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Types and Sources of Antioxidants that Role in Determining Fertility Level

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Abstract

Lifestyle and exposure to free radicals affect a person's fertility. ROS (Reactive Oxygen Species) in excess can cause oxidative stress and DNA damage (deoxyribonucleic acid). Adequate intake of antioxidants is needed to maintain ROS levels. This review aims to determine the types and sources of antioxidants that play a role in determining a person's fertility level. This research is a narrative review by a literature review method by collecting and concluding data from previous studies. The search for research articles was carried out on Scopus, Science Direct, Clinical Key, SpringerLink, BMC, and Google Schoolar portals with keywords foodstuffs, antioxidants, and infertility which found 8,745 articles. A total of 75 articles met the inclusion-exclusion criteria for use in writing this article. The research took time in 2022. Most antioxidants take a role in determining male fertility, such as glutathione, selenium, carotenoids (beta-cryptoxanthin, lycopene, beta-carotene, and lutein), zinc, vitamin C, vitamin E, and flavonoids. NAM (Nicotinamide) and carvacrol play a role in determining female fertility. These antioxidants can be found in fruits, vegetables, protein sources, and several other plants. Consumption of antioxidant sources is highly recommended to increase fertility, especially for infertile couples.

Introduction

Infertility has the potential to affect various aspects of a person's life, including physical, mental, social health, and overall quality of life (Bakhtiyar et al., 2019). Cognitive reactions and emotional-affective reactions to infertility conditions and the therapeutic process are often experienced by infertile patients (Hasanpoor-Azghdy et al., 2014). As many as 22.3% of infertile patients had stress, with fatigue being the main complaint (38.1%). The duration of infertility showed a significant relationship with the level of stress experienced by the patient ($p < 0.05$) (Wiweko et al., 2017). High-stress levels allow a person to have infertility three times OR=3,89; CI 95%=1,04 to 14,46; p=0,046) (Indarwati et al., 2017).

Lifestyle factors have a role in determining a person's fertility (Acharya and Gowda, 2017). Long-term exposure to chemicals, such as pesticides, fertilizers, and industrial products (plasticizers and phytoestrogens) has been associated with decreased fertility through hormonal pathways (Ding et al., 2016). Free radicals had a physiological role in optimizing sperm performance (Palmieri et al., 2016). Excessive amounts of ROS (reactive oxygen species) can cause oxidative stress and then DNA damage (Cleaver et al., 2014). Nearly 10% of infertile/subfertile women are identified with DOR (Decreased Ovarian Reserve) (Pastore et al., 2014).

The quality of the diet was related to energy and nutritional sufficiency (Mardiana

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et al., 2022). Previous research had shown that healthy food intake is associated with sperm and semen quality (Efrat et al., 2018). Adequate intake of antioxidants is needed to maintain ROS levels (Liu et al., 2018). Antioxidants are compounds capable to stop the chain reaction of the oxidative stress process by capturing free radicals (Ko et al., 2014). Antioxidants act as free radical reducers, enhancing endogenous antioxidant defense systems and oxidative stress-induced gene expression (Bai et al., 2016). Antioxidant levels were significantly related to sperm concentration and count of total motile. The higher of antioxidant levels in a body, the higher the sperm concentration and total motile count (Silberstein et al., 2016). Antioxidant therapy often consumed by patients is vitamin C, vitamin E, minerals (selenium and zinc) (Bardaweel, 2014). This study will combine the results of various previous studies to know the types and sources of antioxidants that play a role in determining a person's fertility level.

Method

This Research is a narrative review using the literature review method by collecting and concluding data from previous studies. The research was conducted in April-May 2022. The search for previous research articles was carried out on Scopus, Science Direct, Clinical Key, SpringerLink, BMC, and Google Schoolar portals with keywords in the form of foodstuffs, antioxidants, and infertility. The evaluation of the articles was carried out according to the inclusion and exclusion criteria of the previous articles. Inclusion criteria were research articles on the role of antioxidants in fertility enhancement, that can be accessed on indexed international journal portals or national journal portals which are minimum accredited in SINTA 2, published in 2013-2022, and was an original article. The exclusion criteria are an article that can be accessed in abstracts and proceedings only.

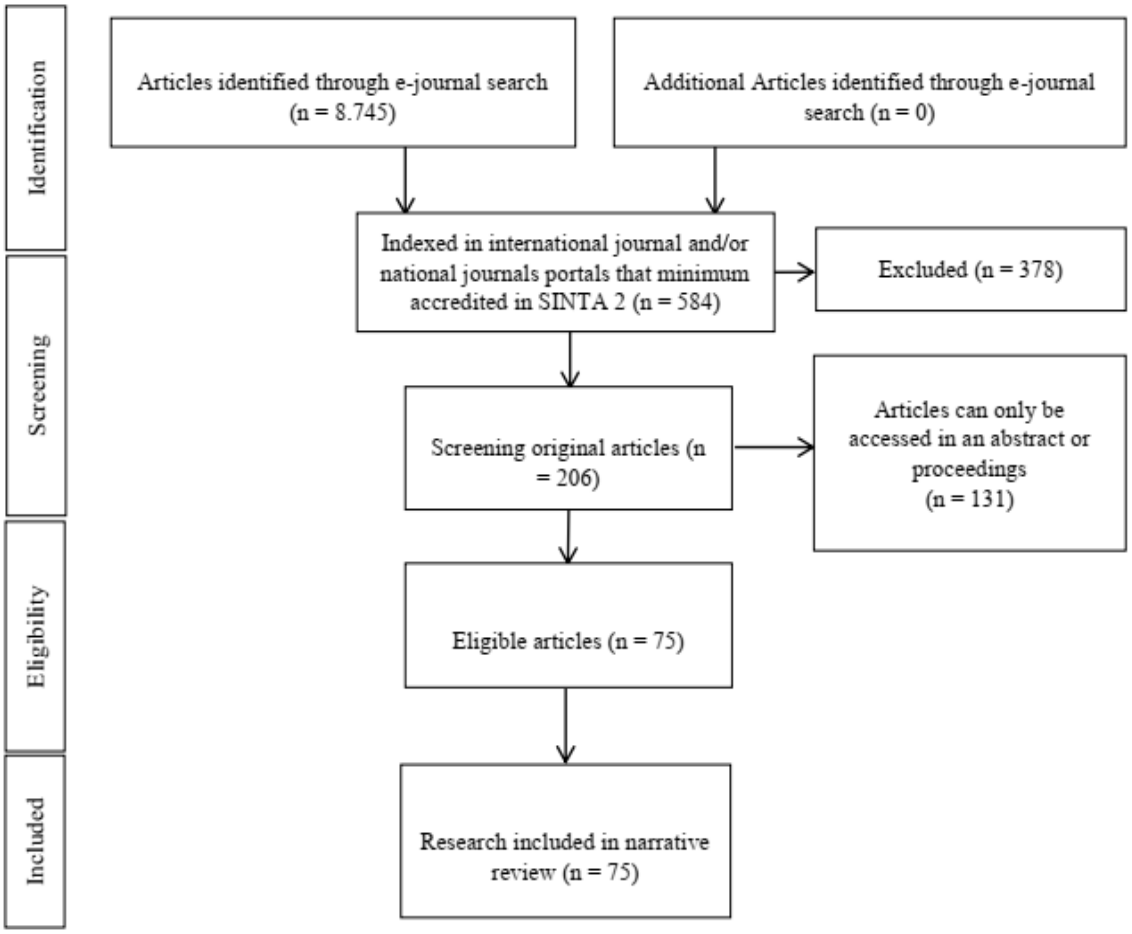

FIGURE 1. Article Selection Flowchart

A total of 584 out of 8,745 articles discussed the role of antioxidants in fertility enhancement were published from 2013-2022. A total of 206 are original can be accessed on indexed international or national journal portals that are, minimum accredited in SINTA 2. A total of 131 articles can only be accessed in abstract form. A total of 75 articles met the inclusion and exclusion criteria, so they were used in writing this narrative review that consisting of 20 articles on the Scopus journal portal, 25 articles on the Science Direct journal portal, 10 articles on the Clinical Key journal portal, 9 articles on the SpingerLink journal portal, 2 articles on the BMC journal portal, and 9 articles on the Google Schoolar with minimum accredited in SINTA 2.

Result and Discussion

Antioxidants have an important role in determining a person's fertility. Most of the antioxidants that play a role in determining male fertility. These antioxidants include glutathione, selenium, carotenoids (beta-cryptoxanthin, lycopene, beta-carotene and lutein), zinc, vitamin C, vitamin E, and flavonoids. NAM and carvacrol play a role in determining female fertility.

TABLE 1. Types of Antioxidants that Play a Role in Determining a Person's Fertility

Types of Antioxidants	Role	Referensi
NAM	NAM is positively correlated with the rate of maturation and fertilization of mouse oocytes	(Guo et al., 2022)
Glutamine	Glutamine prevents decreased sperm quality, reduces oxidative stress, inflammation and apoptosis	(Afolabi et al., 2022)
Carvacrol	Carvacrol is useful in the treatment of ovarian ischemia-reperfusion injury and infertility	(Sahin et al., 2022)
β-cryptoxanthin	β-cryptoxanthin has a positive effect on sperm motility	(Haeri et al., 2022)
Lycopene	Lycopene can protect sperm from oxidative stress and damage to sperm DNA	(Babaei et al., 2021)
	There is a positive relationship between lycopene intake and sperm morphology	(Zareba et al., 2013)
Selenium	Selenium can increase semen volume and total sperm motility	(Talebi et al., 2021)
Zinc	The effect of zinc supplementation through the pretesticular pathway can increase serum FSH, LH, and testosterone	(Shahraki et al., 2015)
Vitamin C	Vitamin C can improve the motility and morphology of spermatozoa	(Cyrus et al., 2015)
Vitamin E	Vitamin E is able to repair oxidizing radicals directly and prevent the process of lipid peroxidation	(Yan et al., 2014)
Beta-Carotene	There is a relationship between beta-carotene intake and sperm motility	(Talebi et al., 2021)
Lutein	There is a relationship between lutein intake with sperm motility and normal sperm morphology	(Zareba et al., 2013)
Flavonoids	Flavonoids can promote hydrogen ions, so they can neutralize the toxic effects of these free radicals and increase motility and morphology of normal spermatozoa.	(Jamalan et al., 2016)

Source : Primary Data. 2022

Antioxidants that play a role in determining a person's fertility can be found in foodstuffs in the form of fruits, vegetables, and protein sources. The fruits in question include watermelon, tomatoes, mango, and kiwi. The vegetables in question include banana blossoms, bamboo shoots, purple carrots, and parsley. Sources of protein in question include legumes, bay shellfish, meat and eel. In addition, antioxidants that play a role in determining a person's fertility are also found in male date flowers, mulberry leaves, sour soup leaves, and green algae.

TABLE 2. Source of Antioxidants

Source of Antioxidants	Types of Antioxidants	Reference
Banana Blooms	Phenolic	(Panyayong and Srikaeo, 2022)
Bamboo Shoots	Fenol, Flavonoids, Vitamin C	(Singhal *et al*., 2021)
Spinach	Peptide	(Fillería *et al*., 2021)
Pod	Polyphenol, Flavonoids, Saponins, isoflavonoid	(Asati *et al*., 2022)
Purple Carrots	Flavonoids	(Perez *et al*., 2022)
Soya bean	Isoflavonoiddan peptide	(Tkaczewska *et al*., 2022)
Male Date Flower	Polyphenol, flavonoids	.(Karra *et al*., 2020
Parsley	Phenolic acid, Flavones, Flavonoid, dan Carotenoids	(Ferreira *et al*., 2022)
Sorghum seeds	Phenolic	(Miafo *et al*., 2022)
Mulberry leaf	Phenolic acid, flavonoids, dan alkaloids	(Polumackanycz *et al*., 2021)
Soursop leaf	Flavonoids, chlorogenic acid	(Leal *et al*., 2022)
Green algae	Phenolic, flavonoids, Vitamin C, Vitamin D, dan Ferron	(S *et al*., 2022)
Tamarind	Papain Hydrolyzate	(Bagul *et al*., 2018)
Purple Head Broccoli	Isothiocyanates	(Chaudhary *et al*., 2018)
Watermelon	Lycopene	(Mahamat *et al*., 2021)
Tomatoes	carotenoids, lycopene, β-carotene, flavonoids, and anthocyanins	(de Souza *et al*., 2021)
Mango	phenolic, glutathione, thiobarbituric acid reactive substances (TBARS), and 8-hydroxydeoxyguanosine	(Zapata-Londoño *et al*., 2020)
Gulf shell	Selenium	(Zhang and Yang, 2014) Se-methyl-seleno-cysteine (MeSeCys
Kiwi	Polyphenol, flavonoids, flavanol, tannins, vitamin C, lutein, zeaxanthin and fiber	(Leontowicz *et al*., 2016)
Meat	Meat contains protein, ferron, vitamin B12 and other B-complex vitamins, zinc, selenium and phosphorus.	(Pereira and Vicente, 2013)
Eel	The moisture, protein, carbohydrate, fat, ash, vitamin A and vitamin E	(Wijayanti and Setiyorini, 2018)
Mushroom	Vitamin B3, nicotinic acid, nicotinamide	(Çat and Yaman, 2019)

Source : Primary Data. 2022

Glutathione is a natural antioxidant consisting of three amino acids. Namely cycteine, glutamine, and glycine (Adeoye et al., 2018). Glutathione prevented the formation of free oxygen due to the reconstruction of the thiol group (-SH)(Palani, 2018). Glutamine is an amino acid that forms glutathione, prevent a decrease in sperm quality, and reduce oxidative stress, inflammation, and apoptosis (Afolabi et al., 2022). Glutamine prevents NF-kB activation, thereby decreasing transcription of downstream pro-inflammatory genes, preventing cytokine storms, and DNA damage (Hamed et al., 2022). Glutathione plays a role in the maintenance of the thiol redox status of a cell, protection against oxidative damage, endogenous and exogenous detoxification of reactive metals and electrophiles, storage and transport of cysteine, as well as for protein and DNA synthesis, cell cycle regulation, and cell differentiation. A reduced glutathione system causes cytotoxic and destructive lesions (Fafula et al., 2017). Consumption of glutathione food sources is considered capable of maintaining sperm quality. Mango fruit contains glutathione, phenolic, TBARS, and 8-hydroxydeoxyguanosine. Daily consumption of mango juice (cv. Azúcar) increases the antioxidant capacity of plasma (Zapata-Londoño et al., 2020).

Selenium is vital in growth, immunity, reproductive system, and endogenous antioxidant system support (McLaughlin and Gunderson, 2022). Selenium can increase semen volume and total sperm motility (Talebi et al., 2021). Selenium modulates DNA repair and suppresses testicular toxicity through free radical targeting. Selenium supplementation has been shown to reduce the toxicity of non-steroidal anti-inflammatory drugs in rat testes (Sharma et al., 2020). A higher level of seminal selenium is associated with live births and a higher chance of pregnancy (Wu et al., 2020). Consumption of selenium food sources, such as meat and bay shellfish, is recommended to improve the quality of spermatozoa, especially for infertile couples. Meat and shellfish are proven to contain selenium (Pereira and Vicente, 2013; Zhang and Yang, 2014).

Carotenoids are bioactive compounds found in many fruits and vegetables. Carotenoids had many types of pigments. Beta-cryptoxanthin is a yellow pigment in the carotenoid pro-vitamin A. Beta-cryptoxanthin has antioxidant properties proven to fight free radicals (Brahma and Dutta, 2022). The ability to fight free radicals can reduce ROS, so it positively affects the percentage of sperm motility (Haeri et al., 2022). Lycopene is a red pigment in carotenoids. Lycopene intake is associated with normal spermatozoa morphology. The percentage of morphologically normal sperm among men in the highest quartile of lycopene intake was 1.7 percent higher than among men in the lowest quartile (Zareba et al., 2013). Lycopene can protect sperm from oxidative stress and damage to sperm DNA (Babaei et al., 2021). Beta-Carotene is a red-orange pigment in carotenoids. Beta-carotene acts as a potent oxidative stress mitigation agent and can modulate oxidative stress through the regulation of ROS turnover (Nishino et al., 2017). Beta-carotene intake is positively related to sperm motility (Zareba et al., 2013). Lutein is a natural carotenoid containing many unsaturated double bonds, which can prevent free radicals and can produce an antioxidant effect (Zhao et al., 2022). Lutein intake is related to sperm motility. Men with high lutein intake had a 4.4 higher percentage of progressive motility than men with low lutein intake (Zareba et al., 2013). Lutein reversed vascular endothelial dysfunction, significantly upregulated the mRNA and protein expression of SOD2 and GPx1, and down regulated the expression of NF-κB p65 and ICAM-1 (Wang et al., 2014).

Consumed carotenoid sources are recommended to increase the antioxidant capacity in the body, so that it can increase the percentage of sperm motility and normal sperm morphology. Tomato is a fruit rich in antioxidants. Tomatoes contain carotenoids, lycopene, β-carotene, flavonoids, and anthocyanins (de Souza et al., 2021). Parsley also contains carotenoids (Ferreira et al., 2022). Lycopene can be found in watermelon, which is 10.46 to 42.83 mg.kg-1 watermelon extract (Mahamat et al., 2021). Kiwi fruit contains Lutein (Leontowicz et al., 2016).

Zinc is a mineral needed by every cell in the body, including the reproductive organs. Zinc deficiency causes spermatozoa abnormalities, such as fibrous sheath hypertrophy and hyperplasia, axonema disorders, and an abnormal midpiece(Majzoub and Agarwal, 2017). Zinc increases total antioxidant activity (serum SOD/Superoxide Dismutase and -tocopherol)(Omu et al., 2015). The results of another study, zinc supplementation for 12 weeks showed an increase in the average number of spermatozoa: 14.83 million/mL (p-value < 0.01), spermatozoa motility 16.30% (p-value < 0.01), motility fast spermatozoa 11.96% (p-value < 0.01), and spermatozoa morphology: 4.26% (p-value < 0.001) (Fatima et al., 2015). In the pretesticular pathway, zinc can increase serum FSH, LH, and testosterone (Shahraki et al., 2015). Zinc played a role in the amelioration of gonadal dysfunction and decreased oxidative stress in the testes (Mohamad and Hassan, 2014). Zinc modulates the activity of Ca2+, ATPase enzymes and reduces anti-sperm antibodies, specifically Immunoglobulin G (IgG) (Zhao et al., 2016). In the testicular pathway, zinc maintains chromatin stabilization, repairs DNA damage, and plays a role in DNA transcription and translation (Zhao et al., 2016). In the post-testicular pathway, zinc regulate the growth and apoptosis of prostate epithelial cells so that the prostate can function optimally in

increasing semen volume (Zhao et al., 2016). The consumption of foods containing zinc can be an alternative to taking zinc supplements to improve sperm quality. Meat is one of the zinc sources (Pereira and Vicente, 2013). Besides that, meat is also rich in protein, iron, vitamin B12, other B-complex vitamins, selenium, and phosphor (Pereira and Vicente, 2013).

Vitamin C, or ascorbic acid, is an antioxidant with the fewest side effects (da Cruz et al., 2018). Vitamin C can improve the motility and morphology of spermatozoa (Cyrus et al., 2015). Vitamin C neutralizes free radicals, so it can prevent and/or reduce the presence of ROS (Agarwal et al., 2014). Vitamin C is able to captured hydroxyl free radicals by donating a single electron (Zhao et al., 2013). Vegetables and fruits serve as natural sources of vitamin C intake. Vitamin C is found in kiwi fruit (Leontowicz et al., 2016), bamboo shoots (Singhal et al., 2021), and green algae (S et al., 2022).

Vitamin E is a fat-soluble antioxidant. Vitamin E can repair oxidizing radicals directly and prevent the process of lipid peroxidation (Yan et al., 2014). Spermatozoa DNA fragmentation can be reduced by taking vitamin E, thus increases the morphology of normal spermatozoa(Egwurugwu et al., 2013). Vitamin E can increase semen volume and sperm motility (Muhammad, 2017). Malondialdehyde (MDA) levels decreased significantly in the vitamin C and E. supplementation groups. MDA levels are markers of oxidative stress. Decreased MDA levels is along with decreased oxidative stress (Rusiani et al., 2019). Consumption of sources of vitamin E is recommended, especially for individuals who had oxidative stress. One source of vitamin E is eel. Vitamin E content of the wild eel was 0.21%, and 0.224% of cultural eel (Wijayanti and Setiyorini, 2018).

Flavonoids are one of a compounds group. It can be used as anticancer, antidepressant, and antioxidant. Flavonoids can be found in plant extracts (Mouradov and Spangenberg, 2014). Flavonoids can neutralize the toxic effects of free radicals because they can encourage hydrogen ions to increase the motility and morphology of normal spermatozoa (Jamalan et al., 2016). Flavonoids have a strong relationship with the antioxidant test results and have a negative relationship with the concentration of ROS (Šola et al., 2018). Flavonoids-contain food is considered positive on human health (Asati et al., 2022). Parsley consumption can reduce oxidized compounds that come from oxidative processes (Ferreira et al., 2022). Beside parsley, other food that contain flavonoid compounds, such as bamboo shoots (Singhal et al., 2021), pods (Asati et al., 2022), purple carrots (Perez et al., 2022), mulberry leaves (Polumackanycz et al., 2021), tomatoes (de Souza et al., 2021), and kiwi (Leontowicz et al., 2016).

NAM or niacin or vitamin B3 is a type of B vitamin that plays a role in enzymatic reactions in carbohydrate, fat, and protein metabolism formed from nicotinic acid and nicotinamide (Çat and Yaman, 2019). Niacin can capture free radicals and reduce ROS (El Sheikh et al., 2020). The level of NAM in follicular fluid is associated with the development of larger follicles, and the level of niacin is also associated with the oocyte maturation and fertilization rate (Guo et al., 2022). Consumption of mushrooms can contribute to the need for vitamin B3 as much as 5.384 mg/100g, consisting of 66% nicotinic acid and 34% nicotinamide (Çat and Yaman, 2019).

Phenol is one type of phenolic compound with a simple group, which is beneficial for the body because of its antioxidant properties that can protect tissues from oxidative damage. Carvacrol or also known as monoterpenoid phenol, is a part of phenol that has high activity as an antioxidant, increased antioxidant defenses lead to increased immune system response (Hashemipour et al., 2014). Carvacrol has a positive impact on infertility treatment because carvacrol plays a role in the treatment of ischemia-reperfusion ovarian injury and infertility (Sahin et al., 2022). Some plants that contain carvacrol include banana blossom (Panyayong and Srikaeo, 2022), bamboo shoots (Singhal et al., 2021), pod(Asati et al., 2022), male date flower(Karra et al., 2020), parsley (Ferreira et al., 2022), sorghum seeds(Miafo et al., 2022), mulberry leaf(Polumackanycz et al., 2021), green algae(S et al., 2022), mango(Zapata-Londoño et al., 2020) and kiwi (Leontowicz et al., 2016).

Conclusion

Antioxidants can increase fertility in both men and women. Most antioxidants play a role in improving sperm quality through the ROS suppression. Antioxidants for increasing male fertility include glutathione, selenium, carotenoids (beta-cryptoxanthin, lycopene, beta-carotene, and lutein), zinc, vitamin C, vitamin E, and flavonoids. Only 2 antioxidants play a role in determining female fertility in this review, namely NAM and carvacrol. These antioxidants can be found in several sources antioxidants. Sources of antioxidants in the form of fruit, namely watermelon, tomatoes, mango, and kiwi. Sources of antioxidants in vegetables, namely banana heart, bamboo shoots, purple carrots, and parsley. Antioxidants are also found in protein sources, including legumes, bay scallops, meat, and eel. In addition to fruit, vegetables, and protein sources, antioxidants that play a role in determining a person's fertility are also found in male date flowers, mulberry leaves, soursop leaves, and green algae. Consumption of antioxidant sources is recommended to increase fertility levels, especially for infertile couples.

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