781788016216-00001
48. Torquato P, Marinelli R, Bartolini D, Galli F. Vitamin E: nutritional aspects. *Mol Nutr*. 2020:447-485. doi: 10.1016/B978-0-12-811907-5.00019-1
49. Du R, Cheng X, Ji J, et al. Mechanism of ferroptosis in a rat model of premature ovarian insufficiency induced by cisplatin. *Sci Rep*. 2023;13(1):4463. doi: 10.1038/s41598-023-31712-7
50. Gürgen SG, Erdoğan D, Elmas C, Kaplanoğlu GT, Özer C. Chemoprotective effect of ascorbic acid, α-tocopherol, and selenium on cyclophosphamide-induced toxicity in the rat ovarium. *Nutr.* 2013;29(5):777-784. doi: 10.1016/j.nut.2012.11.004
51. Zhai Q, NArbad A, Chen W. Dietary strategies for the treatment of cadmium and lead toxicity. *Nutr.* 2015;7(1):552-571. doi: 10.3390/nu7010552
52. Omotoso DR, Ehiemere WP. Comparative histomorphological assessment of Vitamin E and Green tea (Camellia sinensis) extract-mediated amelioration of Lead–induced hepatopathy in experimental Wistar rats. *Am J Physiol Biochem Pharmacol.* 2020;10(1):18-24. doi: 10.5455/ajpbp.20191105104249
53. Fan Y, Jiang X, Xiao Y, Li H, Chen J, Bai W. Natural antioxidants mitigate heavy metal induced reproductive toxicity: prospective mechanisms and biomarkers. *Crit Rev Food Sci Nutr.* 2023;64(31):11530-11542. doi: 10.1080/10408398.2023.2240399

54. Steinberg FM, Rucker RB. Vitamin C. In: *Encyclopedia of Biological Chemistry*. Elsevier; 2013:530-534. doi: 10.1016/B978-0-12-378630-2.00092-X
55. Akram M, Munir N, Daniyal M, et al. Vitamins and Minerals: Types, Sources and their Functions. *Funct Foods and Nutraceut*. 2020:149-172. doi: 10.1007/978-3-030-42319-3_9
56. Gęgotek A, Skrzydlewska E. Ascorbic acid as antioxidant. *Vitamin Horm.* 2023;121:247-270. doi: 10.1016/bs.vh.2022.10.008
57. Gęgotek A, Skrzydlewska E. Antioxidative and Anti-Inflammatory Activity of Ascorbic Acid. *Antioxidants*. 2022;11(10):1993. doi: 10.3390/antiox11101993
58. Conklin PL, Foyer CH, Hancock RD, Ishikawa T, Smirnoff N. Ascorbic acid metabolism and functions. *J Exp Bot*. 2024;75(9):2599-2603. doi: 10.1093/jxb/erae143
59. Okwuonu UC, Omotoso DR, Bienonwu EO, Adagbonyin O, Dappa J. Histomorphological profile of liver and kidney tissues of albino Wistar rats following exposure to cadmium-induced damage and ascorbic acid supplementation. *Acad Anat Int*. 2020;6(1):15-19. doi: 10.21276/aanat.2020.6.1.5
60. Myszczyszyn A, Krajewski R, Ostapow M, Hirnle L. Folic acid: role in the body, recommendations, and clinical significance. *Nurs 21st Century.* 2019;18(1):66. doi: 10.2478/pielxxiw-2019-0007
61. Harris ED. Cofactors: organic. In: *Encyclopedia of Human Nutrition*. Elsevier; 2013:366-377. doi: 10.1016/B978-0-12-375083-9.00058-1
62. Gliszczyńska-Świgło A. Folates as antioxidants. *Food Chem.* 2007;101(4):1480-1483. doi: 10.1016/foodchem.2006.04.022
63. Asbaghi O, Ghanavati M, Ashtary-Larky D, et al. Effects of Folic Acid Supplementation on Oxidative Stress Markers: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Antioxidants*. 2021;10(6):871. doi: 10.3390/antiox10060871
64. Liao K, Wang Y, Zheng L, et al. Effect of folic acid supplementation on diminished ovarian reserve: study protocol of a single-centre, open-label, randomised, placebo-controlled clinical trial. *BMJ Open*. 2022;12(7):e057689. doi: 10.1136/bmjopen-2021-057689
65. Kadir M, Hood RB, Mínguez-Alarcón L, et al. Folate intake and ovarian reserve among women attending a fertility center. *Fertil Steril*. 2022;117(1):171-180. doi: 10.1016/j.fertnstert.2021.09.037
66. Shohda AA, El-Banna A, Fattah FA. The possible protective effect of folic acid against methotrexate induced ovarian damage in female albino rats: light and electron microscopic study. *Bull Natl Nutr Inst Arab Repub Egypt.* 2017;49(1):1-24. doi: 10.21608/bnni.2017.4247