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The Use of Astaxanthin as a Natural Antioxidant on Ovarian Damage

Abdulsamed Kükürt, Mahmut Karapehlivan and Volkan Gelen

Abstract

The ovaries are defined as the organs that secrete sex hormones and ensure the formation of the ovum in females. The proper functioning of the physiological functions of the ovaries is very important for the health of both the body and the female reproductive system. Reactive oxygen species are produced as byproducts of the normal physiological metabolism of the ovary. Antioxidants are among the factors that work to maintain the balance between the production and excretion of reactive oxygen species. Since the deterioration in the antioxidant system can cause pathological results, antioxidant supplementation is considered a possible strategy for the treatment of reproductive diseases by keeping oxidative stress under control. This chapter provides information about the use of astaxanthin as a natural antioxidant against ovarian damage.

Keywords: astaxanthin, *haematococcus pluvialis*, oxidative stress, antioxidant, ovarian damage

1. Introduction

The ovaries, which are the main reproductive organs of female mammals, consist of structures called follicles. These follicles contain granulosa cells in the early developmental stages and oocyte that can be translated by two somatic cell types called theca cells in the later stages of follicular development. These granulosa and theca cells together produce the sex steroid hormones estrogen and progesterone. At birth, an ovarian follicle reserve is established, which is generally regarded as a nonrenewable pool. It is noted that these limited number of follicles are required to support fertility throughout a female's lifetime through the production of a fertilizable gamete [1].

Reserve follicles that exist in the ovary after birth are activated by developmental stages called follicular waves throughout life. Follicle excretion occurs with the onset of ovulation cycles, especially with puberty. Therefore, a female continues her life with the number of oocytes present in her ovaries at birth. The number of these reserves, which exist with follicular waves, decreases over time and is depleted. In humans, this situation appears as menopause [2, 3].

Due to today's bad environmental conditions, uncontrolled use of pesticides, cheats in the food sector and various poisonings, there is a decrease in fertility rates or serious decreases in fertility in males and females. Infertility occurs and reproductive

ability is disrupted, especially as the chemicals taken to impair the quality of the oocyte, prevent implantation, impair the quality of life of the sperm in the female genital tract after mating, cause early embryonal deaths, and directly or indirectly affect sexual activity [4].

It has been reported that physiologically low levels of reactive oxygen species (ROS) play an important role as an important regulator in various signal transduction pathways from folliculogenesis, oogenesis, embryogenesis, and pregnancy [5]. It has been stated that high levels of ROS, caused by increased production of oxidant species and/or decreased effectiveness of the antioxidant system, can lead to oxidative stress [6]. Nitric oxide is a mediator involved in vital functions such as the release of gonadotropins, steroidogenesis, folliculogenesis, ovulation, luteal development, luteolysis, and pregnancy. Thanks to the functions it has loaded in line with a dynamic order in the body, reproductive activities are fulfilled, while the opposite effect can be seen in excess. However, the fact that nitric oxide and nitric oxide synthases (eNOS, iNOS) are involved in the production of oocyte is an indication that it takes a role even in activities necessary for the continuation of life [7].

Excessive ROS production can occur in the organism due to many factors (exposure to chemicals, infectious agents, diseases, etc.). It has been suggested that the accumulation of high concentrations of ROS in the ovary causes detrimental effects on follicular function and plays an important role in the development of female reproductive diseases [8]. It has been suggested that oxidative stress in the ovaries causes granulosa cell apoptosis and follicular atresia in the follicles and damages oocytes [9]. Many studies have reported that granulosa cell apoptosis, one of the main causes of follicular atresia in mammals, is caused by oxidative stress [6, 10–12]. There are many defense mechanisms to prevent the formation of ROS so that it does not harm the organism. These mechanisms are often referred to as “antioxidant defense systems” or “antioxidants”. Antioxidants control the metabolism and free radical levels that occur in normal metabolic or pathological conditions and prevent or repair the damage that these radicals can cause [13–15].

It is reported that antioxidants are defense agents that play an important role in maintaining oxidative balance in the organism and protecting cells from the harmful effects of oxidative stress [6, 16, 17]. This chapter aimed to provide information about the use of antioxidants against experimentally induced oxidative ovarian damage.

2. Astaxanthin

Astaxanthin is a xanthophyll carotenoid found in various microorganisms and marine organisms [18]. Carotenoids can be synthesized naturally by cyanobacteria, algae, plants, some fungi, and some bacteria, but not by mammals. It has been noted that intake of carotenoids from food sources reduces the risk of many diseases such as breast, lung, ovary, colorectal, prostate cancer, and cardiovascular or eye diseases due to the antioxidant properties of carotenoids [19]. It has been reported that astaxanthin has stronger biological activity than other carotenoids [20].

Astaxanthin is obtained from seafood or *Haematococcus pluvialis*. *Haematococcus pluvialis* is a green microalgae that accumulates high astaxanthin content under stress conditions such as high salinity, nitrogen deficiency, high temperature, and light [21]. Astaxanthin produced from *Haematococcus pluvialis* is the main source for human consumption [22]. Astaxanthin is used as a pigment source in salmon, trout, and shrimp feeds [18]. It is stated that the consumption of astaxanthin, which is used as a dietary

supplement in humans and animals, can prevent or reduce the risks of various disorders in humans and animals [23]. It is stated that the use of astaxanthin as a nutritional supplement is increasing rapidly in foods, feeds, nutraceuticals, and drugs [24].

Natural sources of astaxanthin are algae, moss, yeast, salmon, trout, krill, shrimp, and crayfish. Commercial astaxanthin is mainly produced by *Phaffia* yeast, *Haematococcus*, and chemical synthesis. *Haematococcus pluvialis* constitutes one of the best sources of natural astaxanthin [25]. It has been reported that shrimp, crab, and salmon can be preferred for dietary astaxanthin intake. It is suggested that 3.6 mg of astaxanthin supplementation per day may be beneficial for health [26].

Astaxanthin is a carotenoid containing carbon, hydrogen, and oxygen atoms in its structure (Figure 1). Consisting of two terminal rings linked by a polyene chain, this molecule has two asymmetric carbons located at the 3,3' positions of the β -ionone ring with a hydroxyl (-OH) group at both ends. If the -OH group reacts with a fatty acid, a mono-ester is formed, and when both -OH groups react with fatty acids, a di-ester is formed as a result [18].

Astaxanthin can be found in various forms such as stereoisomer, geometric isomer, free and esterified [18]. Stereoisomers (3S, 3'S) and (3R, 3'R) are the most abundant in nature. While *Haematococcus* biosynthesizes the (3S, 3'S)-isomer, yeast produces the *Xanthophyllomyces dendrorhous* (3R,3'R)-isomer [27]. It consists of synthetic astaxanthin (3S, 3'S) (3R, 3'S) and (3R, 3'R) isomers [28]. Astaxanthin has the molecular formula $C_{40}H_{52}O_4$ and its molar mass is 596.84 g/mol [18].

Astaxanthin contains conjugated double bond, -OH, and keto groups and has both lipophilic and hydrophilic properties [18]. The red color is due to the conjugated double bond in the middle of the compound. It is noted that due to the presence of such double bonds, they act as a strong antioxidant by donating electrons and reacting with free radicals to become a more stable product [23]. It has been reported that the ability to bind with the cell membrane from the inside out gives astaxanthin the ability to display better biological activity than other antioxidants [29, 30]. It is noted that oxidative molecules, which are reported to cause oxidative damage, can be inhibited by endogenous and exogenous antioxidants such as carotenoids, and astaxanthin is one of the antioxidant molecules that can inhibit oxidation [31].

Carotenoids are composed of a long-conjugated double-linked polyene chain that exerts antioxidant activity by quenching singlet oxygen and scavenger radicals to terminate chain reactions. It has been suggested that the biological benefits of carotenoids are due to their antioxidant properties resulting from their physical and chemical interaction with cell membranes and that astaxanthin has higher antioxidant activity compared to various carotenoids such as lutein, lycopene, α -carotene, and β -carotene [31, 32].

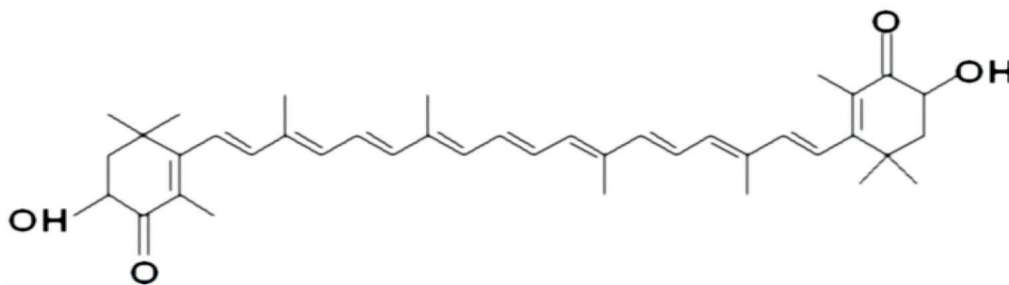


Figure 1.
Molecular structure of astaxanthin [18].

2.1 Possible effects of astaxanthin on ovaries

The ovarian follicle reserve created in fetal life is not renewed throughout the life of the creature. These limited number of reserve follicles are activated by developmental stages called follicular waves throughout life. Especially with the onset of ovulating cycles with puberty, follicle excretion occurs. Therefore, a female continues her life with the gradual decrease in the number of oocytes in her ovaries. Today, due to bad environmental conditions, uncontrolled use of pesticides, cheats in the food sector and various poisonings, there is a decrease in fertility rates or serious decreases in fertility in males and females. The chemicals taken especially impair the quality of the oocyte, prevent implantation, impair the quality of life of the sperm in the female genital tract after mating, cause early embryonal deaths, or affect sexual activity directly or indirectly, causing infertility and hindering reproductive ability [4, 33].

Physiologically low levels of ROS play a role as an important regulator of various signal transduction pathways in folliculogenesis, oogenesis, embryogenesis, and pregnancy [5]. High levels of ROS, caused by increased production of oxidant species and/or decreased effectiveness of the antioxidant system, lead to oxidative stress [14, 34–39]. Therefore, ovarian oxidative stress models will make important contributions to the understanding of these relationships, since the relationships between oxidative stress induced by ROS and the female reproductive system are not fully understood [40].

In the study in which experimental ovarian damage was created with 3-nitropropionic acid, the protective effect of astaxanthin against oxidative damage caused by 3-nitropropionic acid-induced ovarian toxicity was associated with its strong antioxidant effect. It was determined by the researchers that 3-nitropropionic acid injection caused a decrease in total antioxidant capacity levels and significant increases in total oxidant capacity and oxidative stress index levels in both ovaries and plasma. Also, while 3-nitropropionic acid caused an increase in sialic acid levels, this increase was suppressed by astaxanthin. In the study, it was determined that astaxanthin stopped the decrease in 3-nitropropionic acid-induced paraoxonase activity. It has been suggested that the use of astaxanthin may be beneficial in the prophylaxis and treatment of oxidative stress-related diseases, especially in infertility problems caused by ovarian degeneration [17].

In a study by Toktay et al. [41], they tried astaxanthin treatment against oxidative stress caused by ischemia-reperfusion in rat ovaries and achieved positive results. In the study, it was found that astaxanthin decreased lipid peroxidation and increased superoxide dismutase activity. In the same study, it was determined that astaxanthin decreased the increased caspase 3, IL-1 β , and IL-6 expressions. In another study, it was found that oxidative stress (total antioxidant status, total oxidant status, and oxidative stress index), apoptosis (caspase-3), and inflammation (c-reaktif protein, inducible nitric oxide synthase, granulocyte colony-stimulating factors) caused by methotrexate treatment in the urogenital tissue were improved with astaxanthin [42]. Ebrahimi et al. [43] reported that the administration of astaxanthin could reduce the oxidative stress factor H_2O_2 and apoptosis, while it increased the level of AKT protein expression.

A histopathological study revealed that the reduction in apico-basal height and cellular disruption in the uterine epithelium elicited by ovariectomy, signs of degeneration of the uterine glands, and inflammation in the stroma showed near-control improvement in astaxanthin-treated rats [44]. In an in vitro study, Kamada et al. [45] found that low concentrations of astaxanthin (0.1 to 10 nM) increased progesterone

production in cultured bovine luteal cells, demonstrating the potential to improve corpus luteum function in cows. In ruminants, the oxidative stress index in the luteal phase where progesterone is high is higher than in the follicular phase. During the critical period of pregnancy, the high index of oxidative stress-induced progesterone causes embryonic death. Stress-inducing factors in high milk-yielding cows may affect the amount of progesterone synthesis by inhibiting luteal cell function due to excessive free radical production [46]. Abdel-Ghani et al. [47] showed that astaxanthin significantly increased the synthesis and secretion of estradiol in follicles and decreased the synthesis and secretion of progesterone. Li et al. [48] revealed that astaxanthin improves the development of follicles and oocytes by increasing the antioxidant capacity of follicles and oocytes and alleviating bisphenol A-induced oxidative stress during follicular development and oocyte maturation. Jia et al. [49] reported that astaxanthin treatment significantly reduced the production of reactive species in oocytes and improved the quality of oocytes. Xiu-Zhen et al. [50] showed that astaxanthin combined treatment considerably inhibited nuclear factor kappa B expression and translocation to the nucleus, thereby improving the astaxanthin-induced cytotoxic effect on the ovarian cystadenocarcinoma cell line.

3. Conclusion

The reproductive ability of the ovaries, which have an important role in female health, is impaired and infertility occurs due to many other problems that directly or indirectly affect sexual activity, such as bad environmental conditions, uncontrolled pesticide use, cheating in the food sector, and various poisonings. It is necessary to protect the health of the ovaries against the aforementioned negative factors for the prevention of infertility and therefore the continuation of the living species. For this purpose, the effects of the use of astaxanthin as a protective or therapeutic antioxidant agent against various agents that negatively affect ovarian health are discussed. As a result, when the studies were viewed, it was seen that astaxanthin can be used as a preventive and therapeutic in various ovarian damage cases due to its antioxidant, anti-inflammatory, antiapoptotic, and anticancer effects. In the light of all these data, we believe that the use of astaxanthin, a natural antioxidant agent, will be beneficial for the protection of the ovaries.

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