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REVIEW

Ameliorating Effects of Natural Antioxidant Compounds on Female Infertility: a Review

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Abstract

The prevalence of female infertility cases has been increasing at a frightening rate, affecting approximately 48 million women across the world. However, oxidative stress has been recognized as one of the main mediators of female infertility by causing various reproductive pathologies in females such as endometriosis, PCOS, preeclampsia, spontaneous abortion, and unexplained infertility. Nowadays, concerned women prefer dietary supplements with antioxidant properties over synthetic drugs as a natural way to lessen the oxidative stress and enhance their fertility. Therefore, the current review is an attempt to explore the efficacy of various natural antioxidant compounds including vitamins, carotenoids, and plant polyphenols and also of some medicinal plants in improving the fertility status of females. Our summarization of recent findings in the current article would pave the way toward the development of new possible antioxidant therapy to treat infertility in females. Natural antioxidant compounds found in fruits, vegetables, and other dietary sources, alone or in combination with other antioxidants, were found to be effective in ameliorating the oxidative stress-mediated infertility problems in both natural and assisted reproductive settings. Numerous medicinal plants showed promising results in averting the various reproductive disorders associated with female infertility, suggesting a plant-based herbal medicine to treat infertility. Although optimum levels of natural antioxidants have shown favorable results, however, their excessive intake may have adverse health impacts. Therefore, larger well-designed, dose–response studies in humans are further warranted to incorporate natural antioxidant compounds into the clinical management of female infertility.

Keywords Female infertility · Amelioration · Oxidative stress · Antioxidant · Medicinal plants · Reproductive disorders

Introduction

The inability to have children affects approximately 48.5 to 186 million people across the world, and surrounding it, many cultural and social stigmas vary, apart from the emotional burden to the couple itself [1, 2]. Infertility, defined as the failure to conceive a known pregnancy after a year or more of regular unprotected sexual intercourse, has now become a global health issue affecting 15–25% of couples in the western countries [3, 4]. Generally, approximately 84% of the couples conceive after 1 year of sexual intercourse, and 92% after 2 years [5]. Recently, a declining trend in semen quality of Asian men have been observed over the past few decades [6] that may be accountable for the rising infertility cases due to the male factor. On the other side, female infertility affects an estimated 48 million women with the highest prevalence affecting people in South Asia, Sub-Saharan Africa, North Africa/Middle East, Central Europe, and Central Asia [7]. Although male and female factor together contributes 20–30% of total infertility cases [8], however, in most of the cases (40–50%), its etiology has been attributed to the female partner [9]. The mechanisms, by which multivariable factors affects female fertility, are not well understood yet. Some studies have proposed that the high frequency of this disease is likely to rise as the postponement of childbearing increases, mostly in developed regions of the world [10, 11]. However, the abundantly documented literature studies related to the pathology of the couple's infertility involved oxidative stress (OS) in the pathophysiology of female infertility [12–14]. Moreover, it has also been involved in the pathology of unexplained infertility, affecting approximately 15% of the cases [8].

OS is generated from the disruption of the delicate balance between reactive oxygen species (ROS) produced from aerobic metabolism of cells and defending antioxidants [15]. ROS

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can also be produced from exogenous sources including water and air pollution, alcohol, smoking, heavy metals, radiation, and various kinds of drugs [16]. Excessive production of ROS disturbs the reproductive function of males through lipid peroxidation, germ cells' apoptosis, and sperm DNA fragmentation and negatively affects the assisted reproductive technique (ART) media [17]. Moreover, ROS-induced damage to spermatozoa is considered as the main factor responsible for reproductive pathology of males (about 30–80% of idiopathic male infertility) [18]. Likewise, OS is considered as one of the major factors involved in the initiation of reproductive pathologies of females [19, 20], such as preeclampsia, recurrent pregnancy loss, embryonic resorption, intrauterine growth restriction (IUGR), and fetal death [21]. Normal levels of ROS are essential for various signal transduction pathways of oocyte maturation, folliculogenesis, luteolysis, and feto-placental development [22]; however, overabundance of ROS exerts damaging effects. They have a close association with reproductive functions, so tightly controlled ROS is an essential process. It is considered as one of the critical elements for maintenance of redox homeostasis, gene expression, cell signaling, and various signal transduction pathways involved in cell growth, function, differentiation, and death [23, 24]. The body has different enzymatic and nonenzymatic antioxidant defense mechanisms to work against the OS. However, the body's endogenous defense systems are incomplete without the natural antioxidant compounds which act in vivo through enhancing the exhausted levels of endogenous antioxidant defenses in the organism's body [25]. Natural antioxidant compounds found in fruits, vegetables, various medicinal plants, and other dietary sources can be broadly divided into three groups: vitamins, carotenoids, and phenolic compounds. Natural antioxidant compounds have recently snared the interest of the scientific community and the general public due to their immense biological health benefits. Numerous studies in animals and humans have shown a decrease in the levels of OS markers after consumption of vegetables and fruits or antioxidant supplements [26–29]. Low consumption of antioxidant sources such as fruits and vegetables by females seems to increase their risk to endometriosis, one of the causative factors for female infertility [30]. Although the relationship of the dietary factors with human infertility is not completely understood, some research has reported improvement in female infertility by the consumption of some micronutrients [31]. Consumption of food and beverages enriched with polyphenols elevated the antioxidant capacity of plasma in humans [32] and reduced the in vitro and in vivo OS in the human placenta and placental trophoblasts, respectively [33]. A study has demonstrated the significance of natural antioxidants vitamin C and vitamin E in reducing the OS in intrauterine growth–restricted (IUGR) pregnant women [34]. Additionally, recent studies have also demonstrated the relationship between diet and female infertility and the involvement of various lifestyle factors that affect female fertility through OS [35, 36], suggesting that antioxidants are the most important components of having healthy fertility that every women and man needs to focus on. However, in spite of numerous antioxidant compounds present in plant-derived food, in several cases, plants itself or their parts are used by humans as a source of medicine to improve the various fertility aspects of females. For example, *Ceratonia siliqua* (locust bean) and *Anastatica hierochuntica* (dinosaur plant) are widely used by traditional healers as herbal medicines to treat the female infertility in rural areas of West Bank/Palestine [37]. Cinnamon (*Cinnamomum zeylanicum*) is one of the most commonly prescribed herbs in China used for treating endometriosis-induced symptomatic discomfort [38] and also for improvement in menstrual cyclicity of polycystic ovarian syndrome (PCOS) women [39]. The protective effect of *Ocimum basilicum* on ovarian histopathology due to its antioxidant potential has been illustrated in rats exposed to the electromagnetic field [40]. Thus, it is imperative to investigate the effects of various antioxidant compounds either present in plant-derived food or plant itself in improving the OS-mediated infertility problems in females. Consequently, based on the accumulated shreds of evidence from in vitro and in vivo animal and human studies, the current review evaluates the efficacy of most abundantly studied natural antioxidant compounds including vitamins, carotenoids, and plant polyphenols in improving the fertility status of females. However, in addition to this, the review also focuses on the role of mostly used medicinal plants in female infertility management. The review further focuses on the utilization of various natural antioxidant compounds in ART, and possible antioxidant therapies involving natural antioxidant for female reproductive disorders along with their safety measures of utilization are also discussed in the review.

Factors Contributing to Oxidative Stress and Altered Reproduction in Females

Although there is little information about the factors implicated in the generation of OS that has been associated with altered reproductive physiology of females, several literature studies in the last few years have documented the role of lifestyle and environmental factors in inducing OS in females [16, 41–43]. Alcohol and smoking are both known to decrease fertility in females [44, 45]. Increased rates of fetal loss and decreased growth of fetus have been linked with maternal smoking [46]. Nicotine receptors and their functions have been linked with reproductive pathologies induced by smoking in females; however, OS has recently become a major concern [47]. Similar to smoking, even a moderate amount of alcohol consumption during pregnancy leads to IUGR, low birth weight, and increased risk of congenital anomalies. Loss

of early pregnancy and spontaneous abortion may also be attributed to maternal alcohol consumption [48]. Regular consumption of alcohol leads to the excessive production of ROS, causing lipid peroxidation and reducing superoxide dismutase (SOD) activity and GSH levels [47].

Apart from alcohol and use of tobacco, various other environmental pollutants (e.g., pesticides, plastics, heavy metals, and other industrial compounds) may also induce OS that could interfere with the processes such as ovarian development, steroidogenesis, and folliculogenesis, thus impairing the normal fertility of females [13, 49–51]. Both organochlorine and organophosphate pesticides have been shown to induce the OS-mediated apoptosis of granulose cells by impairing the antioxidant defense mechanism in caprine ovary [52, 53]. Exposure to another group of compounds called polychlorinated biphenyls (PCBs) has been associated with problems of miscarriages in women [54]. PCBs can induce OS via endothelial dysfunction and damage the membrane with subsequent ROS formation [13]. In a cross-sectional study, elevated blood levels of lead [55] have been found to be associated with prolonged time-to-pregnancy [56]. Another similar study showed that even low levels of cadmium and lead may have deleterious impact on female fecundity [57].

In addition to these environmental and lifestyle factors, recently, studies have documented the influence of early life nutritional status on reproductive physiology of females [58, 59]. However, during mammalian development, the transduction of environmental information (e.g., nutritional status) from mother to her embryo or fetus occurs through the placenta or to her infants through lactation [60]. Therefore, it is imperative to determine the potential contribution of maternal nutritional status (undernutrition/overnutrition) during the critical windows of development in setting the pace of reproductive functions in the offspring. Intriguingly, a study by Bernal et al. has been carried out to examine the effects of maternal undernutrition (UN) during pregnancy and lactation on offspring's ovarian functions. Results showed a significant decrease in the number of primordial, secondary, and antral follicles associated with reduced mRNA levels of genes essential for follicle maturation and ovulation in ovaries of offspring born to mothers undernourished throughout pregnancy and lactation [61]. However, these changes in offspring's ovary may be mediated via the generation of oxidative stress as revealed by the presence of increased protein carbonyl contents and hyperoxidized peroxiredoxin 3 in ovarian tissue of offspring, suggesting their compromised antioxidant defenses [61]. Maternal overnutrition (MO) itself is a state of inflammation that has been shown to induce a lipotoxic placenta associated with enhanced production of free radicals and inflammatory cells [62]. Recently, a study has documented that MO leads to altered metabolic functions and disrupted redox balance of the fetus [63]. In another study, administration of a high-fat diet during pregnancy has been shown to induce hyperlipemia in offspring via reduced expression of glutathione peroxidase 1 and superoxide dismutase [64]. Since both maternal undernutrition and overnutrition are related to the altered production of free radicals and impaired antioxidant defenses, OS is considered to be the major link between poor intrauterine environment and increased risks of reproductive dysfunctions in females [65].

Physiological and Pathological Role of ROS in Female Reproduction: a Brief Overview

As mentioned previously, a threshold level of ROS facilitates the vital physiological functions of the reproductive system, but an excessive amount of ROS leads to the reproductive dysfunctions that contribute to infertility [66]. In males, physiological levels of ROS are essential for sperm maturation, capacitation, hyperactivation, acrosome reaction, and fertilization; however, a supraphysiological level of ROS causes lipid peroxidation, sperm DNA fragmentation, apoptosis of germ cells, and thus infertility [67]. Numerous studies have confirmed the damaging effect of ROS on semen parameters and fertility potential. Sperm motility, sperm viability, and fertilization capacity are abolished by OS in the reproductive tissues as significantly higher levels of ROS were observed in the semen of infertile men compared with those of fertile men [68]. OS has been implicated in patients with idiopathic [69] and unexplained male infertility [70]. Moreover, it has also been implicated in the pathological conditions such as varicocele [71, 72], inflammation, infection [73], and spinal cord injury [74] that could compromise fertility in males. However, in females, large numbers of follicles start to develop and grow in the ovary every month, but only one of them reaches maturity, the dominant follicle. This process is targeted by an enhancement in ROS and inhibited by antioxidants [13]. Enhanced steroid production in the growing follicle causes an increase in P450 that in turn leads to ROS production. ROS produced by pre-ovulatory follicles are essential inducers of ovulation [75]. ROS are also generated in the corpus luteum and therefore considered as key factors for reproduction. Furthermore, ROS can influence the development of early embryo through manipulating the key transcriptional factors and thus modifying the expression of genes [76]. ROS concentration can also play an important role in the fertilization of eggs and implantation [77].

Additionally, numerous studies have shown that regulated levels of free radicals in the ovaries, oviduct, uterine endometrium, embryos, and peritoneal fluid have a significant role in ovarian steroidogenesis, folliculogenesis, hormone signaling, tissue remodeling, oocyte maturation, the functioning of the oviduct and cyclic changes in the endometrium [78–80]. It has also been considered that the decline in fertility with age is

inflected by OS [81, 82], and it plays a role during pregnancy [83], normal parturition [84, 85], and in preterm labor initiation [86, 87]. OS affects the whole reproductive lifespan of a woman and even thereafter (i.e., menopause). Moreover, the ability of OS to influence the reproduction of females has been studied on various endpoints in terms of the oocyte, fertilization, estrus or menstrual cycle, embryo, and pregnancy [88, 89]. There are enough lines of evidence for the involvement of OS in the pathogenesis of reproductive disorders of females, such as preeclampsia [90], hydatidiform mole [91, 92], free radical-induced birth defects [93], and other conditions like abortion [94]. Furthermore, studies have implicated OS in the pathology of endometriosis, PCOS, unexplained infertility, and tubal and peritoneal factor infertility [20, 95–97]. Thus, OS affects female reproduction in two ways (Fig. 1), that is, it is not only required for the various physiological processes but also involved in different pathologies of the reproductive system that cause infertility in females. However, different mechanisms of OS-mediated reproductive damage in females have been proposed. Excessive level of ROS in the follicle can overcome the antioxidant defense of follicular fluid and causes damage directly to the oocyte. DNA of spermatozoa and oocytes could be damaged and results in impaired fertilization when the OS in the environment of peritoneal cavity is very severe [88]. Furthermore, if fertilization occurs, the induction of apoptosis by OS may lead to abortion, fragmentation of embryo, failure of implantation, abnormal placentation, and congenital abnormalities [88]. Excessive ROS may obstruct the endometrium that physiologically functions to support the developing embryo [98]. OS causes regression of the corpus luteum and, thus, results in inadequate hormonal supply essential for the maintenance of pregnancy [20].

Antioxidant Defense System

An antioxidant may be defined as a molecule having the propensity to neutralize or inhibit the free radical reactions and thus delay or prevent cellular damage. Although the antioxidant defense systems vary from one species to another, its presence in living organisms is universal [99]. Moreover, there are thought to be hundreds or probably thousands of substances that may act as antioxidants, each one acts exclusively and may interact with one another, helping the body to work effectively. Antioxidant is not the name of a substance, but rather, it represents what a variety of substances can do.

Antioxidant Classification and Antioxidant Process

Antioxidant may function as singlet oxygen quencher, electron donor, hydrogen donor, radical scavenger, enzyme inhibitor, peroxide decomposer, co-antioxidants, and metal-chelating agents [100]. Broadly, antioxidants can be classified in many ways (Fig. 2), based on their activity (enzymatic and nonenzymatic), source (endogenous and exogenous), and solubility (liposoluble and hydrosoluble). Furthermore, the eukaryotic antioxidant defense system is highly compartmentalized, where different levels of mitochondrial, nuclear, and cytoplasmic antioxidants function independently or they may work synergistically in a network type of system [101].

The process of antioxidants can work in two ways: prevention or chain breaking. In the preventive function, antioxidant enzymes such as catalase (CAT), glutathione peroxidase (GPx), and SOD may stop the oxidation reactions via reducing the rate of chain initiation, either through scavenging the initiating free radicals or through the transition metals' (copper and iron) radical stabilization [102]. In the chain-breaking process, electron

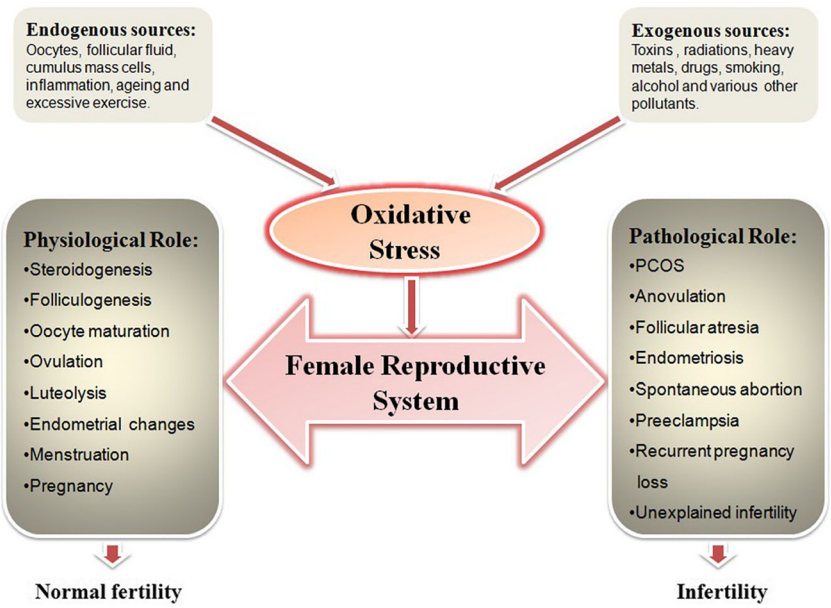

Fig. 1 Relationship between oxidative stress and female reproduction

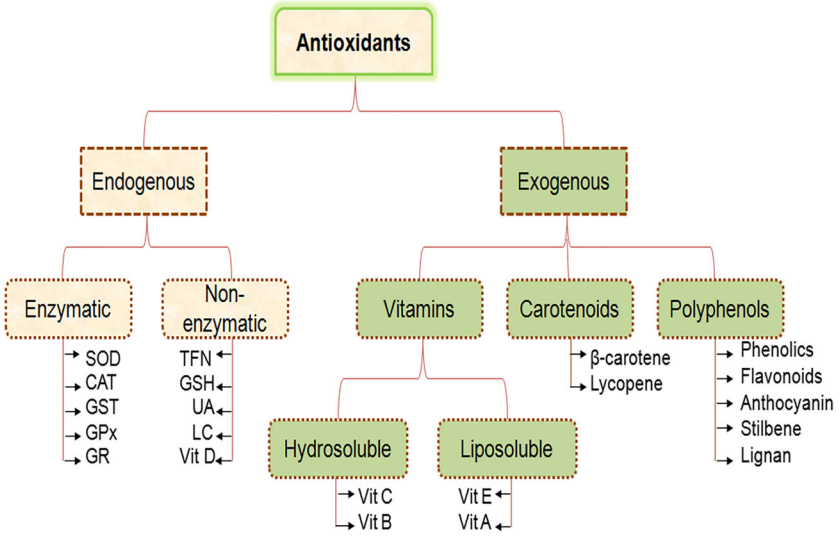

Fig. 2 Schematic representation of general antioxidant classification. SOD, superoxide dismutase; CAT, catalase; GST, glutathione-S-transferase; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, reduced glutathione; TFN, transferrin; UA, uric acid; LC, L-carnitine

released by one radical leads to the formation of another radical. This second radical has a similar effect on another cellular molecule and functions continuously in this manner until its stabilization by the chain-breaking antioxidant (e.g., vitamin E) and its breakdown into a harmless product. Lipid peroxidation is a common example of a chain reaction [103].

The female reproductive microenvironment is protected from OS through an interacting network of endogenous and exogenous antioxidant defense systems. However, the body's endogenous antioxidant defense consists of enzymatic and nonenzymatic systems, in which the latter one is primarily represented by glutathione [104]. Glutathione (GSH), considered as the mother of all antioxidants, a central detoxifier, and master of the immune system [105], is ubiquitously distributed thiol in both somatic cells and germ cells of the organism. It has been shown to protect the egg from oxidative damage during folliculogenesis in females, thus maintaining the egg in a healthy state. Moreover, studies have demonstrated that elevated levels of intracellular glutathione result in a healthier and stronger embryo [106]. However, Adeoye et al. have recently reviewed the antioxidative effects of GSH against OS-mediated female infertility [66]. Amino acids like taurine and hypotaurine are essential for the redox homeostasis of gametes and their concentration fluctuates during folliculogenesis. Both are involved in the neutralization of lipid peroxidation products and hypotaurine also neutralizes the hydroxyl radical [107]. However, the iron-binding proteins transferrin and ferritin are also involved in the antioxidant defense through their ability of metal chelation, and thus, inhibit the catalyzation of free radicals [108].

Antioxidant Enzymes

The endogenous antioxidant enzymes directly facilitate the neutralization of free radicals that are highly reactive and unstable species contributes to OS. The different antioxidant enzymes include SOD, CAT, GPx, glutathione reductase (GR), glutathione-S-transferase (GST), and thioredoxin system [51]. It has been considered that alterations of the antioxidant defense system are mediated by downregulation of the genes (GSTMI, GSTA1) encoding GST that perform GSH conjugation and GSH-dependent transformation of xenobiotics [109]. SOD exists in three isoforms: cytosolic SOD1 containing copper (Cu) and zinc (Zn) as cofactors, mitochondrial SOD2 containing manganese (Mn) as metal cofactors, and extracellular SOD3 which is structurally similar to SOD1 [13]. The fundamental reaction of antioxidant enzymes of antioxidative function is initiated by the metallic enzyme SOD via decomposition of superoxide radical into hydrogen peroxide (H_2O_2). Then CAT, GPx, GR, and GST convert the H_2O_2 and other reactive peroxides into H_2O and O_2 in a multistep process, thus preventing the oxidative damage to various cellular components [13].

Regarding female reproductive physiology, all these antioxidant enzymes have been shown to play a crucial role in various physiological processes. All the three isoforms of SOD and their activity were found to be higher in follicular fluid of small- and medium-size follicles as compared with large antral follicles [110–112]. According to these studies, a relatively reduced activity of SOD in the follicular fluid of large follicles is essential to ensure the threshold level of ROS required for ovulation. Luteinizing hormone (LH) is a gonadotropin secreted by the anterior pituitary and is essential for triggering ovulation and the development of corpus luteum in females. A study has demonstrated the LH-induced upregulation in the mRNA and protein levels of antioxidant enzymes SOD1, SOD2, and CAT in bovine corpus luteum [113]. Furthermore, a study has investigated the relationship between FSH stimulation and levels of CAT activity in ovarian granulosa cells during folliculogenesis. It has been found

that after FSH stimulation, with the increase in estradiol level, CAT activity also increased and higher in follicles of large size than the medium- and small-size follicles, suggesting its role in follicle selection and apoptosis prevention [114]. In an in vitro study, exposure of cultured granulosa cells to malathion leads to increased fragmentation of DNA and a decrease in the activity of antioxidant enzymes (CAT and SOD) in antral follicles of goat [53]. In another observational study, during meiotic maturation, CAT has been shown to prevent the genome of mouse oocytes from oxidative injury, while its inhibition leads to chromosomal defects and DNA damage in the oocyte nucleus [115]. The thioredoxin system present in the cells of the placenta includes three antioxidant enzymes, thioredoxin, thioredoxin peroxidase, and thioredoxin reductase that catalyze the decomposition of alkylhydroperoxides and H_2O_2 to alcohol and water in a synergistic manner [116].

Finally, from the above discussion, it is evident that endogenous antioxidant defense plays an indispensable role against OS in the female reproductive system at various time points to maintain the normal reproductive physiology and fertility in females. However, as mentioned earlier, that the endogenous antioxidant defense systems are incomplete without the exogenous natural antioxidant compounds which act interactively or synergistically to boost the endogenous antioxidant system is discussed in the following section.

Ameliorating Effects of Natural Antioxidant Compounds on Female Reproduction

Owing to the significant role that antioxidants play in human health and disease, and their popularity due to greater public interest, numerous studies have documented the beneficial effect of natural antioxidant compounds alone or in combination with other antioxidants or micronutrients on female reproduction (Table 1). In a study, the intake of a diet deficient in vitamins was found to increase the risk of miscarriage [117]. Another observational study established the relationship between the risk of spontaneous early miscarriage and uptake of fruits, green vegetables, and dairy products [118]. Some studies suggested that a lesser intake of micronutrients during pregnancy places women at nutritional deficiencies and affects the growth of the fetus [119]. So, the intake of natural antioxidants from food should be the individual's first choice because they not only play a significant role in the prevention and treatment of diseases but also circumvent the negative effects on human body. Natural antioxidants may enhance female fertility either through enhancing the activities of endogenous antioxidants or via inhibiting the OS-mediated harmful processes in the female reproductive tract (Fig. 3).

Antioxidant Vitamins

Vitamin E

Food like green vegetables, vegetable oil, kiwi fruits, and nuts such as almonds, walnuts, etc. are enriched with vitamin E. It is the most potent lipid-soluble and chain-breaking antioxidant, functions to inhibit the lipid peroxyl radicals ($LOO^{\cdot}$) during the lipid peroxidation process, and thus results in the termination of the cascade of harmful reactions in cellular membranes [120]. Apart from the various functions it performs in the body, it is principally essential to maintain the normal fertility potential of both human and livestock species [121]. In fact, it was first recognized as the critical dietary factor for the reproductive potential of both male and female rats [122, 123].

During normal pregnancy, the level of oxidative-stabilized vitamin E has been shown to rise in maternal blood [124]. Additionally, it was considered that vitamin E requirement may enhance in situations like smoking during pregnancy [125]. In a study involving co-incubation of media with H_2O_2 and γ-tocotrienol, γ-tocotrienol was reported to improve the porcine embryo's development by the modification of apoptotic genes Bax and Bcl-xL [126]. Another comprehensive study using in vivo laboratory animal models showed that co-administration with 5 mg/kg body weight (bw) of nicotine and 60 mg/kg of tocotrienol-rich fraction (TRF) has increased the pregnancy rates to 83.3% in rats, in comparison to those treated with nicotine alone and had a pregnancy rates of 33.3% [127]. Furthermore, a study showed the protective effect of γ-tocotrienol supplementation in reducing the damaging effect of nicotine on the oocyte's ultrastructure [128]. Simultaneous administration of tocotrienol (T3) with cyclophosphamide helps in the preservation of ovarian function during chemotherapy and also protection against apoptosis in ovaries induced by oxidative stress [129, 130]. Another in vitro study investigated the protective effect of vitamin E on the development of preimplanted buffalo embryos. The results indicated that 100 μM vitamin E supplementation in culture under 20% O_2 increased the frequency of blastocyst formation and total cell count and also reduced comet tail in comparison to control [131]. A parallel study in sheep was also conducted to investigate the effect of α-tocopherol supplementation on in vitro oocyte maturation and preimplantation embryo development. Results showed that supplementation of α-tocopherol significantly enhanced the cleavage rate, formation of morulae (at 200 μM) and blastocyst (at 100 μM, 200 μM, and 400 μM), and total cell number of the blastocyst (at 200 μM) when compared with the control group [132]. Simultaneous treatment of γ-tocotrienol (30, 60, and 90 mg/kg) with nicotine reversed the nicotine-induced deleterious effects on embryo development through its antioxidant capacity in mice [133].

Table 1 Ameliorating effects of natural antioxidant compounds on female infertility

Antioxidant compound	Experimental animal	Study type (in vivo/in vitro)	Dose and durations	Improved reproductive outcome(s)	References
γ-Tocotrienol or tocotrienol	Porcine	In vitro	100, 200, and 400 μM for 6 days	Improved embryonic development by modification of apoptotic genes Bax and Bcl-xL	[126]
	Mice	In vivo	30, 60, 90 mg/kg/day for 7 days	Improved the nicotine-induced cessation of embryonic development; reduced lipid peroxidation	[133]
	Mice	In vivo	60 mg/kg/day for 30 days	Preservation of ovarian function during chemotherapy and protection against apoptosis induced by OS	[129, 130]
Vitamin E	Human	In vivo	100 mg/day p.o. for 14 days	No significant differences of ovulation rate, clinical pregnancy rate, and ongoing pregnancy rate	[344]
Vitamin E + pentoxyfylline (PTX)	Human	In vivo	Vit E—1000 IU PTX—800 mg daily for 8.1 months	Improved the endometrial growth in women with thin endometrium undergoing assisted conception	[345]
Vitamin C	Rat	In vivo	250 mg/kg daily for 30 days	Decreased total oxidant status (TOS) and oxidative stress index (OSI) in ovarian, fallopian tubal, and uterine tissues Reduced anti-mullerian hormone (AMH) Diminished caspase-3 and caspase-8 expressions in ovarian and uterine tissue	[141]
	Mice	In vitro	50 μg/mL for 14–18 days	Enhanced the survival and growth of primary follicles cultured in alginated hydrogel and also their structural integrity	[140]
	Mice	In vivo	45 mg/kg/day for 22 days	Increased AMH concentration Decreased levels of 8-OHdG and Bax/Bcl-2 ratio	[139]
Vitamin C and vitamin E	Human	In vivo	Vit C—1000 mg Vit E—1200 IU for 8 weeks	Reduced chronic pain, dysmenorrhea, and dyspareunia in women with endometriosis	[185]
	Goat	In vitro	0.5 and 1 mM for 24, 48, 72 h	Reduced granulose cell apoptosis; increased antioxidant enzymes (SOD, GST, CAT) activity; decreased MDA level and FRAP activity	[186]
LC + metformin	Human	In vivo	LC—3 g Metformin—850 mg from day 3 till day 7 of menstrual cycle	Improvement in menstrual regularity, ovulation rate, and pregnancy rate	[177, 346]
LC and N-acetyl-cysteine (NAC)	Human	In vivo	LC- 3 g NAC- 600 mg from day 3 until day 7 of menstrual cycle	Improved menstrual pattern, FSH, LH, and free testosterone; improved pregnancy and ovulation rate	[347]
Vitamin C and LC	Hen	In vivo	Vit C—1 g/kg diet LC—100 and 200 mg/kg diet for 3 weeks	Enhanced egg production and egg quality Reduced oxidative stress	[190]
LC and coenzyme Q10	Rabbit	In vivo, in vitro	LC—40 mg/kg bw Coenzyme Q10–10 mg/kg bw for 21 days	More number of follicles and embryo and higher ovulation rate; higher rates of in vitro blastocyst production	[188]
Retinol	Bovine	In vitro	1, 5, and 10 μM	Improved oocyte and subsequent embryo development	[147]
9-*cis*-Retinoic acid	Bovine	In vitro	5, 50, and 200 nM	Improved oocyte maturation rate (5 nM) Higher mitochondrial membrane potential and reduced accumulation of ROS (5 nM) Upregulated antioxidant-related (SOD1, CAT, GPx4, PRDX1, HMOX1) genes (5 and 50 nM)	[144]
Tretinoin	Bovine	In vitro	0.25, 0.5, and 1 μM	Improved in vitro blastocyst formation (0.25 μM) Reduced ROS production in embryos (0.25 and 0.5 μM) Reduced Bax and SHC1 expression level	[354]
β-Carotene and vitamin A	Holstein cows	In vivo	200 mg β-carotene and 50,000 IU vit A at the time of estrus induction	Improved the corpora lutea development and follicular growth in cows having fertility problems	[169]
Lycopene	Rat	In vivo	5 mg/kg/day for 14 days	Reduced ovarian MDA levels Increased total GSH, GR, and SOD activities in cisplatin-damaged ovarian tissue	[170]
			5 mg/kg/day for 5 days		[171]

Table 1 (continued)

Antioxidant compound	Experimental animal	Study type (in vivo/in vitro)	Dose and durations	Improved reproductive outcome(s)	References
				Ameliorated the methotrexate-induced oxidative ovarian injury and infertility due to prolonged gestation and reduced number of offspring	
Green tea polyphenols	Bovine	In vitro	10, 15, 20, and 25 μM	Progress in the rate of blastocyst development and pregnancy	[205]
EGCG	Porcine	In vitro	2.5, 5, 10, and 25 μg/mL	Increased rate of fertilization (5 μg/mL) during in vitro fertilization (IVF)	[355]
	Mice	In vitro	100 mg/kg bw	Improved oocytes' developmental competence and further embryo quality during maternal hyperthermia	[206]
Green tea leaves extract	Sheep	In vitro	0.3, 0.6, and 1.2 mg/mL	Enhanced oocytes maturation rate Improved morula and blastocyst formation rate	[207]
Resveratrol	Human	In vitro	10^{-5} M for 7 days	Increased the fraction of growing follicles during culture of human ovarian follicles	[356]
	Human	In vivo	800 mg/day for 40 days	Reduction in the expression of VEGE and HIF1 genes in granulose cells Higher rate of high quality oocyte and embryo	[348]
	Human	In vivo	400 mg for 12–14 weeks	Reduced the mRNA and protein level of matrix metalloproteinases (MMP-2 and MMP-9) in the endometrium Lowered their serum and endometrial fluid concentration	[349]
Resveratrol and EGCG	Human	In vivo	1500 mg p.o. for 3 months	Significant decrease of total testosterone and dehydroepiandrosterone (DHEAS) in PCOS women	[312]
	Mice	In vivo, in vitro	30 and 100 mg/kg/day for 2 weeks; (0–200 μM)	Alleviated OS-mediated oogonial stem cell apoptosis and aging Attenuated H_2O_2-induced cytotoxicity through activating Nrf2	[357]
	Human	In vitro	Resveratrol—25, 50, 100 μM EGCG—20, 40, 80, 100 μM	Induced reduction in human endometrial epithelial cells' (EECs) proliferation Increased apoptosis in primary cell culture	[350]
Quercetin	Mice	In vitro	0–50 μM until day 5.5 of embryo culture	Protection of zygotes from H_2O_2-induced oxidative damage during in vitro development of preimplantation embryos by decreasing ROS level, maintaining mitochondrial function and total antioxidant capability	[226]
	Human	In vivo	1000 mg/day for 12 weeks	Significantly decreased resistin concentration and mRNA level Reduced the testosterone and LH concentration in PCOS women	[351]
	Human	In vivo	1 g daily for 12 weeks	Reduced the level of testosterone and LH Increased the level of adiponectin in PCOS women	[352]
	Rat	In vivo, in vitro	12.5, 25, and 50 mg/kg for 90 days 5, 20, 50 μM for 6 h	Increased mRNA levels of OS-related genes SOD1, CAT, and GSH in menopausal rat ovaries Prevented the reduced viability of granulose cells by H_2O_2-induced OS in ovary	[227]
	Porcine	In vitro	1, 10, and 100 ng/mL for 24 h	Enhancement of total antioxidant status (TAS), and activities of GPx and SOD	[358]
Genistein	Rat	In vivo	0.5, 1, or 2 mg/kg for 14 days	Inhibited the cyclophosphamide-mediated decrease in AMH and E_2 Alleviated the OS and inflammation in ovarian tissue	[242]
			160 mg/kg/day for 4 weeks and 4 months	Higher percentage of primordial follicles in 4-month-old rats Greater number of surviving follicles in 15-month-old rats	[240]
Curcumin	Mice	In vivo	200 mg/kg bw for 3 weeks; from day 6 of gestation till parturition	Decrease the benzo[*a*]pyrene-induced follicular atresia and ameliorated the histological architecture of both uterus and ovary Improved the neonatal growth retardation	[359]

Table 1 (continued)

Antioxidant compound	Experimental animal	Study type (in vivo/in vitro)	Dose and durations	Improved reproductive outcome(s)	References
	Mice	In vivo	100 mg/kg/day for 10 days	Enhanced proliferation and decreased apoptosis of ovarian cells in mice exposed to whole body ionizing radiation	[215]
	Mice	In vivo	100 μg/g 4 times a week	Promoted folliculogenesis and steroidogenesis in ovarian cells	[216]
	Human	In vitro	0.001–50 μM for 24, 48, 72 h	Increased the human granulose cells' viability Decreased the ROS/RNS formation after stress induction at lower concentration	[353]

Vitamin C

Vitamin C is a key representative of the nonenzymatic antioxidant system in the aqueous milieu of the organism [134]. It is an important vitamin for primates, bats, guinea pigs, and humans, as they are deficient in L-gulono-g-lactone oxidase, the enzyme responsible for its biosynthesis from glucose [135] and so must be provided through food. Vitamin C is commonly found in fresh vegetables and fruits, particularly in citrus fruits. It works through the chain-breaking process by donation of an electron to the lipid radical and thus terminating the lipid peroxidation chain reaction. Furthermore, it helps

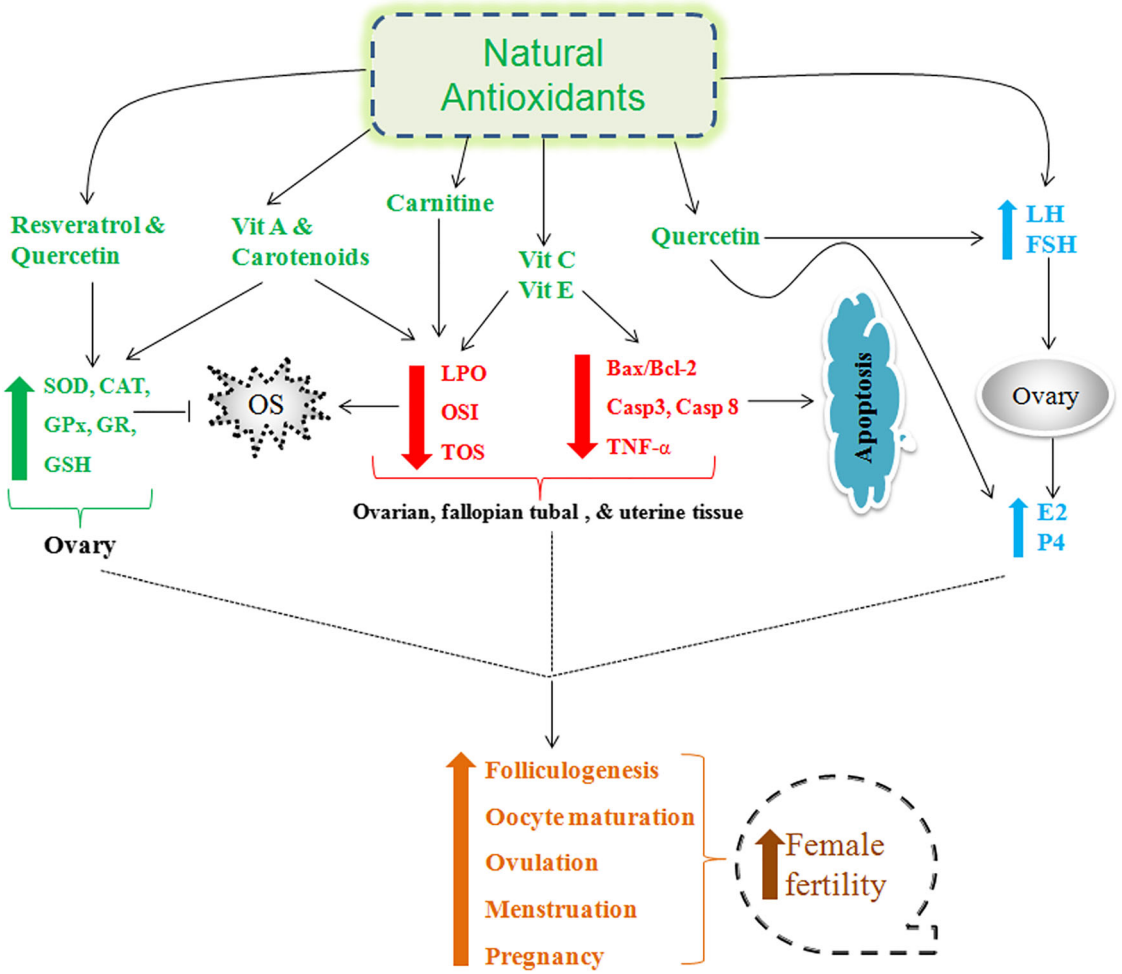

Fig. 3 Natural antioxidants may enhance the female fertility by upregulating (⬆) the activities of endogenous antioxidants or gonadotropins (LH, FSH) and by downregulating (⬇) or inhibiting the OS or OS-induced damage in the female reproductive tract. LPO, lipid peroxidation; OSI, oxidative stress index; TOS, total oxidant status; TNF-α, tumor necrosis factor-α; LH, leutenizing hormone; FSH, follicle-stimulating hormone; Casp3, caspase-3; Casp8, caspase-8; E2, estradiol; P4, progesterone

in the regeneration of vitamin E in association with GSH and other endogenous reducing equivalents [120].

Ascorbic acid mainly has three natural functions of specific interest to reproduction, which are dependent on its reducing power: it is necessary for collagen synthesis, for peptide and steroid hormone synthesis, and for prevention of oxidation of biological molecules. Ascorbic acid concentration is found to be much more in the follicular fluid of humans than in the blood serum. This suggests its transport is actively against a concentration gradient [136, 137] and that it may play a role of the antioxidant vitamin during the process of folliculogenesis [138]. Administration of vitamin C (45 mg/kg/day) has been shown to alleviate the $PM_{2.5}$-mediated decrease in anti-mullerian hormone (AMH) in female mice. Furthermore, a decrease in the levels of tumor necrosis factor-α (TNF-α), 8-hydroxy-2′-deoxyguanosine (8-OHdG), Bax/Bcl-2, and caspase-3 was observed in vitamin C–treated groups compared with control groups [139]. A study has investigated the role of ascorbic acid in extracellular matrix (ECM) deposition/remodeling to protect the primary ovarian follicles cultured in alginate hydrogel. Results showed that supplementation of ascorbic acid (50 μg/mL) significantly augmented the survival of primary follicles and improved their structural integrity through modifying the expression of ECM and cell adhesion molecules [140]. Supplementation of vitamin C (250 mg/kg/day) for 30 days revealed a significant decrease in total oxidant status (TOS) and oxidative stress index (OSI) in ovarian, fallopian tubal, and uterine tissues of rats exposed to electromagnetic radiation. Moreover, treatment with vitamin C also diminishes the increased caspase-3 and caspase-8 expressions in ovarian and uterine tissues [141].

Vitamin A

Vitamin A is a fat-soluble vitamin and an essential nutrient consisting of unsaturated nutritional organic compounds including retinal, retinol, and retinoic acids and several provitamin A carotenoids that must be included in the diet in adequate amounts. It is vital for various processes of life including reproduction, immune system function, and cellular differentiation [142]. It can quench singlet oxygen and cooperate with various antioxidant compounds [143]. Vitamin A is found to play an important role in the reproduction of females including steroidogenesis, follicular growth, and oocyte and embryo development [144]. However, earlier, it has been considered that retinoids are responsible for maintaining the optimum level of endogenous antioxidants used to protect oocyte maturation and embryo development from the accumulation of ROS [145]. The effect of vitamin A therapy on the cascade of free radicals in pregnancy-induced hypertension (PIH) was evaluated in third trimester patients. A significant reduction in lipid peroxidation was found with no effect on CAT and SOD, suggesting its role as a chain-breaking antioxidant [146]. The administration of retinol (5 μM) to in vitro maturation medium under atmospheric O_2 conditions was reported to have a positive effect on bovine oocyte and subsequent embryo development, suggesting an important antioxidant effect of retinol [147]. A lower dose (5 nM) administration of 9-*cis*-retinoic acid, vitamin A metabolite, to the oocyte maturation media of buffalo has been shown to improve the maturation rate via a mechanism maintaining optimum levels of antioxidant transcripts and improving the activity of mitochondria [144].

Vitamin D

Vitamin D is a fat-soluble vitamin found in different forms. Two forms are mainly essential for humans: D_2 (ergocalciferol) and D_3 (cholecalciferol). Vitamin D_2 is primarily produced by plants upon ultraviolet irradiation and, thus, consumed by humans as part of their diet, while vitamin D_3 is synthesized in the skin exposed to sunlight [148]. The classical function of vitamin D involves the regulation of calcium/phosphorous metabolism and bone health [149], but the presence of vitamin D receptors (VDRs) in various reproductive tissues of females suggests its role in reproductive physiology [150]. Furthermore, although information relevant to the antioxidant functions of vitamin D on female reproduction is scarce or altogether absent, recently, studies have reported the association of vitamin D with female fertility [151–153]. Animal studies have demonstrated that female rodents with vitamin D–deficient diet and VDR gene knockout have reduced fertility due to anovulation, uterine hypoplasia, and impaired follicular development [154–156]. Initially, a study involving vitamin D and fertility after in vitro fertilization (IVF) showed that the rates of pregnancy were four times higher in women having sufficient vitamin D levels compared with vitamin D–deficient women [157]. Subsequently, several studies have shown similar effects [158, 159], while others have reported no association [160, 161]. Despite this unclarity of data regarding the role of vitamin D on female fertility, studies have documented the relationship between vitamin D and various reproductive pathologies of females including PCOS, endometriosis, uterine myoma and leiomyoma, and primary dysmenorrhea that causes infertility [151, 152, 162].

Carotenoids

Carotenoids are the fat-soluble pigments naturally found in red or dark green and yellow fruits and vegetables. Carotenoids are powerful natural antioxidants that are considered to be very potent physical quenchers of singlet oxygen and also participate in scavenging other ROS [163]. There are some carotenoids (α- and β-carotene, β-cryptoxanthin) which can be converted into vitamin A in humans and, thus, aid in providing this essential vitamin to the body [164]. A study has

reviewed the importance of β-carotene as a source of vitamin A with special emphasis on lactating and pregnant women [165]. Women with spontaneous preterm birth defects have been found to have a lower concentration of carotenoids in the serum, and premature birth risk is reduced with elevated serum concentrations of α- and β-carotene, α- and β-cryptoxanthin, and lycopene [166]. In preventing premature birth, consumption of a diet containing fruits and vegetables rich in carotenoids has also been documented [167]. In a study, the daily administration of β-carotene considerably improved the β-carotene availability in the microenvironment of the oocyte, regardless of the energy balance, thus affecting oocyte quality and development of follicles during maternal metabolic stress [168]. Periovulatory supplementation of β-carotene was shown to improve the corpora lutea development and follicular growth in cows having fertility problems [169]. In an experimental study, lycopene (0.5 mg/kg) administration for 14 days alleviated the cisplatin-induced ovarian damage in rats by reducing the MDA levels and enhancing total GSH, GR, and SOD activities [170]. In another similar study, pretreatment with lycopene (5 mg/kg) for 5 days prevented the methotrexate-induced oxidative injury in rat ovary via its antioxidant potential [171].

Carnitines

Carnitines belong to a class of nutrients called "quasi-vitamins" or "conditionally essential" nutrients [172]. Both L-carnitine (LC) and its acetylated form, acetyl-carnitine (ALC), have been reported to exert beneficial effects in infertility management by improving the mitochondrial activities [173, 174]. LC is an intramitochondrial vehicle for acyl group and facilitates the β-oxidation process via transporting fatty acids into the mitochondria [175]. LC has been reported to have a preventive effect on free radical-induced oxidative damage to DNA [176], suggesting its antioxidant function. Since LC possesses antioxidant properties with very few side effects, recently, studies are considering its implementation as a treatment option for female infertility [173, 177, 178]. A recent study has shown that oral supplementation of LC (250 mg for 12 weeks) to PCOS patients improved their total antioxidant capacity (TAC), reduced lipid peroxidation, and also augmented their general and mental health parameters [179]. Oral administration of ALC (1 g/day for 16 weeks) to functional hypothalamic amenorrhea (FHA) patients has been reported to have a significant increase in the patients' LH levels by counteracting a neuroendocrine pathway having an inhibitory effect on the reproductive axis [180]. During in vitro studies, carnitine supplementation has been implemented to reduce the free radical-induced delay of embryonic development, DNA fragmentation, and morphologically abnormal blastocysts' development after culture of extended periods [176, 181, 182]. The role of carnitines (LC and ALC) in improving the fertility of females along with their possible mechanism of action has recently been summarized by Agarwal and his coworkers involving various in vivo and in vitro animal and human studies [183].

Combination Effects of Vitamins and Other Micronutrients

Given that antioxidant works synergistically with other antioxidants to counteract the damage induced by free radicals, researchers have started to assess the combination effect of antioxidant vitamins or other micronutrients (although many of them are technically not antioxidants) in female fertility. Naziroglu et al. have investigated the effect of dietary vitamin C (1 g) and vitamin E (600 mg) combination (VCE) on lipid peroxidation and antioxidant enzyme activities in streptozotocin-induced diabetic pregnant rats. Results indicated that supplementation of VCE with moderate exercise significantly enhanced the antioxidant defense as revealed by reduced MDA levels and enhanced antioxidant enzyme (GPx, CAT) activities in plasma of diabetic pregnant rats [184]. In another study, combined supplementation of vitamin E (1200 IU) and C (1000 mg) for 8 weeks significantly reduced chronic pain (43%), dysmenorrhea (37%), and dyspareunia (24%) as compared with the placebo group in women with endometriosis [185]. However, co-incubation of vitamin C and vitamin E (0.5 mM and 1.0 mM) have significantly reduced the OS-mediated apoptosis induced by glyphosate in granulosa cells of caprines during in vitro culture consisting durations of 24, 48, and 72 h [186]. In an in vitro study, combination therapy of vitamin E (5 μM) and folate (0.01 μM) ameliorated the H_2O_2-induced decrease in cell viability, GPx and GR activities, and GSH levels in rat primary endometrial cells [187]. Another in vitro study has shown that combined formulation of coenzyme Q10 (10 mg/kg) and LC (40 mg/kg) for 21 days improved the ovulatory response, embryo vitrification, and embryo recovery in rabbits [188]. Attenuating effects of α-lipoic acid (100 mg/kg/day) and α-tocopherol (20 mg/kg/day) combination for 30 days on bisphenol-A (BPA)-induced oxidative damage in rat ovarian tissue were observed where the combination significantly reduced the BPA-elevated MDA and nitric oxide (NO) levels [189]. Co-treatment with vitamin C (1 g/kg diet) and LC (100 and 200 mg/kg diet) for 3 weeks has been shown to improve the reproductive parameters in hens in terms of enhanced egg production and egg quality which may be attributed to reduced OS following vitamin C–LC treatment [190].

Plant Polyphenols

Natural polyphenols (also called as phenolics) are important dietary antioxidants found in various food sources of plants

such as vegetables, fruits, chocolate, nuts, wine, tea, and coffee [191, 192]. Studies related to the effects of dietary polyphenol consumption on reproductive health of humans are limited and uncertain. However, based on the accumulated evidence from in vitro and in vivo animal studies, also from human studies in various contexts, some may believe the potential health benefits of polyphenols on reproduction of humans [193].

Resveratrol

Resveratrol is a natural polyphenol present in red wine, grapes, and other plant extracts shown to play a role of cytoprotection against cancer, cardiovascular disease, neurodegeneration, diabetes, and obesity-related disorders [194]. These different biological roles played by resveratrol can be attributed to its antioxidant properties such as elevation in CAT and SOD enzyme activities by resveratrol [195]. Resveratrol efficiently removes superoxides and hydroxyl radicals, thus protecting lipid peroxidation in cellular membranes and damage of DNA due to ROS [196]. Feeding of young mice for 12 months with resveratrol retained their competence of reproduction, whereas mice of the same age group in the control group produced no pups. Moreover, the consistently fed groups have a follicle pool larger than the control group. Resveratrol also resulted in improved number and oocyte quality [197]. Protection of the ovary from hexavalent chromium (CrVI)-induced OS by resveratrol was shown by augmenting the transcription, translation, and endogenous antioxidant enzyme activity and decreasing the lipid peroxide (LPO) and H_2O_2 in plasma and ovary [198]. In an experiment, resveratrol was involved in the protection of human granulosa cells as shown by the absence of cell death, increased mitosis, and reduced oxidative stress markers [199]. Furthermore, resveratrol, mainly at low doses, was shown to protect from cisplatin-induced damage to the ovary in rats by maintaining the numbers of primordial and primary follicles [200]. In an in vitro experiment, inhibition of reproductive toxicity caused by a mycotoxin-deoxynivalenol by resveratrol has also been documented [201].

Catechins

Green tea (GT) is the most popular beverage which is consumed by millions of people across the world. The valuable properties of GT are ascribed to polyphenolic compounds, mainly catechins, accounting for 30% of the dry weight of GT leaves [202]. Many researchers have recognized the effect of GT in the reproduction and fertility of females [203, 204]. Considerable progress was noticed in the blastocyst development rate and pregnancy rate after adding 15 μM epigallocatechin-3-gallate (EGCG) in culture media of bovines. Results showed the two different functions of GT catechins: at low concentration (10 mg/mL), it performs the antioxidant function, while at higher concentration (25 mg/mL), it showed a pro-oxidant effect [205]. Female mice were injected with 0.4 mL of EGCG (100 mg/kg body weight) resulting in improved oocytes' developmental competence and quality of embryo [206]. Addition of a lower dose (0.3 mg/mL) of green tea leaves extract (GTE) in the maturation media as a source of antioxidant has been shown to increase the oocyte maturation rate and also improved the morula and blastocyst formation rate in sheep [207]. Endometriosis causes pelvic pain and infertility in females. In an experiment, endometrial tissue from patients was treated with EGCG that results in the significant inhibition of cell proliferation, migration, and endometrial and endometriotic stromal cell invasion [208]. However, the importance of EGCG in the improvement of the fertility of females with endometriosis is controversial.

Curcumin

Turmeric (*Curcuma longa* L.) is commonly used by people for both cooking purposes and as folk medicine. The rhizome species containing many different biologically active compounds called curcuminoids, among which, the polyphenol curcumin is most prevalent [209], and its antimicrobial, anti-inflammatory, anticancer, and antioxidant activities have been extensively documented [210, 211]. The crucial curative effect of *Curcuma longa* has been credited to curcumin. However, curcumin's pharmacological safety was discovered [212] and its safe consumption for humans was approved by the U.S. Food and Drug Administration (FDA) [213]. Various studies have established the stimulatory effects of curcumin and its analogs on ovarian functions due to its capability to enhance proliferation and decrease apoptosis [214, 215] while promoting folliculogenesis [214, 216] and steroidogenesis in murine ovarian cells [217]. In an experimental study, dietary turmeric was shown to improve the viability of rabbit pups and promote the fecundity of rabbits either by increasing the primary ovarian follicle production or promoting the follicle growth at all stages of folliculogenesis [218]. Curcuminoids exhibited stimulatory effect on smooth muscle relaxation in isolated rat uterus by both receptor-dependent and receptor-independent mechanisms [219]. Recently, a study has investigated the protective function of curcumin against OS in D-galactose (D-gal)-induced premature ovarian failure (POF) in mice. Curcumin was effectively shown to inhibit OS induced by D-gal, apoptosis, and ovarian injury through a mechanism involving the PI3K/Akt and Nrf/HO-1 pathways of signaling, signifying its protective effect against POF [220].

Quercetin

Quercetin is a component of the polyphenolic group of compounds called flavonoids. It is found naturally in vegetables,

fruits, seeds, and nuts and considered as a natural antioxidant present in the diet having different activities in the biological system [221, 222]. Under disease conditions, quercetin is found to have a powerful scavenging effect on the production of free radicals by enhancing the activity of various antioxidant enzymes including CAT, SOD, GPx, and GR [223]. However, quercetin has been shown to play both estrogenic and anti-estrogenic roles in vitro, therefore, suggesting diverse biological effects on the function of the reproductive organ [224, 225]. During development of preimplantation embryos in vitro, quercetin is involved in the protection of zygote from H_2O_2-induced oxidative damage by reducing the level of ROS, maintaining the function of the mitochondria and modifying the total antioxidant capacity and antioxidant enzyme activity such as CAT and GPx to maintain the cellular redox milieu [226]. Another in vitro study indicated that quercetin significantly prevented the reduced cells' viability due to OS produced by H_2O_2 and augmented the expression of OS-related proteins and consequently enhanced the antioxidant capacity in the ovary [227]. However, quercetin results in improved protection from cadmium chloride ($CdCl_2$)-induced unbalancing of reproductive hormones (progesterone, estrogen, LH, and FSH) [228]. Additionally, strengthening of GPx and SOD activities via supplementation of quercetin in granulosa cells of chicken ovarian follicles was also documented [229].

Isoflavones

Isoflavones are the most common phytoestrogens found in grains, nuts, and berries, but most abundant in soy and soy products such as soy flour, soy milk, tofu, and soy beverages [230]. Isoflavones are considered as nonsteroidal compounds which are structurally similar to natural hormone called estrogen and have the capacity to bind estrogen receptors that enable them to perform estrogenic functions [231]. Intriguingly, isoflavones may have both estrogenic and anti-estrogenic functions depending on their concentrations, sex steroids in the body, and target organs. There are two types of estrogen receptors, alpha and beta, that provide the different target organs specificity to isoflavones [231]. Phytoestrogens can also alter the biosynthesis and transport of steroids through synthesis of sex hormone-binding globulin (SHBG) in liver cells [232] and competitively displacing either 17β-estradiol or testosterone from plasma SHBG [233]. In addition to this, disruption of 5α-reductase [234] and aromatase [235–237] by various phytoestrogens in vitro has also been documented in the literature along with their potential beneficial and harmful effects on human and animal health [238]. However, despite the various aforementioned actions of phytoestrogen, data relevant to antioxidant functions of phytoestrogen in female fertility is scarce or often conflicting.

Genistein (GEN) is the most abundant (60%) phytoestrogen present in soybeans [239], while other less common phytoestrogens include daidzein and glycitein. A study by Zhuang et al. has examined the effect of GEN supplementation (160 mg/kg day) on follicular development and follicular reserves in 4-month- and 15-month-old rat ovary after 4 weeks and 4 months, respectively. A higher percentage of primordial follicles by the age of 4 months and more number of surviving follicles at the age of 15 months were observed in GEN-treated rats as compared with the control groups [240]. Another study has investigated the effect of GEN (50 mg/kg/bw for 3 days) on folliculogenesis in immature rat. Results showed that GEN acted as an estrogen antagonist during the initial phase of folliculogenesis and as an estrogen agonist during the later phases, facilitating the transition from the preantral to antral stages of folliculogenesis [241]. Recently, a study has shown that pretreatment with GEN (0.5, 1, or 2 mg/kg for 14 days) inhibited the cyclophosphamide-induced decrease in serum estradiol and AMH, oxidative stress, and inflammation in rat ovarian tissue [242]. A study involving Japanese infertile women showed that consumption of a diet rich in GEN and daidzein may reduce deep endometriosis risks [243]. However, isoflavone-induced trophic effects in female rats were observed, where long-term treatment with isoflavones results in trophism of the vaginal epithelium [244, 245]. In contrast, a randomized double-blind study involving postmenopausal women reported that long-term consumption of soy isoflavones neither affected the endometrial thickness nor enhanced the hyperplasia or cancer of the endometrium [246].

Medicinal Plants in Female Infertility Management

The usage of plants by human beings as a medicinal source has since started from the ancient times for the prevention, protection, and treatment of various health ailments. Indeed, herbals and other natural products, including their different chemical derivatives, constitute approximately 50% of all the medication currently used worldwide [247]. Moreover, herbal medicines play an important role in the healthcare systems of rural areas in both developed and developing countries [248, 249]. Medicinal plants are utilized for the treatment of female infertility as an alternative option to avoid the high cost and adverse health effects associated with various infertility treatment methods available in the form of ART. Recently, the prevalence and factors associated with the use of herbal medicine by infertile women have been assessed by Kaadaaga and his colleagues [250]. Since ethanopharmacological survey is considered as one of the reliable methods for the discovery and production of natural and synthetic drugs [251], researchers have carried out various ethanopharmacological

surveys in different regions of the world to discover the various medicinal plants used for the treatment of infertility or pathologies in females that cause infertility [37, 252, 253], and some of them are discussed below.

Nigella sativa

Nigella sativus is an annual plant of the Renunculaceae family, used in folk medicine for various useful purposes especially during lactation time, and is found in different countries bordering the Mediterranean Sea: India, Pakistan, and Iran [254]. It has been used in traditional medicine for the treatment of asthma, cough, headache, and rheumatism and as a diuretic, galactogogue, and vermifuge [255]. *N. sativa* and its most active component called thymoquinone have several pharmacological properties such as antioxidant, anti-inflammatory, anticonvulsant, anti-infertility, and hypotensive effects [256, 257]. Thymoquinone was found to re-establish spermatogenesis in rats after testicular injury induced by chronic exposure to toluene [258]. In a randomized trial on PCOS women, treatment with *N. sativa* (2 g/day for 16 weeks) significantly increased the average duration of menstrual cycle and decreased the menstrual cycle interval, serum cholesterol, LH, and insulin level [259]. Recently, a significant enhancement in the reproductive functions of rat was observed after the supplementation of 100 mg/kg of *N. sativa* [260]. The prophylactic effect of *N. sativa* against cyclophosphamide has been demonstrated by Kamarzaman et al., where its treatment significantly increased the number of primary and secondary follicles and also the ovarian diameter [261].

Cimicifuga racemosa

Cimicifuga racemosa or black cohosh is a phytoestrogen-producing perennial plant of the buttercup family, originally used by native Americans for the treatment of musculoskeletal complaints and gynecological diseases [262]. The constituents of the root rhizome extract include organic acids (isoferulic acid, cimicifugic acid), triterpene glycosides (acetin, cimicifugoside), caffeic acid, salicylic acid, tannins, and phytosterin [263, 264]. The combination of *C. racemosa* with tamoxifene was found to be effective for the 12-month relief of postmenopausal hot flushes, probably due to its antidepressant activity [265]. Recently, the addition of *C. racemosa* rhizome dry extract (120 mg/day) to clomiphene citrate (CC) induction has improved the pregnancy and cycle outcomes in patients with unexplained infertility and PCOS [262, 266, 267]. In another randomized trial of PCOS women, higher rate of ovulation, greater thickness of the endometrium, and higher rates of pregnancy were observed in the *C. racemosa* (20 mg/day)–treated group as compared with the CC group [268].

Cinnamomum zeylanicum

Cinnamomum zeylanicum is an herbaceous plant and an important spice of the Lauraceae family, used by people across the globe. Compounds isolated from cinnamon such as flavonoids and polyphenols have free radical–scavenging activities and antioxidant properties [269]. Administration of cinnamon bark oil (100 mg/kg for 10 weeks) significantly improved the testicular oxidant–antioxidant status and sperm quality and decreased the germ cell apoptosis in male rat [270]. In another similar study, oral administration of cinnamon bark oil markedly alleviated the taxane-induced decrease in testosterone, sperm quality, and oxidant–antioxidant balance and increased germ cell apoptosis [271]. Both in vivo and in vitro studies showed that polyphenol polymers isolated from cinnamon increase the insulin-dependent glucose metabolism, activate insulin receptor, and alter the transport of glucose [272, 273]. During a randomized controlled trial, supplementation of cinnamon improved the antioxidant status, serum lipid profiles, and menstrual cyclicity in women with PCOS, suggesting an effective therapy for PCOS treatment [39, 274].

Trigonella foenum-graecum

Trigonella foenum-graecum (fenugreek) is one of the oldest known medicinal herbs in history. Fenugreek seed has anti-inflammatory, antispasmodic, and emmenagogue properties. This easily available and globally distributed herb also has various pharmacological properties such as anti-inflammatory, diuretic, analgesic, and immunomodulatory [275, 276]. During a clinical trial, administration of fenugreek seed extract (500 mg/day for 12 weeks) to male volunteers significantly improved the free testosterone level, sperm count, sperm morphology, and their libido [277]. In a randomized controlled study, supplementation (600 mg/day) of fenugreek seed extract (libifem) to healthy menstruating women for two menstrual cycles significantly increased their free testosterone and estradiol levels along with improvement in their sexual desire and arousal [278]. A significant decrease in both ovarian volume and numbers of cysts along with the restoration of regular menstrual cycle was observed in PCOS patients following treatment with the seed extract (1000 mg for 90 days) of *Trigonella foenum-graecum* [279]. During a randomized controlled study, supplementation of fenugreek seed powder (3 g for 3 months) reduced lower abdominal pain in patients with primary dysmenorrhea without any adverse effects [280].

Foeniculum vulgare Mill.

Foeniculum vulgare Mill. (fennel) is a medicinal herb that is consumed in brewed form, such as tea [281]. It has various effects, including estrogen phase formation, weight gain in mammary glands and endometrium, and cervical and

antioxidant effects [282]. In traditional Persian medicine, fennel is commonly used to treat menstrual disorders. It also relieves uterine pain and increases lactation and also used to treat infertility [283] and PCOS [284]. In a recent study, treatment with *F. vulgare* Mill. (5 g for 6 months) significantly reduced the menstrual cycle interval and dysmenorrheal severity in PCOS patients without any side effects [285].

Miscellaneous

The ovarian-inducing potential of *Justicia insularis* was illustrated in immature female mice where administration of its leaf extract (12.5, 50, and 100 mg/kg) for 20 days results in early vaginal opening, more number of implantation sites, and reduced ovarian cholesterol level [286]. In another study, oral administration of *Acmella oleracea* (L.) extract to Wistar rats increased the frequency of proestrous and estrous phases and decreased the frequency of metaestrous and diestrous phases, respectively [287]. Administration of β-caryophyllene (a phytochemical constituent) to endometriotic rat for 21 days has shown significant reduction in the growth of endometriotic implants, without affecting fertility [288]. β-Caryophyllene is present in huge quantities in many plants such as *Cannabis sativa*, *Origanum vulgare*, *Eugenia caryophyllata*, *Zingiber nimmonii*, and *Piper nigrum* [288]. Further information including the name of the plant, part used, respective doses, and the improved reproductive parameters in females has been discussed in Table 2. However, in addition to the aforementioned fertility-enhancing potential, numerous medicinal plants are also used for their antifertility potential to regulate fertility in females [289].

Role of Natural Antioxidants in Assisted Reproduction

Since the delivery of the first human through IVF, more advancement in the field of reproductive medicine allowed many infertile couples to have children by using ART [290]. In vitro fertilization and intracytoplasmic sperm injection (ICSI) are the two most common methods utilized in ART for medical infertility treatment [290]. However, despite all these advancements, only 35% of the infertile couples seeking ART are able to give a live birth [291]. Numerous physiological factors have been identified that affect the ART success rate, among which ROS and the consequent generation of OS are of great concern in the medical literature [292]. During ART settings, OS is the major cause of poor gamete/embryo quality [293]. Sources of ROS during ART could either be endogenous (spermatozoa, oocytes, and embryo) or exogenous (culture media, pH, temperature, visible light, oxygen concentration, etc.) [294]. However, among the complex factors lacking in ART procedures is the effective regulation of ROS within the physiological range by antioxidants in vitro [290]. Therefore, one effective method to improve OS-mediated poor gamete/embryo quality and the resulting ART outcomes is the use of natural antioxidants to curb the excessively produced ROS. In the ART procedures, antioxidant treatment can be employed in two general modes, either as oral supplementation of infertile couples prior to their ART cycles or as in vitro administration in culture media during the ART protocol itself [294]. Table 3 summarizes the different antioxidants used both as oral supplementation or in vitro administration to culture media during ART methods along with their effect on reproductive outcomes in females.

The levels of vitamin C in the serum or follicular fluid of women with endometriosis were increased after 2 months of oral supplementation of vitamin C (1000 mg/day), while the OS markers were unaffected [295]. The combined supplementation of vitamins C (100 mg/kg bw) and E (200 mg/kg bw) has been shown to increase the oocyte maturation rate, fertilization rate, implantation rate, and embryo development in first-generation mice pups exposed to mancozeb in utero [296]. Intake of vitamin C (1, 5, or 10 g/day) with dydrogesterone as a luteal support by women showed no beneficial effects on clinical pregnancy and implantation rates [297]. In contrast, oral supplementation of ascorbic acid (750 mg/day) has significantly augmented the serum progesterone level with simultaneous improvement in clinical pregnancy rates [298]. In another study, administration of vitamin E (400 IU/day) was not related to the implantation and pregnancy rates in women undergoing controlled ovarian stimulation (COS) and intrauterine insemination (IUI). However, an improved endometrial response was observed [299]. Co-supplementation of vitamin E (400 mg/day) and D_3 (50,000 IU) enhanced the pregnancy, clinical pregnancy, and implantation rates in PCOS women. Moreover, a positive weak relationship was noticed between vitamin D levels, implantation rate, and enhanced clinical pregnancy [300]. Oral supplementation of vitamins C (1 g) and E (400 IU) for 4 weeks in children produced through ART improved their plasma NO bioavailability and alleviated the high altitude-induced pulmonary hypertension [301]. In a prospective cohort study, higher folate intake was shown to be associated with increased rates of implantation, clinical pregnancy, and live birth [302]. Supplementation of LC (1 mM) to culture media increased the clinical outcomes including implantation, clinical pregnancy, and ongoing pregnancy rates in both mouse and human subjects [303]. Another experimental study has revealed the increased blastocyst formation rates of aged bovine oocytes following supplementation of LC to culture media [304]. Retinol (100 μM) treatment significantly enhanced the embryo hatchability rate and TAC, SOD, and GPx activities during in vitro development of rabbit embryos [305]. Cryopreservation-mediated injuries during the vitrification process of mouse oocytes have been alleviated by

Table 2 Utilization of different medicinal plants in female infertility management

Plant species	Part used	Study candidate/ animal	Treatment	Improved reproductive functions	References
Trigonella foenum-graecum	Seed	PCOS women	2 capsules of 500 mg each/day for 90 days	Decrease in ovarian volume and number of ovarian cysts Return of regular menstrual cycles Increase in LH and FSH levels	[279]
		Healthy women	600 mg/day seed extract for 2 menstrual cycles	Significant increase in free testosterone and estradiol Improvement in sexual desire and arousal	[278]
Justicia insularis	Leaf	Immature rat	12.5, 50, and 100 mg/kg bw extract daily for 20 days	Early vaginal opening Increase in the number of hemorrhagic points, corpus luteum, implantation sites, ovarian weight, uterine and ovarian proteins (induces folliculogenesis) Decrease in ovarian cholesterol level	[286]
Acmella oleracea	Flowers	Rat	88.91 mg/kg and 444.57 mg/kg daily for 21 days	Increased frequency of proestrous and estrous phase Decreased frequency of metaestrous and diestrous phase	[287]
Cimicifuga racemosa	Rhizome	Infertile women	120 mg/day dry extract	Higher oestradiol and LH concentration Higher serum progesterone, endometrial thickness, and clinical pregnancy rate	[262, 267]
		PCOS women	20 mg dry extract daily for 10 days	Higher progesterone level, indicating better ovulation Greater endometrial thickness Higher pregnancy rate	[268]
Zingiber officinale	Rhizome	Rat	100 mg ginger powder daily for 5 and 10 days	Increased antral follicle count and ovarian stromal VEGF; Increased endometrial VEGEF and ovarian stromal eNOS	[360]
			100 mg/kg/day of 6-gingerol-rich fraction for 35 days	Protected against chlorpyrifos-induced increase in OS (H_2O_2 and NO) Improved the activities of antioxidant enzymes (CAT, SOD, GPx, and GST) and GSH levels in ovarian and uterine tissue	[361]
Nigella sativa	Seed	Mice	0.2, 0.5, and 1.0 mL/100 g *N. sativa* oil for 5 days	Increased the number of normal, primary, and secondary follicles and ovarian diameter in cyclophosphamide-treated rats	[261]
		Rat	0.5 and 1.0 g/kg daily from day 3 to day 15 of lactation	Increased milk production and pups' weight during lactation	[362]
		PCOS women	2 g/day powdered seed as capsules for 16 weeks	Increased the average duration of the menstrual cycle and ratio of cycle per month Decreased menstrual cycle interval	[259]
Hypericum perforatum	Flowering tops	Women with premenstrual syndrome	900 mg/day for 2 menstrual cycles	Improved the physical and behavioral symptoms of premenstrual syndrome	[370]
Crocus sativus	Stigma	Women with premenstrual syndrome	30 mg/day for 2 menstrual cycles	Effective in relieving symptoms of premenstrual syndrome	[371]
Cinnamomum zeylanicum	Bark	PCOS women	3 cinnamon capsules (each containing 500 mg cinnamon) for 8 weeks	Increased total antioxidant capacity (TAC) Decreased serum MDA levels	[274]
			1500 mg/day for 6 months	Improved menstrual cyclicity	[39]
Urtica dioica	Leaves and root	Women with hyperandrogen-ism	300–600 mg dried extract daily for 4 months	Significant decrease in total testosterone level, free testosterone level, and DHEA level	[372]
Linum usitatissimum	Seed	PCOS women	15 g flaxseed powder for 3 months	Reduced ovarian volume and follicle numbers Improvement in menstrual cyclicity and pregnancy	[369]

Table 2 (continued)

Plant species	Part used	Study candidate/ animal	Treatment	Improved reproductive functions	References
Aloe buettneri, *Dicliptera verticillata*, *Hibiscus macranthus*, and *Justicia insularis*	Leaf	Rat	50 mg/kg mixture extract for 5 days (to evaluate synergistic effect)	Increased serum LH, FSH, and estradiol level Increased the number of hemorrhagic points in PMSG-primed immature rats	[363]
Nardostachys jatamansi and *Tribulus terrestris*	Rhizome Fruit	Rat	5 and 10 mg extract powder for 12 days	Improved estrous cyclicity Decreased serum testosterone concentration Disappearance of follicular cysts and atretic follicles Restored the estradiol and progesterone to normal level in PCOS-induced rats	[364]
Coccinia cordifolia	Aerial part	Rat	500 and 1000 mg/kg plant extract for three estrous cycles	Increased serum estrogen level Increased the number of uterine implants in hyperprolactimemia-induced infertility models	[365]
Schisandra chinensis	Fruit	Rat	40, 200, and 1000 mg/kg/day for 8 days	Increased body weight, uterus embryonic total index, ovarian index, and number of implantations in early pregnant rats exposed to benzo[*a*]pyrene	[366]
Anthemis austriaca and *Melilotus officinalis*	Flower and aerial part	Endometriotic rat	100 mg/day plants extract for 4 weeks	Reduced adhesion scores, endometriotic volume, and cytokine (TNF-α, VEGF, IL-6) levels in peritoneal fluid	[367, 368]

resveratrol (25 and 50 μM) treatment through its antioxidant potential [306]. A study has shown that the use of NAC for females undergoing treatment cycles of ICSI results in the lower early and late rate of apoptosis in granulosa cells in comparison to control. Also, a negative type of correlation was noticed between the apoptosis and fertilization rates [307]. Thus, the use of NAC can be beneficial for women planning to undergo different ARTs.

Possible Antioxidant Therapies in Female Reproductive Disorders

Polycystic Ovary Syndrome

PCOS is another gynecological endocrinopathy, estimated to affect 2–20% of premenopausal women and characterized by menstrual disorders, hyperandrogenism, and infertility [308]. Current remedies utilized for PCOS only include the management of its signs and symptoms, and they are not completely able to prevent the disease and also cause side effects. Several antioxidant compounds present in plant-derived food have been shown to effectively improve the reproductive health of PCOS patients with very less or no side effects, indicating an alternative therapeutic approach for its management.

A randomized double-blinded clinical trial was conducted to evaluate the effect of vitamin E and coenzyme Q10 on metabolic and hormonal profile of PCOS patients. Results revealed that supplementation of vitamin E (400 IU) and coenzyme Q10 (200 mg) combination for 8 weeks led to a significant decrease in homeostasis model assessment of insulin resistance (HOMA-IR) and serum testosterone levels along with improvement in SHBG levels compared with the placebo group [309]. Administration of vitamin C (150 mg/kg bw for 15 days) to DHEA-induced PCOS rats revealed a significant reduction in MDA, cytokines and estrogen levels, and enhancement in antioxidant enzyme (CAT, GST, SOD) activities in ovarian tissue [310]. Treatment of PCOS-induced mice with LC (500 mg/kg for 28 days) significantly increased the total ovarian volume, number of antral follicles, serum FSH concentration, and FRAP activity, whereas a significant decrease in serum testosterone, LH, and MDA level with less percentage of apoptotic cells was observed, indicating improved endocrine functions and folliculogenesis in PCOS mice [311]. In a randomized double-blinded study, resveratrol treatment (1500 mg/kg for 3 months) to PCOS women led to a significant decrease in total testosterone level, dehydroepiandrosterone sulfate (DHEAS), and fasting insulin level with significant elevation in insulin sensitivity index [312]. In another randomized double-blinded placebo-controlled study, co-supplementation of vitamin D (5000 IU every 2 weeks) and probiotic (8×10^9 CFU/day) for 12 weeks revealed a significant decline in total plasma concentration of testosterone and MDA and an increase in TAC and total GSH level in PCOS patients [313]. Recently, a study by Jahan et al. has demonstrated that quercetin (30 mg/kg/day for 21 days) treatment to letrozole-induced PCOS mice significantly decreased the ovarian diameter and cysts and restored the number of

Table 3 Effects of natural antioxidant compounds on assisted reproductive outcomes

Antioxidant compound(s)	Study objective: to evaluate	Intervention (dosage durations)	Study outcome(s)	References
Vitamin C	Effect of vitamin C supplementation on outcomes of IVF-ET in endometriosis patients	1000 mg/day vitamin C from 2 months before IVF-ET treatment until 2 weeks after ET	Increased vitamin C levels in the serum and follicular fluid than the control group No significant differences in fertilization rate, implantation rate, and clinical pregnancy rate	[295]
Vitamin C	Effect of ascorbic acid supplementation in patients of luteal phase defects	750 mg/day orally started on the first day of the third menstrual cycle until positive urine pregnancy test	Increased serum progesterone levels Improved clinical pregnancy rate	[298]
Vitamin C	Effect of ascorbic acid as additional support during luteal phase in infertility treatment	Oral intake (1, 5, or 10 g/day) with 30 mg dydrogesterone for 14 days after follicle aspiration for the IVF-ET procedure	No differences in clinical pregnancy rate and implantation rates	[297]
Vitamin E	Effect on treatment outcomes of women with unexplained infertility undergoing controlled ovarian stimulation (COS) and intrauterine insemination (IUI)	Vitamin E (400 IU/day) administered from the 3rd to the 5th day of menstrual cycle until the hCG injection day of COS	Improved the endometrial thickness response via likely the antioxidant and anticoagulant effects No significant increase in implantation and pregnancy rates	[299]
Vitamins C and E	Protective effects against mancozeb-induced alteration in oocyte maturation of first-generation mice pups and their fertilization rate, embryo development, and pregnancy rate	Vitamin C (100 mg/kg bw) and vitamin E (200 mg/kg bw) by oral gavage every 2 days from the 2nd day of gestation until the end of lactation	Increased total number of collected oocytes, oocyte maturation, fertilization rate, implantation rate, fecundity rate, and embryo development	[296]
Vitamins C and E	Effect on pulmonary vascular dysfunction and NO bioavailability in ART children	Vitamin C (1.0 g) and vitamin E (400 IU) orally for 4 weeks	Increased plasma NO bioavailability Attenuated altitude-induced pulmonary hypertension	[301]
Folate	Prospective association of folate intake with ART outcomes	Dietary assessment before ART treatment via food frequency questionnaire (FFQ)	Higher folate intake was associated with the higher rate of implantation, clinical pregnancy, and live birth	[302]
L-carnitine	Whether supplementation of LC in culture media affects embryo development and its clinical outcomes in mouse and humans	1 mM	Higher number of good quality embryos Increased implantation rate, clinical and ongoing pregnancy rates	[303]
L-carnitine	Effect of L-carnitine supplementation on aged bovine oocytes in vitro	2.5 mM (30 h incubation of IVM)	Enhanced subsequent developmental capacity Increased blastocyst formation rate after IVF	[304]
Vitamins E and D	Effect of vitamin E and D co-supplementation on ICSI outcomes in PCOS subjects	Vitamin E (400 mg/day) and vitamin D_3 (50,000 IU/one in 2 weeks) started consuming tablets 2 weeks prior to COCP intake and continued until hCG administration	Increased pregnancy, clinical pregnancy and implantation rates No significant association between either serum or follicular fluid MDA, TAC, and ICSI outcomes	[300]
Retinol	Antioxidant and developmental capability of retinol on in vitro development of rabbit embryos	10, 100, and 1000 nM (48 h culture)	Increased the embryo hatchability rate at 100 nM Increased TAC, SOD, and GPx activities	[305]
Resveratrol	Effect of resveratrol on developmental potential of vitrified mouse oocytes after IVF	1, 10, 25, and 50 μM	Increased the blastocyst formation rate at 25 and 50 μM Reduced OS of vitrified oocytes Alleviated the abnormal mitochondrial pattern of oocytes after vitrification	[306]

healthy follicles. In addition to this, a decrease in testosterone and estradiol levels and an increase in progesterone levels were observed following quercetin treatment [314]. In another similar study, quercetin (25 mg/kg/day for 21 days) has been shown to enhance the levels of antioxidant enzymes (SOD, CAT, GPx) and reduced the activities of steroidogenic enzymes with simultaneous decrease in testosterone and estradiol levels in letrozole-induced PCOS mice [315].

Endometriosis

Endometriosis is a chronic gynecological disorder characterized by the growth of endometrial glands and stromal tissue outside the uterine cavity. It affects approximately 10% of women during their reproductive time periods and considered as a major contributor to infertility [316]. Since OS has been considered as one of the major factors involved in the pathogenesis of endometriosis [317], the use of natural antioxidant compounds with fewer adverse effects as a possible treatment therapy is gaining much interest [318].

Studies have indicated the effectiveness of vitamin C in reducing the volume of endometriotic tissue and, thus, suggest the importance of antioxidant therapy in endometriosis [319]. In a prospective cohort study, an inverse relationship was observed between intake of vitamin C, vitamin E, folate, and thiamine from food sources and the risks of endometriosis [320]. Pro-EGCG treatment (50 mg/kg/day) for 4 weeks significantly reduced the growth of endometrial implants with high efficacy and antioxidative and anti-angiogenesis competence in experimental mice [321]. A study by Jana et al. has investigated the effect of curcumin nanoparticles (40 mg/kg bw for 14 days) on endometriosis with or without letrozole in mice. Results showed a significant decrease in serum lipid peroxidation and ROS level and an increment in TAC in curcumin-treated groups as compared with the control groups [322]. The dose-dependent treatment of vitamin C was shown to reduce the weight and volume of the endometriotic cysts [323]. Daily supplementation of vitamins C and E in women with endometriosis for 4 months was shown to decrease the markers of OS. However, the amount of daily intake of vitamins C, E, and A in those patients was also less than the other women [324, 325].

Others

During a randomized controlled trial (RCT), supplements of 2 mg lycopene were given to subjects in the second trimester which shows a reduction in the development of preeclampsia and intrauterine growth retardation incidences [326]. However, in another study, supplementation of antioxidant lycopene was unable to reduce the preeclampsia incidences in women with higher risk, but played a role in reducing the incidence of intrauterine growth–restricted babies [327]. Another randomized double-blinded study investigated the role of maternal vitamin C and E supplementation in preventing spontaneous preterm birth. However, maternal administration of vitamin C (1000 mg/day) and vitamin E (400 IU) daily from 9 to 16 weeks' gestation until delivery did not decrease the rate of spontaneous preterm birth [328]. In a randomized double-blinded study, supplementation of vitamin D_3 (400 IU/day) led to the decreased incidence of abortion and serum IL-23 levels in women with unexplained recurrent spontaneous abortion [329]. Supplementations of antioxidants in some gynecological diseases (e.g., preeclampsia and spontaneous abortion) were found to be ineffective [330–332]. Therefore, more comprehensive studies are required to explore the role of natural antioxidant compounds as a possible treatment therapy for these diseases in females.

Safety Measures for Utilizing Natural Antioxidants

Antioxidants have their own range of efficacy at different doses. However, some may have adverse impacts beyond a specific level of intake. Therefore, selecting the type of antioxidants and its doses forms an important criterion. Both in vivo and in vitro studies suggest that excessive intake of natural antioxidants and their supplements may negatively impact the reproductive health of females. The safety of high doses of vitamins has always been questioned. A prospective cohort study has reported a small increase in the incidence of severe preeclampsia/eclampsia/HELLP in women with higher vitamin E intake from dietary source and supplements. For vitamin E intake aggregated from diet and supplements (n = 49,373), with an intake of 10.5–13.5 mg/day as reference, the "severe preeclampsia/eclampsia/HELLP" odds ratio (OR) was 1.46 (1.02 to 2.09) for an intake exceeding 18 mg/day [333]. Another randomized, placebo-controlled study reported that co-supplementation of vitamin C (1000 mg) and vitamin E (400 IU) daily from the second trimester of pregnancy until delivery does not prevent preeclampsia [334], but increased the rates of gestational hypertension in women at risk of preeclampsia and low birth weight in neonates [335].

Using a mouse model, Chen and Chan demonstrated that dietary curcumin consumption reduced the number of implantations, surviving fetuses, and fetal weight, whereas it enhanced the resorption sites [336]. Another study has demonstrated that higher isoflavone intake (> 40 mg/day) by North American Adventist women (30–50 years old) was associated with higher risks of nulliparity and nulligravidity compared with women with lower intake (10 mg/day) of isoflavone [337]. During an experimental study, genistein administration to neonatal rats caused multi-oocyte follicles in mice [338]; however, such types of follicles are associated with lower rates of fertility during IVF [339]. Moreover, a recent study has demonstrated that the presence of isoflavones (genistein, biochanin A, formononetin) at higher concentration (25 μg/mL) in maturation media during IVM reduced the cleavage rate and inhibited the blastocysts' hatching [340]. Long-term treatment by *Ballota undulata* may lead to a negative impact on female fertility and pregnancy in rats [341] through decreased weight of the ovary, number of viable fetuses and implantation sites, and percentage of pregnancies and by arresting of ovarian follicles at the primary and secondary stages

[342]. The use of *Trigonella foenum-graecum* (fenugreek) is again highly contraindicated during pregnancy and breastfeeding due to its efficacy of uterine stimulation [343]. Overall, these negative impacts of antioxidants are necessary to consider and justify further explorations to better understand the effects of natural antioxidants on fertility of females.

Conclusion and Future Perspectives

Infertility influences females more or less around the world and brings with it considerable psychological sufferings to couples. Inevitably, an optimum level of free radicals is essential for normal reproductive functions of females; however, excessive levels of free radicals may be deleterious and cause infertility. Since high levels of free radicals and a lower antioxidant status have been reported to induce infertility, employing treatment strategies that involve the use of highly efficient antioxidant compounds to retard the free radical-induced oxidative damage and prevent infertility is intuitive. Natural antioxidant compounds act by efficiently removing the free radicals and upregulating the antioxidant system within the body. Thus, the role of natural antioxidant compounds enlisted in the article for female infertility management is worth exploring. Moreover, recently, there is a rising interest in the use of antioxidants, either natural or synthetic.

The preliminary studies conducted on medicinal plants showed promising therapeutic effect on female infertility, but unluckily, the majority of them are deficient in scientific evidence of pharmacological or toxological nature. The information presented in the current article may provide a scientific basis for future research to assess their efficacy and safety for the development of new plant-based medicine to treat female infertility.

Furthermore, the production of OS during ART procedures associated with reduced clinical outcomes cannot be ignored. Due to their high accessibility and low cost, natural antioxidant compounds could be an economic treatment and adjunct to the ART procedures like IVF and ICSI to enhance fertility outcomes. However, even though studies to date suggest an effective treatment advantage, more well-designed randomized placebo-controlled clinical trials focusing on important clinical outcomes such as pregnancy and live birth are required in the future to effectively understand the role of natural antioxidants.

Despite the considerable benefits of natural antioxidants on reproductive pathologies of females such as endometriosis and PCOS, clinical trials exploring the utilization of natural antioxidants to treat various reproductive pathologies have produced sturdily conflicting results. Moreover, the majority of the studies in support of possible therapeutic effects of antioxidant compounds have been conducted on experimental animals under different laboratory conditions. Therefore, more clinical trials in the future involving human subjects are needed to delineate the efficacy of natural antioxidants as a possible treatment therapy for these reproductive pathologies.

Conclusively, optimal intake of natural antioxidants could decrease OS and improve female fertility; however, excessive intake may have adverse effects on reproductive health. A consensus about the type and quantity of natural antioxidants is still required to produce more successful results. Therefore, larger well-designed, dose–response studies in humans are further warranted to incorporate natural antioxidant compounds into the clinical management of female infertility. Additionally, it is well known that different antioxidants work interactively within the body to prevent cellular damage, and studies focusing on the combination effect of different natural antioxidant compounds are also required in the future.

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Compliance with Ethical Standards

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

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