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Review Article

Natural antioxidants and their impact on female reproductive health

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ABSTRACT

Antioxidants are essential for fertility and reproductive health. Cellular oxidative and nitrosative stress induced by free radicals might negatively impact fertility and reproductive organ function. Numerous reproductive complications and disorders, such as endometriosis, polycystic ovarian syndrome, oocyte aging, dysmenorrhea and premenstrual syndrome, spontaneous abortion, and infertility, have been linked to imbalances in the oxidant/antioxidant interaction. Studies have examined dietary antioxidant supplementation that has been the focus of dietary antioxidant treatment for the treatment and/or prevention of recurring spontaneous abortions and infertility that cannot be explained. The sources are exploited which can abolish reactive oxygen species from our system for the management of reproductive diseases and in promoting fertility and normal reproductive physiology. This review focuses on the antioxidant therapies for the prevention and treatment of reproductive disease linked to oxidative stress, as well as the function antioxidants play in female reproductive health and fertility.

Keywords: Antioxidants, Female reproduction, Reactive oxygen species, Nitrosative stress, Oxidative stress

INTRODUCTION

Cellular aerobic respiration leads to the generation of metabolic by-products accompanied by free radicals. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are the two categories of free radicals. These lead to oxidative and nitrosative stress, respectively, a condition where cellular structure and function are more damaged, thereby disrupting intracellular homeostasis. Free radical effects are mediated through lipid peroxidation, structural and functional alterations in proteins and deoxyribonucleic acid (DNA), and begin a cascade of progressive reactions to generate free radicals further, which ultimately affect cell membrane permeability and electrophysiological signaling, bring about apoptosis, altered gene expression, diminished gonadotrophins and anti-steroidogenic action, and inhibited production of protein adenosine triphosphate (ATP) and hence eventual damage of tissue.[1,2] Superoxide radicals (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radicals (.OH), nitric oxide (NO.), and peroxynitrite anion are the common ROS that are involved in mammalian reproduction. An imbalance between the generation of pro-oxidants such as RNS and ROS and antioxidant capability is known as oxidative stress. Antioxidants are compounds with a low molecular weight that can neutralize the free radicals by donating an electron and hindering the free radical formation. The unbalanced interaction between oxidants and antioxidants has an impact on reproductive pathologies such as abnormalities in oocyte metabolism endometrial maturation through the activation of nuclear factor-kappa B (NF-κβ) and nuclear factor erythroid 2-related factor 2 (Nrf

2) antioxidant signaling pathways, endometriosis, polycystic ovarian syndrome (PCOS), infertility, prenatal development disorders, and complications.[3] Different types of reproductive health problems due to ROS/RNS are shown in Figure 1.

The respiratory chain of the mitochondria produces the majority of ROS. Exogenous exposures to teratogens, alcohol, tobacco, smoking, environmental pollutants, and dietary toxins can also result in the formation of these. Antioxidants in the form of vitamins prevent free radical generation. The intent of this review is to study antioxidants' function and effects on female fertility and reproductive health and how antioxidant rich therapies can be exploited to cure and prevent reproductive diseases associated with free radical stress.[4] The intake of these antioxidants to reduce the free radical stress serves as an important therapy as it is effective, inexpensive, and non-invasive and enhances overall reproductive health.

TYPES OF NATURAL DIETARY ANTIOXIDANTS

Dietary antioxidants include isoflavones, antioxidant vitamins, antioxidant enzymes, and metallic cofactors. Figure 2 shows the different types of antioxidants and their role in female reproductive health.

Isoflavones

Dietary phytoestrogens are found in soya products. The predominant ones are isoflavones, including daidzein, genistein, and glycitein, while flavonols include catechins.[4] Sexual development, puberty, gamete production, pregnancy, lactation, and other processes can all be impacted by soy phytoestrogen, which can change the body's natural hormone synthesis, secretion, metabolism, and transport. Isoflavones displace testosterone and 17- β estradiol from sex hormone-binding globulin (sHBG) sites and control the levels of aromatase, 5-α reductase, and plasma sHBG.[5-7]

Antioxidant vitamins

The main dietary antioxidant vitamins include vitamin E, vitamin C, vitamin A, vitamin B9, and the carotenoids. The primary source of provitamins A and C, B-carotene, are crucial antioxidants that scavenge ROS.[8]

Polyphenols

Quercetin and resveratrol are the two main polyphenols while flavonoids include quercetin, myricetin, catechin, etc. Resveratrol's effects on mitochondrial membrane potential, ATP, oxidative stress levels, and decreased inflammation have been shown to improve follicular pool and oocyte quality in age-related infertility, according to research on both humans and animals.[9] Resveratrol may improve age-related infertility by influencing a variety of molecular factors, such as Sirtuin 1 (SIRT1), p53, which regulates apoptosis, NF-κB, which is involved in inflammation; the Ak strain transforming/mammalian target of rapamycin (Akt/mTOR) pathway, which is linked to mitochondrial function; and Nrf2, which is involved in the expression of antioxidant enzymes like superoxide dismutase (SOD).[9]

Antioxidant enzymes and cofactors

Cofactors for copper, zinc-SOD (Cu, Zn-SOD, or SOD1), manganese SOD (Mn-SOD or SOD2), and selenium glutathione peroxidase (GPx) include copper, zinc, manganese, and selenium, respectively.[10] Table 1 shows the various natural dietary sources of these antioxidants.

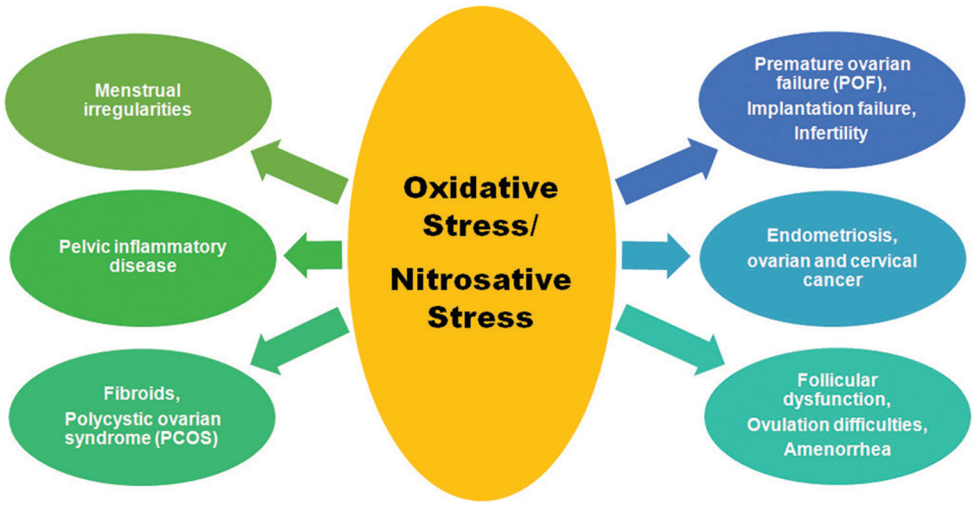

Figure 1: Different types of reproductive health problems due to reactive oxygen species/reactive nitrogen species.

Table 1: Sources of various antioxidants and their important roles.

S. No.	Antioxidants	Source	Role	References
1.	Vitamin A	Carrot, pumpkin, spinach, kale, sweet potato, and tuna	Cell differentiation and antioxidant	Couto *et al.*[11]
2.	Vitamin B9	Liver, legumes, pulses, yeast, fermented foods, and leafy vegetables	Coenzyme aids in nucleic acid production	Lewis *et al.*, Vaskova *et al.*, Oh *et al.*[12-14]
3.	Vitamin C	Citrus fruits, guava, kiwifruit, bell pepper, and broccoli	Cofactor of enzymes, antioxidant, and wound healing	Lewis *et al.*, Vaskova *et al.*, Oh *et al.*[12-14]
4.	Vitamin E	Olive oil, sunflower seeds, avocado, and almonds	Antioxidant, signal transduction, cell membrane integrity, and division	Vaskova *et al.*, Vitagliano *et al.*[13,15]
5.	Selenium	Dairy, fish, meat, cruciferous vegetables, legume, garlic, and onion	Intracellular antioxidant enzyme and part of glutathione peroxidase	Oh *et al.*, Hu *et al.*[14,16]
6.	Zinc	Chicken, beef, tofu, pumpkin seeds, lentils, and low-fat yogurt	Signal transduction and role in zinc-finger motifs	Oh *et al.*, Garner *et al.*[14,17]
7.	Melatonin	Walnut, cherries, salmon, milk, and eggs	Antioxidant, anti-angiogenic, and pro-apoptotic	Espino *et al.*, Batioglu *et al.*, Wdowiak *et al.*[18-20]
8.	Resveratrol	Grapes skin, wine, peanut, blueberries, and apple	Antioxidant, gene expression, and immunity regulator	Vaskova *et al.*, Alesci *et al.*[13,21]
9.	Curcumin	Rhizome and roots of turmeric plant	Antioxidant, immunomodulation	Kamal *et al.*, Sirotkin *et al.*[22,23]
10.	Quercetin	Fruits, vegetables, seeds, and nuts	Antioxidant, anti-inflammatory, antiviral, and antibacterial	Vaskova *et al.*, Kim *et al.*[13,24]

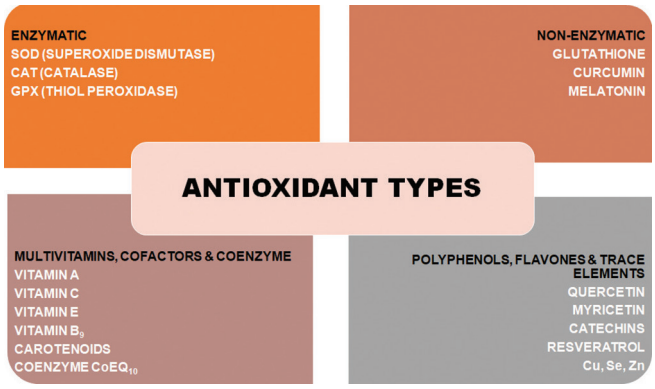

Figure 2: Different types of antioxidants involved in female reproductive health.

MECHANISM OF ACTION

Antioxidants play a function in the hormonal modulation of vascular activity by activating antioxidant signaling pathways Nrf 2 and suppressing NF-κβ.[25,26] Through NF-κB activation, ROS activation has been shown to increase prostaglandin F2α (PGF2α) secretion. Myometrial contractions can result in spiral artery vasoconstriction and epithelial ischemia due to PGF2α, which is generated by cyclooxygenase (COX-2). Tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein (MCP)-1, interleukin (IL)-6, and IL-1 are also expressed as a result of ROS-mediated NF-κB activation, which promotes neutrophil migration into the stroma. ROS interacts with particular cysteine residues on KEAP1 in response to oxidative stressors, causing a structural change. As a result, this alteration stops Nrf2 from being ubiquitinated, which allows it to go into the nucleus and attach to antioxidant response elements (ARE) found in the promoter regions of antioxidant genes to increase their production.

The mechanism of action of major categories of antioxidants includes:

Mechanism of action of enzymatic antioxidants

Antioxidants boost fertility by increasing the activity of antioxidant enzymes. Key enzymatic antioxidants, such as glutathione reductase (GR), catalase (CAT), GPx, and SOD, are essential for maintaining cell membrane integrity and preventing lipid peroxidation.[11] The preservation of female

reproductive health is greatly aided by non-enzymatic dietary antioxidants, such as polyphenols (quercetin, baicalin, and resveratrol), carotenoids (β-carotene, lutein, and lycopene), and low-molecular-weight antioxidants such as glutathione and uric acid. The trace elements zinc and selenium, as well as Vitamins A, E, C, and B9, and additional antioxidants such acetyl cysteine, melatonin, and L-carnitine (LC), play a crucial role in maintaining reproductive health in females.[27,28]

Mechanism of action of vitamins as antioxidants

The most effective form of Vitamin E is A-tocopherol, while γ-tocopherol is the most common form, which scavenges the peroxyl radicals in cell membranes and arrest lipid peroxidation chain reactions. To reduce oxidative stress, Vitamin E also modifies the expression of transcription factors. The promoter regulatory element ARE and the activator protein-1 transcription factor family control redox homeostasis, which can impact Nrf 2, NF-κβ, Extracellular signal-regulated kinase/Mitogen-activated protein kinase/ Phosphatidylinositol 3-kinase (ERK/MAPK/PI3K) pathways, and protein kinase C reduction. This reduces ERK/MAPK activation and, through COX_2 inhibition, the inflammatory response.[29] Vitamin E also promotes the thickness of the endometrium so that there are reduced chances of failure of implantation.[30]

Vitamin E, along with zinc, iron, L-arginine, and selenium, can increase ovulation and the rate of pregnancies with decreased production of prostaglandins.[20,31,32] Vitamin C and Vitamin E combination can prevent preeclampsia and pre-term birth and reduced endometriosis pains.[33,34] Vitamin E alone can scavenge peroxyl radicals, helping in arresting the lipid peroxidation cascade and protecting the cells from oxidative damage.[35,36]

Ascorbic acid, or Vitamin C, is a component of the antioxidant enzyme system known as ascorbate peroxidases-glutathione reductase (GR), which has the ability to scavenge O_2^- and OH.[37] It helps in collagen synthesis, vasculogenesis, cell proliferation, and differentiation with increased progesterone levels and pregnancy rates, along with anti-aging potential through mesenchyme stem cells' inhibited ROS generation and AKT/mTOR signaling with reduced apoptosis due to controlled expression of caspase-3 or 8 and decreased levels of anti-Mullerian hormones.[38-40]

Carotenoids and Vitamin A can absorb peroxyl radicals and singlet oxygen and regulate the expression of COX-2, NO, production, cell differentiation, bone metabolism, and vision.[35,41] Retinoic acid receptors and retinoid X receptors are transcription factors that bind to retinoic acid response elements (RARE) sites in DNA to stimulate the production of developmental genes.[42] Retinoids mediate their effect through important embryonic pathways such as transforming growth factor/ fibroblast growth factor /hedgehog/ wingless-type protein (TGF/ FGF/Hh/Wnt) to ensure lung development in the uterus and to prevent premature birth and maternal anemia.[43] The quality of the oocytes and their maturation, implantation, embryogenesis, placentation, fetal growth, and organogenesis depend on folate and Vitamin B9. They also help reduce immature oocytes during PCOS in in vitro fertilization (IVF) therapy and prevent intrauterine growth retardation, neural tube defects, spina bifida, miscarriages, and anencephaly.[44]

Mechanism of action of polyphenols

Quercetin's anti-inflammatory, pro-oxidative, anti-proliferation, apoptosis induction, and cell cycle arrest inducing properties prevent ovarian cancer. Quercetin was found to trigger endoplasmic reticulum (ER) stress, apoptosis, and autophagy through the phosphorylated signal transducer and activator of transcription 3 (p-STAT3) / B-cell lymphoma (Bcl)-2 protein axis. Quercetin activates P53, causes pro-apoptotic Bcl-2-associated X (Bax) and caspase-3, 9 to increase, and triggers a decrease in anti-apoptotic Bcl-2 and survivin.[45]

Mechanism of action of coenzymes as antioxidants

Coenzyme Q10, myo-inositol, and intake of vitamins rich in antioxidants are regarded as a safe and efficient treatment for ovarian aging in women as this supplementation can improve ovarian reserve and oocyte quality. This is mediated also by lowering the rate of apoptosis.[46]

Mechanism of action of trace elements

As a transcription regulator of Nrf2, metallothionein mediates the antioxidant effect of zinc by oxidizing zinc and sulfur in a reduced protein state. It can also stabilize the zinc-finger domain of NF-κβ and react to damage from ROS.[47,48] Zinc with copper forms a co-factor of Zn-SOD/SOD1 that plays a major role in scavenging ROS during women's menstruation cycle and prevents cells from oxidative damage.[49] They ensure the early development of the fetus by enhancing STAT3/ matrix metalloproteinases (MMPs) axis.[50] Copper, zinc, manganese, and selenium are trace elements that can alter an enzyme's activity by acting as cofactors at the catalytic site. Two superoxide radicals are transformed by SODs into oxygen and H_2O_2. CAT decomposes H_2O_2 and thus prevents the generation of free radicals.[46] Although insufficient selenium is believed to negatively impact GPx activity, selenium itself is not regarded as an antioxidant.[51] The majority of GPx isoforms in mammals rely on selenium for their activity and contain it as a critical component.[52] The GPx family catalyzes the conversion of lipid hydroperoxides to alcohol or H_2O_2 to water.

Mechanism of action of carnitine, melatonin, and curcumin

The β-oxidation of fatty acids, ROS scavenging, anti-inflammatory and anti-apoptotic actions, and enhanced pregnancy rates are some of the ways that LC contributes to increased energy generation.[53] Moreover, LC can raise levels of antioxidant enzymes such as SOD and CAT as well as Vitamins C and E and, therefore, prevents the generation of ROS.[54] By blocking TNF-α, IFN-γ, and IL-2/4/6, as well as by boosting PGE1/2, cytokine release, and uterine abnormalities, it mediates apoptosis.[55]

Melatonin and its derivatives directly scavenge free radicals by modifying the transcription of genes encoding antioxidant enzymes, and melatonin and α-tocopherol supplementation was found to prevent oxidative stress on oocytes. Melatonin plays a role in ROS and NOS detoxification, suppression of pro-oxidants, and stimulation of enzymatic antioxidants.[56] It increases CAT, GPx, SOD, and Bcl-2 activity while decreasing COX-2 protein levels through the upregulation of Nrf 2 pathways. Upregulation of E_2 can cause endometriosis or PCOS, while melatonin decreases levels of Eαin ovaries and ERβ in uterine tissue by suppressing E_2 production through MAPKs.[57]

Similarly, curcumin, a well-known antioxidant and anti-inflammatory component of turmeric, can accelerate apoptosis in endometrial implants through a cytochrome-c mediated mitochondrial pathway and induce endometriosis regression by blocking NF-kβ translocation and MMP-3 expression.[4]

EFFECTS ON REPRODUCTIVE HEALTH

Treatment with melatonin can increase oocyte quality and promote angiogenesis and neovascularization by reducing the expression of Ang-1/2, vascular endothelial growth factor (VEGF), and vascular endothelial growth factor receptor during hypoxia and can inactivate MMPs also, thus helping endometriosis patients.[57,58]

Resveratrol inhibits the production of prostaglandins and, therefore, acts as antidiabetic, antitumorigenic, antimicrobial, antioxidant, anti-inflammatory, and neuroprotective. It binds to estrogen receptors because it is structurally and functionally similar to estrogen to regulate estrogen-like actions.[59] Resveratrol, therefore, can inhibit aryl hydrocarbon receptor, and Th17 cells and modulate suppression of NF-κβ, IL-1β, COX, and lipopolysaccharide (LPS) to decrease inflammation and levels of ROS.[60] Resveratrol can regulate the downregulation of inflammatory genes, such as insulin-like growth factor-1, and, hence, is promising in endometriosis and uterine fibroids.[61,62]

Deficiency of Zn leads to underdevelopment of the brain, preterm birth, post-term pregnancy, pre-eclampsia, and prolonged labor.[63] Proteins contain selenium in the form of selenium-methionine and selenium-cysteine, which replace methionine. It enhances antioxidant potential by activating Nrf 2 and mediates the suppression of NF-κβ and inflammatory cytokine expression, hence reducing ROS-induced cytotoxicity.[64] In addition, selenium has anti-microbial, anti-carcinogenic, anti-inflammatory, and chemopreventive properties.[65]

Deficiency of Selenium in blood can lead to subfertility, fetal defects, ovarian cysts, miscarriages, still births, unexplained fertility, premature ovarian failure, lower embryo quality, and decreased number of good oocytes in IVF therapy. Hence, these effects can be reversed with Se supplementation.

Regularity of the menstrual cycle is also reported to be enhanced with the intake of multivitamins and the corresponding decline in ovulatory disorders.[66,67] Reduced antioxidant status is related to spontaneous abortions, and oxidative stress is associated with preeclampsia.[68-70] Glutathione is a natural antioxidant produced by the human body, which maintains a balance and its deficiency leads to problems associated with oocyte maturation.[71] Excessive consumption of antioxidant supplements has been connected to greater death rates and an increased risk of developing several types of cancer. For example, several studies have linked Vitamin A, Vitamin E, and beta-carotene supplementation to higher mortality rates. Recent study shows a negative correlation between female infertility and the composite dietary antioxidant index, suggesting that a lower risk of female infertility may be linked to higher dietary antioxidant intake. However, to validate these findings, further well-planned prospective trials are required.[72]

CONCLUSION

The harmful effects of oxidation in a living organism can be countered by antioxidants. Free radical attacks are thwarted by the cellular antioxidant defense mechanism. O_2^-, H_2O_2, and ·OH are the three primary forms of ROS and RNS, which are the two main categories of free radicals. Given the elevated levels of free radical damage during egg maturation and fertilization, antioxidants are essential for the healthy operation of female reproduction. Consequently, an imbalance between too much ROS and not enough antioxidants may have a detrimental effect on female fertility. This review summarizes the natural antioxidants that have been chosen and shown to boost the uterine lining's endometrial thickness, which is crucial for the embryo's successful implantation. Antioxidant supplements during infertility therapy may enhance the results of assisted reproduction methods. Certain antioxidants show promise in reducing preterm birth and pre-eclampsia. When individuals with reproductive abnormalities such as PCOS, endometriosis, or functional hypothalamic amenorrhea were given antioxidants, their conditions improved. Pregnant

women should not take all antioxidants, though. Despite the benefits of supplementing with resveratrol and quercetin for gynecological conditions, it is advised to stay away from these polyphenols during pregnancy.

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REFERENCES

1. Mylonas C, Kouretas, D. Lipid peroxidation and tissue damage. *In-Vivo* 1999;13:295-309.
2. Behrman HR, Kodaman PH, Preston SL, Gao S. Oxidative stress and the ovary. J Soc Gynecol Investig 2001;8(Suppl 1 Proceedings):S40-2.
3. Agarwal A, Gupta S, Sharma RK. Role of oxidative stress in female reproduction. Reprod Biol Endocrinol 2005;3:1-21.
4. Darché RL, Ruder EH, Blumberg J, Hartman TJ, Goldman MB. Antioxidants in reproductive health and fertility. Berlin: Springer International Publishing AG; 2017. p. 113.
5. Patisaul HB, Jefferson W. The pros and cons of phytoestrogens. Front Neuroendocrinol 2010;31:400-19.
6. Cederroth CR, Zimmermann C, Nef S. Soy, phytoestrogens and their impact on reproductive health. Mol Cell Endocrinol 2012;355:192-200.
7. Kim SH, Park MJ. Effects of phytoestrogen on sexual development. Korean J Pediatr 2012;55:265-71.
8. Weber P, Bendich A, Schalch W. Vitamin C and human health - A review of recent data relevant to human requirements. Int J Vit Nutr Res 1996;66:19-30.
9. Podgrajsek R, Ban Frangez H, Stimpfel M. Molecular mechanism of resveratrol and its therapeutic potential on female infertility. Int J Mol Sci 2024;25:3613.
10. Rahman K. Studies on free radicals, antioxidants, and co-factors. Clin Interv Aging 2007;2:219-36.
11. Couto N, Wood J, Barber J. The role of glutathione reductase and related enzymes on cellular redox homoeostasis network. Free Radic Biol Med 2016;95:27-42.
12. Lewis ED, Meydani SN, Wu D. Regulatory role of vitamin E in the immune system and inflammation. IUBMB Life 2019;71:487-94.
13. Vaškova J, Klepcová Z, Špaková I, Urdzík P, Štofilová J, Bertková I, *et al*. The importance of natural antioxidants in female reproduction. Antioxidants (Basel) 2023;12:907.
14. Oh C, Keats EC, Bhutta ZA. Vitamin and mineral supplementation during pregnancy on maternal, birth, child health and development outcomes in low- and middle-income countries: A systematic review and meta-analysis. Nutrients 2020;12:491.
15. Vitagliano A, Petre GC, Francini-Pesenti F, De Toni L, Di Nisio A, Grande G, *et al*. Dietary supplements for female infertility: A critical review of their composition. Nutrients 2021;13:3552.
16. Hu W, Zhao C, Hu H, Yin S. Food sources of selenium and its relationship with chronic diseases. Nutrients 2021;13:1739.
17. Garner TB, Hester JM, Carothers A, Diaz FJ. Role of zinc in female reproduction. Biol Reprod 2021;104:976-94.
18. Espino J, Macedo M, Lozano G, Ortiz Á, Rodríguez C, Rodríguez AB, *et al*. Impact of melatonin supplementation in women with unexplained infertility undergoing fertility treatment. Antioxidants 2019;8:338.
19. Batıo˘glu AS, Sahin U, Gürlek B, Oztürk N, Unsal E. The efficacy of melatonin administration on oocyte quality. Gynecol Endocrinol 2012;28:91-3.
20. Wdowiak A, Filip M. The effect of myo-inositol, vitamin D3 and melatonin on the oocyte quality and pregnancy. In *in vitro* fertilization: A randomized prospective controlled trial. Eur Rev Med Pharmacol Sci 2020;24:8529-36.
21. Alesci A, Nicosia N, Fumia A, Giorgianni F, Santini A, Cicero N. Resveratrol and immune cells: A link to improve human health. Molecules 2022;27:424.
22. Kamal DA, Salamt N, Yusuf AN, Kashim MI, Mokhtar MH. Potential health benefits of curcumin on female reproductive disorders: A review. Nutrients 2021;13:3126.
23. Sirotkin AV. The influence of turmeric and curcumin on female reproductive processes. Planta Med 2022;88:1020-5.
24. Kim JK, Park SU. Quercetin and its role in biological functions: An updated review. EXCLI J 2018;17:856.
25. Toporcerová S, Špaková I, Šoltys K, Klepcová Z, Kľoc M, Bohošová J, *et al*. Small non-coding RNAs as new biomarkers to evaluate the quality of the embryo in the IVF process. Biomolecules 2022;12:1687.
26. Ashino T, Yamamoto M, Numazawa S. Nrf2/Keap1 System regulates vascular smooth muscle cell apoptosis for vascular homeostasis: Role in neointimal formation after vascular injury. Sci Rep 2016;6:26291.
27. Ambrozova N, Ulrichova J, Galandakova A. Models for the study of skin wound healing. The role of Nrf2 and NF-KB. Biomed Pap 2017;161:1-13.
28. Chen N, Du B, Zhou H, Shen F, Li J, Xie Z. Abnormal expression of Nrf2 may play an important role in the pathogenesis and development of adenomyosis. PLoS One 2017;12:e0182773.
29. Edwards G, Olson CG, Euritt CP, Koulen P. Molecular mechanisms underlying the therapeutic role of vitamin E in age-related macular degeneration. Front Neurosci 2022;16:890021.
30. Hashemi Z, Sharifi N, Khani B, Aghadavod E, Asemi Z. The effects of vitamin E supplementation on endometrial thickness, and gene expression of vascular endothelial growth factor and inflammatory cytokines among women with implantation failure. J. Matern Fetal Neonat Med 2019;32:95-102.
31. Partearroyo T, Samaniego-Vaesken MD, Ruiz E, Olza J, Aranceta-Bartrina J, Gil Á, *et al*. Dietary sources and intakes of folates and vitamin B12 in the Spanish population: Findings from the ANIBES study. PLoS One 2017;12:e0189230.
32. Asbaghi O, Sadeghian M, Nazarian B, Sarreshtedari M, Mozaffari-Khosravi H, Maleki V, *et al*. The effect of vitamin

E supplementation on selected inflammatory biomarkers in adults: A systematic review and meta-analysis of randomized clinical trials. Sci Rep 2020;10:17234.
33. Villar J, Merialdi M, Gülmezoglu AM, Abalos E, Carroli G, Kulier R, *et al*. Nutritional interventions during pregnancy for the prevention or treatment of maternal morbidity and preterm delivery: An overview of randomized controlled trials. J Nutr 2003;133:S1606-25.
34. Amini L, Chekini R, Nateghi MR, Haghani H, Jamialahmadi T, Sathyapalan T, *et al*. The effect of combined vitamin C and vitamin E supplementation on oxidative stress markers in women with endometriosis: A randomized, triple-blind placebo-controlled clinical trial. Pain Res Manag 2021;2021:5529741.
35. Vašková J, Patlevič P, Vaško L, Kluchová D. Prenatal effects of retinoic acid on lumbar spinal cord development and liver antioxidants in rats. Acta Histochem 2014;116:855-62.
36. Sadeghi F, Alavi-Naeini A, Mardanian F, Ghazvini MR, Mahaki B. Omega-3 and vitamin E co-supplementation can improve antioxidant markers in obese/overweight women with polycystic ovary syndrome. Int J Vitam Nutr Res 2020;90:477-83.
37. Akram NA, Shafiq F, Ashraf M. Ascorbic acid-A potential oxidant scavenger and its role in plant development and abiotic stress tolerance. Front Plant Sci 2017;8:613.
38. Abdollahifar MA, Azad N, Sajadi E, Shams Mofarahe Z, Zare F, Moradi A, *et al*. Vitamin C restores ovarian follicular reservation in a mouse model of aging. Anat Cell Biol 2019;52:196.
39. Mumford SL, Browne RW, Schliep KC, Schmelzer J, Plowden TC, Michels KA, *et al*. Serum antioxidants are associated with serum reproductive hormones and ovulation among healthy women. J Nutr 2016;146:98-106.
40. Saygin M, Ozmen O, Erol O, Ellidag HY, Ilhan I, Aslankoc R. The impact of electromagnetic radiation (2.45 GHz,Wi-Fi) on the female reproductive system: The role of vitamin C. Toxicol Ind Health 2018;34:620-30.
41. Geier DA, Geier MR. L-Carnitine exposure and mitochondrial function in human neuronal cells. Neurochem Res 2013;38:2336-41.
42. Metzler M, Sandell L. Enzymatic metabolism of vitamin A in developing vertebrate embryos. Nutrients 2016;8:812.
43. Radhika MS, Bhaskaram P, Balakrishna N, Ramalakshmi BA, Devi S, Kumar BS. Effects of vitamin A deficiency during pregnancy on maternal and child health. BJOG Int J Obstet Gynaecol 2002;109:689-93.
44. Papaleo E, Unfer V, Baillargeon JP, Fusi F, Occhi F, De Santis L. Myo-Inositol may improve oocyte quality in intracytoplasmic sperm injection cycles. A prospective, controlled, randomized trial. Fertil Steril 2009;91:1750-4.
45. Shafabakhsh R, Asemi Z. Quercetin: A natural compound for ovarian cancer treatment. J Ovarian Res 2019;12:55.
46. Hornos Carneiro MF, Colaiacovo MP. Beneficial antioxidant effects of coenzyme Q10 on reproduction. Vitam Horm 2023;121:143-67.
47. Lee SR. Critical role of zinc as either an antioxidant or a prooxidant in cellular systems. Oxid Med Cell Longev 2018;2018:9156285.
48. Lu X, Zhang Q, Xu L, Lin X, Fu J, Wang X, *et al*. Zinc is essential for the transcription function of the PGC-1_/Nrf2 signaling pathway in human primary endometrial stromal cells. Am J Physiol Cell Physiol 2020;318:C640-8.
49. Wang S, He G, Chen M, Zuo T, Xu W, Liu X. The role of antioxidant enzymes in the ovaries. Oxid Med Cell Longev 2017;2017:4371714.
50. Supasai S, Aimo L, Adamo AM, Mackenzie GG, Oteiza PI. Zinc deficiency affects the STAT1/3 signaling pathways in part through redox-mediated mechanisms. Redox Biol 2017;11:469-81.
51. Fujii J, Iuchi Y, Okada F. Fundamental roles of reactive oxygen species and protective mechanismsin the female reproductive system. Reprod Biol Endocrinol 2005;3:43.
52. Brigelius-Flohe R, Galli F. Vitamin E: A vitamin still awaiting the detection of its biological function. Mol Nutr Food Res 2010;54:583-7.
53. Placidi M, Di Emidio G, Virmani A, D'Alfonso A, Artini PG, D'Alessandro AM, *et al*. Carnitines as mitochondrial modulators of oocyte and embryo bioenergetics. Antioxidants 2022;11:745.
54. Li JL, Wang QY, Luan HY, Kang ZC, Wang CB. Effects of L-Carnitine against oxidative stress in human hepatocytes: Involvement of peroxisome proliferator-activated receptor alpha. J Biomed Sci 2012;19:32.
55. Li J, Liu L, Weng J, Yin T, Yang J, Feng HL. Biological roles of L-carnitine in oocyte and early embryo development. Mol Reprod Dev 2021;88:673-85.
56. Reiter RJ, Mayo JC, Tan DX, Sainz RM, Alatorre-Jimenez M, Qin L. Melatonin as an antioxidant: Under promises but over delivers. J Pineal Res 2016;61:253-78.
57. Li Y, Hung SW, Zhang R, Man GC, Zhang T, Chung JP, *et al*. Melatonin in endometriosis: Mechanistic understanding and clinical insight. Nutrients 2022;14:4087.
58. Zheng M, Tong J, Li WP, Chen ZJ, Zhang C. Melatonin concentration in follicular fluid is correlated with antral follicle count (AFC) and *in vitro* fertilization (IVF) outcomes in women undergoing assisted reproductive technology (ART) procedures. Gynecol Endocrinol 2018;34:446-50.
59. Horgan X, Tatum H, Brannan E, Paull D, Rhodes L. Resveratrol analogues surprisingly effective against triple-negative breast cancer, independent of ER. Oncol Rep 2019;41:3517-26.
60. Dull AM, Moga MA, Dimienescu OG, Sechel G, Burtea V, Anastasiu CV. Therapeutic approaches of resveratrol on endometriosis via anti-inflammatory and anti-angiogenic pathways. Molecules 2019;24:667.
61. Novakovic R, Rajkovic J, Gostimirovic M, Gojkovic-Bukarica L, Radunovic N. Resveratrol and reproductive health. Life 2022;12:294.
62. Bruner-Tran KL, Osteen KG, Taylor HS, Sokalska A, Haines K, Duleba AJ. Resveratrol inhibits development of experimental endometriosis *in vivo* and reduces endometrial stromal cell invasiveness *in vitro*. Biol Reprod 2011;84:106-12.
63. Nasiadek M, Stragierowicz J, Klimczak M, Kilanowicz, A. The role of zinc in selected female reproductive system disorders. Nutrients 2020;12:2464.
64. Xue H, Cao H, Xing C, Feng J, Zhang L, Zhang C, *et al*. Selenium triggers Nrf2-AMPK crosstalk to alleviate cadmium-induced autophagy in rabbit cerebrum. Toxicology 2021;459:152855.
65. Hosnedlova B, Kepinska M, Skalickova S, Fernandez C, Ruttkay-Nedecky B, Malevu TD, *et al*. A Summary of new findings on the biological effects of selenium in selected animal species-a critical review. Int J Mol Sci 2017;18:2209.
66. Czeizel AE, Metneki J, Dudas I. The effect of preconceptional

multivitamin supplementation on fertility. Int J Vitam Nutr Res 1996;66:55-8.
67. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Use of multivitamins, intake of B vitamins, and risk of ovulatory infertility. Fertil Steril 2008;89:668-76.
68. Vural P, Akgul C, Yildirim A, Canbaz M. Antioxidant defence in recurrent abortion. Clin Chim Acta 2000;295:169-77.
69. Bilodeau JF, Hubel CA. Current concepts in the use of antioxidants for the treatment of preeclampsia. J Obstet Gynaecol Can 2003;25:742-50.
70. Chappell LC, Seed PT, Briley A, Kelly FJ, Hunt BJ, Charnock-Jones ds, *et al*. A longitudinal study of biochemical variables in women at risk of preeclampsia. Am J Obstet Gynecol 2002;187:127-36.
71. Lobo V, Patil A, Chandra N. Free radicals, antioxidants and functional foods: Impact on human health. Pharmacogn Rev 2010;4:118-26.
72. Shao Y, Ma L, Zhou J, Wu K, Tang X. Impact of dietary antioxidants on female infertility risk: Evidence from NHANES. Sci Rep 2024;14:22623.

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