SAR Journal of Anatomy and Physiology

Abbreviated Key Title: *SAR J Anat Physiol*
Home page: https://sarpublication.com/journal/sarjap/home
DOI: https://doi.org/10.36346/sarjap.2025.v06i02.001

ISSN 2707-7713 (P)
ISSN 2709-6874 (O)

Review Article

Role of the Antioxidants in Improving Oxidative Stress in Women with PCOS: Review Article

Reham Hassan Thamer[1*], Asmaa Abdulkareem Alwan[2], Lamyaa Khames Naif[2]
[1]Department of Clinical Laboratory Sciences, Pharmacy College, Tikrit University, Tikrit, Iraq
[2]Department of Biology, College of Science, Tikrit University, Tikrit, Iraq

***Corresponding Author:** Reham Hassan Thamer
Department of Clinical Laboratory Sciences, Pharmacy College, Tikrit University, Tikrit, Iraq

Article History: | Received: 03.02.2025 | Accepted: 10.03.2025 | Published: 13.03.2025 |

Abstract: Oxidative stress (OS) is the result of an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize and detoxify them. Infertility, endometriosis, preeclampsia, and polycystic ovarian syndrome (PCOS) are among the disorders of the reproductive system that it may cause. PCOS is a common reproductive endocrine disorder marked by irregular or absent ovulation, high testosterone levels, and the presence of polycystic ovaries as seen on an ultrasound. Patients with PCOS can have a wide range of signs. The etiology of PCOS remains unclear; however, it is believed to be associated with genetic, metabolic, endocrine, and environmental variables. Oxidative stress (OS) is when the body's oxidative and antioxidative systems are not working together properly. It is linked to the start and progression of many diseases. Research indicates that OS adversely impacts ovarian follicles and interferes with normal follicular growth and maturation. Reactive oxygen species (ROS) that are too high can hurt granulosa cells and oocytes in the follicles, making them less healthy and threatening fertility. The link between oxidative stress (OS) and polycystic ovarian syndrome (PCOS) needs to be studied in order to understand how OS affects the pathophysiology of PCOS and to find effective treatments that will improve the quality of life for women with PCOS. The possible therapeutic role of antioxidants is also examined.
Keywords: PCOS, Antioxidants, Reactive Oxygen Species, Oxidative Stress.

Copyright © 2025 The Author(s): This is an open-access article distributed under the terms of the Creative Commons Attribution **4.0 International License (CC BY-NC 4.0)** which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited.

1. INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a common gynecological endocrine disorder that impacts 5% to 20% of women of generative age worldwide [1, 2]. Infertility and irregular menstruation are also common symptoms of PCOS [3, 4]. Patients encounter financial challenges and enduring health hazards; several studies have shown that individuals with PCOS are prone to insulin resistance [5]. The diagnosis of this illness relies on the Rotterdam criteria established in 2003, requiring the presence of two out of three characteristics while excluding other etiologies [6]. The precise etiology of PCOS remains unclear; nevertheless, it is thought to include a confluence of genetic and environmental influences [7].

Antioxidants are compounds with high reducing power, characterized by their ability to inhibit free radical activities. The body naturally produces antioxidants, and we can also obtain them from food or by adding synthetic products to it. Antioxidants protect cells from injury caused by oxidative stress and prevent cell destruction. Thus, they form a line of defiance against the destructive activity of free radicals. Antioxidants also work to strengthen the body's immunity [8]. An excess of reactive oxygen species (ROS) and the body's defense mechanism against them, which includes antioxidants, lead to OS. This may alter how genes are expressed and how the immune system reacts [9]. Interestingly, oxidative stress (OS) plays a major role in the development of several gynecological conditions, including PCOS, endometriosis, infertility that can't be explained, and preeclampsia [10-12].

Over time, oxidative stress can lead to metabolic problems, irregular ovulation, and problems with embryo transfer in people with PCOS [5-13]. This may explain the altered metabolic state and diminished fertility observed in PCOS patients. As a result, many studies have looked at how to treat polycystic ovaries by increasing oxidative stress, which has been shown to be somewhat effective [14, 15]. Utilizing antioxidants or pharmacological agents that enhance the body's antioxidant mechanisms may be beneficial in managing PCOS. A complex antioxidant system usually protects against the harmful effects of reactive oxygen species. This system includes enzyme-based antioxidants like superoxide dismutase, catalase, paraoxonase, and peroxidase, as well as nonenzymatic antioxidants like thiols, glutathione, vitamins E and C, selenium, vitamin A, thioredoxin, and zinc [16].

Numerous studies indicate that antioxidant interference may enhance insulin resistance and lipid metabolism in PCOS. However, there is no comprehensive and impartial evaluation of the impacts of different antioxidant therapies on individuals with PCOS. This review examines the function of antioxidants in alleviating oxidative stress in women with PCOS.

2. Oxidative Stresses

The imbalance between the body's oxidative and antioxidative processes is known as oxidative stress (OS). As reactive oxidative species build up in the body, they damage proteins, DNA, and lipids, which eventually causes cells to stop working properly [17]. ROS and reactive nitrogen species (RNS) are two principal categories of oxidative chemicals present in the body. Superoxide anion (O_2), hydroxyl radical (OH), and hydrogen peroxide (H_2O_2) are all common types of reactive oxygen species (ROS). In living things, reactive oxygen species (ROS) mostly come from mitochondrial oxidative phosphorylation. Other sources include cytochrome P450 enzymes, peroxisomes, xanthine oxidase, and activated inflammatory cells [18]. RNS comprises nitric oxide (NO) and nitrogen dioxide (NO_2) [19]. A lot of external oxidizing agents come from ionizing radiation, metallic ions, and airborne contaminants [20]. The aging process of the organism and its inflammatory response can enhance the formation of reactive oxygen species. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) exert dual impacts on cellular activity. Low to moderate amounts of oxidative active molecules help the body do many things, like fighting off infections and acting as second messengers for cellular processes. They do this by making it easier to control gene expression, intracellular signal transduction, and the control of cell proliferation, differentiation, and apoptosis [21]. The body has both enzymatic and non-enzymatic antioxidants. “Superoxide dismutase (SOD), catalase, and glutathione (GSH) peroxidase exemplify antioxidant enzymes. Non-enzymatic antioxidants comprise vitamin C, vitamin E, glutathione (GSH), taurine, hypotaurine, zinc, selenium, carotenoids, and metal-binding proteins”. All have the ability to eliminate reactive oxygen species and maintain the oxidant/antioxidant balance [22]. It is possible for too many reactive species to damage DNA, change proteins, and speed up lipid peroxidation, all of which can make biological parts less useful [23]. An imbalance between oxidants and antioxidants can cause oxidative stress, which can damage cells and other biological processes, if the body's antioxidant defense systems aren't able to get rid of too many oxidized reactive molecules.

3. Oxidative Stress in Polycystic Ovary Syndrome

Research shows that oxidative stress can cause or worsen a number of diseases, such as heart and brain problems, neurological issues, different types of cancer, and type II diabetes [24]. All of these diseases pose serious health risks to people. Previous studies have demonstrated a close relationship between oxidative stress and the onset and progression of polycystic ovarian syndrome. The study was conducted by Papalou *et al*., [25]. The study examined the impact of oxidative stress in POCS and proposed that antioxidant defense systems cannot control the build-up of reactive oxidative species in individuals with PCOS. The ovarian stroma is an important part of the pathophysiology of polycystic ovary syndrome. It affects how the disorder starts and how it progresses, along with other factors that cause it. The study was conducted by Uyanikoglu *et al*., [26]. The study looked into the link between apoptotic markers in the blood and oxidative stress in women with PCOS. It was found that the oxidative stress index, total oxidation state, and total antioxidation state were all much higher in the blood of women with PCOS than in the blood of healthy women in the control group. The cumulative state of oxidation was greater than the cumulative condition of antioxidation. This suggests that there is an imbalance between oxidants and antioxidants in PCOS patients [27].

4. Antioxidant Levels in Women with Polycystic Ovary Syndrome (PCOS)

Recent studies have indicated a significant alteration in the antioxidant profile of women with PCOS. These individuals have diminished levels of crucial antioxidants and elevated indicators of oxidative stress. “Enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase constitute the body's intrinsic antioxidant systems. Non-enzymatic antioxidants include vitamin C, vitamin E, and glutathione”. Studies demonstrate that women with PCOS often have lower levels of non-enzymatic antioxidants and decreased activity of enzymatic antioxidants [27, 28]. Concurrently, indicators of oxidative stress, such as malondialdehyde (MDA), are significantly elevated in the blood of these individuals [28].

This altered antioxidant profile has a variety of implications. Ovarian syndrome is linked with the development of insulin resistance, inflammation, and endothelial dysfunction, which are frequently observed in PCOS [29, 30]. As a result, the prospective function of antioxidants in the therapy of PCOS has garnered significant scientific attention. The use of exogenous antioxidants, such as vitamins C and E, zinc, and selenium, has been suggested as a possible treatment approach. Preliminary data indicates that these medicines may enhance hormonal regulation and reduce metabolic discrepancies [28].

Still, since the link between antioxidant levels and PCOS is becoming clearer, it is important to study the specific processes and find the best ways to treat the condition. Finding out if the identified ovarian syndrome comes before or after polycystic ovary syndrome is very important for finding the best ways to treat the condition. For example, instead of using traditional treatments, the focus could be on stopping the problem from happening (figure 1) [28].

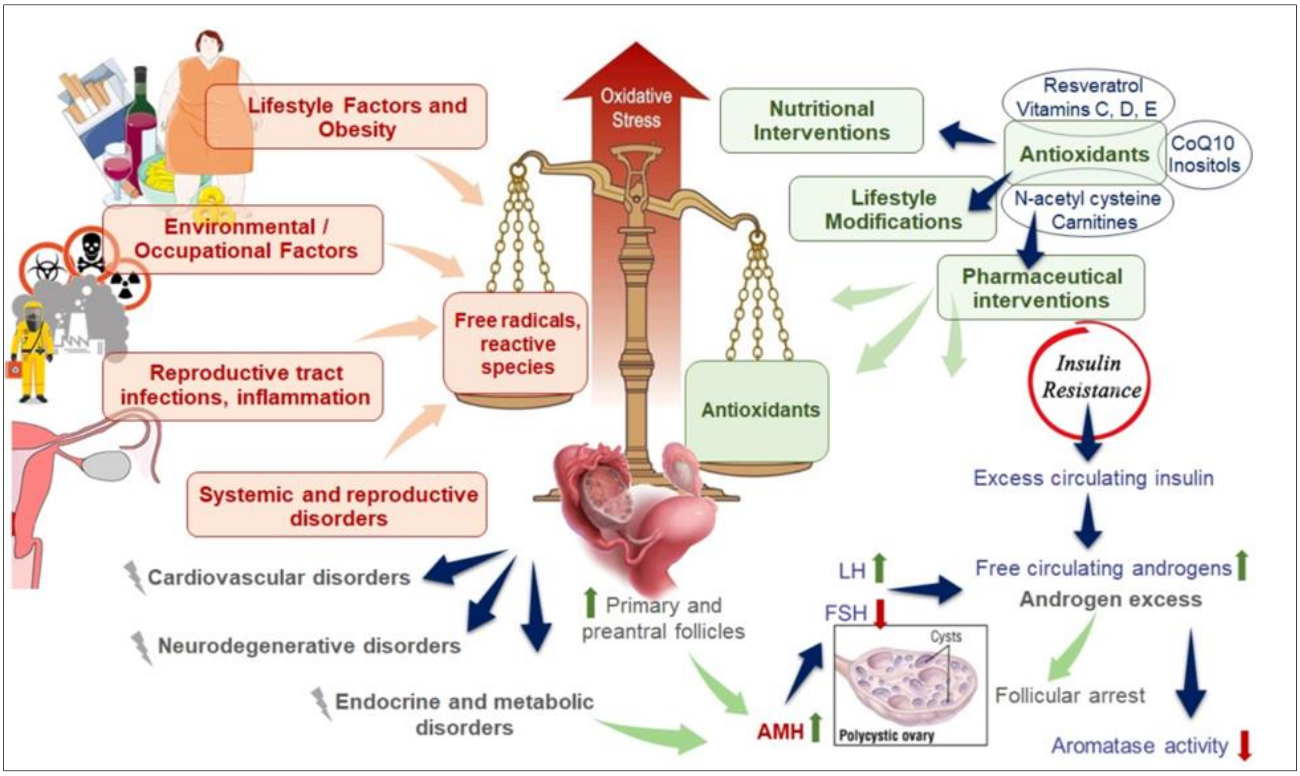

Figure 1: The mechanistic pathophysiology of (PCOS) is largely influenced by oxidative stress (OS). Several variables influence the production of oxidative stress, which in turn leads to metabolic and endocrine disorders. Antioxidants alleviate the consequences of oxidative stress and assist in diminishing the harmful effects of PCOS [28]

5. The Use of Antioxidants in PCOS

Numerous studies indicate that people with PCOS have different levels of oxidative stress, suggesting that antioxidant therapy may be a significant avenue for PCOS treatment [31]. Clinical research is currently underway on the use of antioxidants in individuals with PCOS. There is strong indication that antioxidants can greatly reduce oxidative stress and inflammatory markers in polycystic ovary syndrome, boost the body's antioxidant capacity, and fix an imbalance in oxidative stress. Researchers Jamilian *et al*., [32], looked at how vitamin D and omega-3 fatty acids affected PCOS patients and found that giving them together could significantly lower levels of total testosterone, hs-CRP, and malondialdehyde (MDA), in addition to significantly lower IL-1 gene expression and significantly increase serum "total antioxidant capacity (TAC)" [23].

Additionally, "Jamilian *et al*., [33], studied what happened when vitamin E and omega-3 supplements were given together to women with PCOS. They found that this combination treatment greatly decreased the expression of the IL-8 and TNF-a genes while increasing the expression of PPAR-g. The aforementioned two investigations markedly enhanced the ovarian status of PCOS patients. In a different study, Afshar *et al*., [34], found that giving magnesium and zinc together increases blood total antioxidant capacity and significantly lowers the levels of the proinflammatory cytokines IL-1 and TNF-α. This leads to a big improvement in oxidative stress levels in people with polycystic ovary syndrome (PCOS). Mousavi *et al*., [35], discovered in their investigation of the outcomes of magnesium and/or melatonin on the metabolism of women with PCOS that melatonin considerably decreased TNF-a levels, whereas a combination of magnesium and melatonin markedly elevated TAC levels. Moreover, research has demonstrated that antioxidants might not only diminish oxidative stress levels but also ameliorate the clinical manifestations in people with PCOS. In their study on treating PCOS with magnesium and vitamin D, Shokrpour *et al*., [36], found that giving these nutrients together could greatly lower hs-CRP levels and the number of people who are hirsute, greatly raise TAC and NO levels, and significantly lower the body's oxidative stress levels. In a different study, Gharaei *et al*., [37], discovered that giving astaxanthin significantly increased total antioxidant capacity (TAC) and increased the expression of Nrf2 and HO-1 in women with polycystic ovary syndrome (5 PCOS). Simultaneously, both MII oocytes and high-quality embryos exhibited a significant increase. However, the MDA", SOD, and OS markers within the follicular fluid showed no significant alterations. Antioxidants can significantly improve the insulin resistance condition in individuals with PCOS.

A study by Tauqir *et al*., [38], looked at acetyl levocarnitine (ALC), metformin, and pioglitazone as treatments for PCOS. They found that adding ALC may better lower fasting insulin levels and greatly increase blood levels of total testosterone, "FSH, and LH. In their study on ellagic acid for PCOS treatment, Kazemi *et al*., [39], found that it may lower levels of blood insulin, MDA, and total testosterone; lower TNF-a expression; and significantly raise oxidative stress and insulin resistance in PCOS patients. In their alternative research, Khorshidi *et al*., [40]. Less serum resistin and peripheral blood mononuclear cells were expressed when quercetin was used to treat PCOS. It significantly reduced the concentrations of total testosterone and LH in the serum. However, relative to the control group, there was no significant change in any metric of insulin resistance within the experimental group. The test mentioned earlier shows that antioxidants can help treat PCOS and greatly reduce oxidative stress in people who have it", even though they have different therapeutic effects.

6. Oxidative Stress and Ovarian Morphology in Polycystic Ovary Syndrome

Oxidative stress happens when there is an imbalance among the amount of reactive oxygen species that an organism makes and its ability to use antioxidants to fight their harmful effects [41]. Females with PCOS experience elevated ROS levels in their ovaries, leading to the modification of their ovarian structure [42]. Studies demonstrate that the follicular fluid and serum of women with PCOS have increased amounts of reactive oxygen species compared to those without the condition [43].

A hallmark of PCOS is the presence of several small antral follicles that remain in the pre-antral or antral stages [44]. High levels of ROS can hurt the quality of oocytes by causing lipid peroxidation in the membrane of the oocyte, which could make it harder for the oocyte to mature. This may explain the high occurrence of immature oocytes in individuals with PCOS. Furthermore, the ovarian stroma in polycystic ovary syndrome (PCOS) is often swollen and hyperthecotic. Ovarian stimulation is hypothesized to promote hyperthecosis, characterized by an increase of theca cells. Too many reactive oxygen species (ROS) could make theca cells multiply and stop them from apoptosis, which would cause them to build up in the ovarian stroma [28-45].

7. Oxidative Stress and Ovarian Function in PCOS Impaired Folliculogenesis:

Folliculogenesis, the development of ovarian follicles, is a complex and finely regulated process [46]. Ovarian syndrome can stop folliculogenesis from happening by killing granulosa cells, stopping them from multiplying, and making follicles less sensitive to gonadotropins. Such abnormalities may result in anovulation, frequently observed in PCOS [47].

Steroidogenic Disruption:

Theca cells and granulosa cells collaborate in the manufacture of ovarian steroids. When ROS levels are high in the ovary, they can change the enzyme pathways and send steroidogenesis in the wrong direction [48]. This modification may induce increased androgen synthesis, characteristic of PCOS [49]. Also, OS can stop the enzymes that change androgens into estrogens from working in granulosa cells, which can make the lack of estrogen in some women with PCOS worse [50].

We acknowledge that oxidative stress (OS) induces "endoplasmic reticulum (ER) stress, which in turn triggers the unfolded protein response in cells [51]. When this transpires in ovarian granulosa cells, it can obstruct cellular functions and induce autophagy, a method of cellular degradation. In ovaries affected by PCOS, increased autophagy may result in follicular loss and degeneration" [52].

8. Antioxidants as Potential Therapeutic Approaches

"Antioxidants were examined for their potential advantages in controlling PCOS by mitigating oxidative stress and alleviating symptoms [23-53]. Vitamins C and E, as powerful antioxidants, neutralize reactive oxygen species (ROS) and safeguard cells from oxidative damage [54, 55]. While their exact role in PCOS is still being studied, vitamins C and E have been evaluated for their potential benefits in mitigating PCOS symptoms and improving overall health. Certain research indicates that administering vitamins C and E to women with metabolic syndrome may enhance their insulin sensitivity and glucose metabolism [56]. Vitamins C and E are involved in the synthesis and metabolism of reproductive hormones [57]. Sufficient quantities of vitamins may promote optimal ovarian function and hormonal equilibrium. PCOS frequently exhibits abnormal lipid profiles, characterized by elevated triglycerides and cholesterol levels. Some studies show that taking extra vitamins C and E might improve lipid profiles, possibly by lowering triglyceride levels and speeding up the metabolism of lipids" [57].

N-acetylcysteine (NAC) is a natural molecule that is needed for cellular antioxidant defense processes and may help ease the symptoms of PCOS [58]. It is a precursor to the antioxidant glutathione. The possible benefits of giving NAC to women with PCOS include lowering insulin resistance, increasing ovulation, and lowering oxidative stress [59, 60]. "NAC may also be advantageous in lowering testosterone levels, thereby mitigating symptoms such as hirsutism and acne [61]. NAC supplementation may enhance menstrual regularity, promote ovulation in women with PCOS, and improve fertility" [62, 63].

Interestingly, using these antioxidants seems like a good idea, but more research needs to be done to find the best dose, duration, and effectiveness for managing PCOS. Moreover, individual reactions to antioxidants may differ, and it is advisable to get guidance from a healthcare practitioner prior to commencing any antioxidant treatment. Alongside "antioxidant supplementation, a balanced diet abundant in fruits, vegetables, and whole grains may offer a natural supply of antioxidants" [64]. Lifestyle adjustments, including consistent exercise and weight control, can aid in diminishing oxidative stress in polycystic ovary syndrome [65].

One important and unique thing about using antioxidants is their synergistic activity, which means that when many antioxidants are used together, their effects are amplified and often better overall than when single antioxidants are used alone. Antioxidants function in many ways. Certain antioxidants may eliminate certain forms of reactive oxygen species "(ROS), while others repair oxidative damage or augment the body's intrinsic antioxidant defenses. Integrating antioxidants with diverse methods may potentially address a wider array of oxidative stress-related concerns. Antioxidants like vitamins D and E, coenzyme Q10 (CoQ10)", and inositol's have been looked at to see if they can help ease the symptoms of PCOS, especially insulin resistance, inflammation, and oxidative stress [65]. A meta-analysis indicated that inositol's may enhance SHBG levels and optimize glycolipid metabolism. "Vitamin E may be advantageous for lowering total testosterone levels and elevating SHBG. The homeostatic model assessment of insulin resistance (HOMA-IR) [66], shows that CoQ10 may help lower insulin resistance, either on its own or in combination with vitamin E. Co-supplementation with specific combinations has been linked to enhancements in inflammatory state and antioxidant capability. Putting together probiotics, selenium, vitamin E, and omega-3 fatty acids may help reduce inflammation and boost the body's antioxidant defenses. Inositol supplementation with B vitamins may positively influence inflammation, antioxidant capacity, and general health" [67].

9. CONCLUSION

To sum up, an imbalance in oxidative stress affects the microenvironment of follicular fluid, lowers the excellence of follicles by damaging mitochondria, and may even cause follicles to die. HA and IR influence follicular growth and progress, resulting in slower follicular growth, impeding the selection of leading follicles, and leading to ovulatory dysfunction. In polycystic ovary syndrome, ovarian steroidogenesis, hyperandrogenism, and insulin resistance all work together to make a bad cycle that stops ovulation. The mechanism of oxidative stress in individuals with polycystic ovary syndrome and ovulation abnormalities remains little understood, necessitating more research to validate this concept. Many people with polycystic ovary syndrome may benefit from antioxidant therapy, which may help lower oxidative stress levels. Nevertheless, criticism over this technique continues at this point. Additional clinical trials are necessary to verify if it yields progressively favorable results for the treatment of PCOS in the future. "The link between oxidative stress and polycystic ovarian syndrome is receiving heightened acknowledgment. More research needs to be done to fully understand how oxidative stress affects the pathophysiology of polycystic ovarian syndrome. A variety of antioxidants, such as NAC, vitamin E, and alpha-lipoic acid, have been suggested as therapeutic treatments to aid women with PCOS in mitigating oxidative stress and improving their metabolic and reproductive health. Comprehending the association between OS and PCOS is essential for formulating appropriate treatment options to enhance the quality of life for women impacted" by this condition.

REFERENCES

1. Azziz, R., Carmina, E., Chen, Z., Dunaif, A., Laven, J. S., Legro, R. S., ... & Yildiz, B. O. (2016). Polycystic ovary syndrome. *Nature reviews Disease primers*, *2*(1), 1-18. https://doi.org/10.1038/nrdp.2016.57.
2. Polak, K., Czyzyk, A., Simoncini, T., & Meczekalski, B. (2017). New markers of insulin resistance in polycystic ovary syndrome. *Journal of endocrinological investigation*, *40*, 1-8. https://doi.org/10.1007/s40618-016-0523-8.
3. Fauser, B. C. (2014). Revisiting ovulation induction in PCOS. *Nature Reviews Endocrinology*, *10*(12), 704-705. https://doi.org/10.1038/nrendo.2014.156.
4. Skiba, M. A., Islam, R. M., Bell, R. J., & Davis, S. R. (2018). Understanding variation in prevalence estimates of polycystic ovary syndrome: a systematic review and meta-analysis. *Human reproduction update*, *24*(6), 694-709. https://doi.org/10.1093/humupd/dmy022.
5. Zhao, J., Sui, X., Shi, Q., Su, D., & Lin, Z. (2022). Effects of antioxidant intervention in patients with polycystic ovarian syndrome: A systematic review and meta-analysis. *Medicine*, *101*(32), e30006. https://doi.org/10.1097/MD.0000000000030006.
6. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. (2004). Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome

(PCOS). Human reproduction, 19(1), 41-47. https://doi.org/10.1093/humrep/deh098.
7. Witchel, S. F., Oberfield, S. E., & Peña, A. S. (2019). Polycystic ovary syndrome: pathophysiology, presentation, and treatment with emphasis on adolescent girls. *Journal of the Endocrine Society, 3*(8), 1545-1573. https://doi.org/10.1210/js.2019-00078.
8. Salman, H. A., Hussein, F. K., & Abdulrahman, S. J. (2024). A Comparison of Glutathione and Malondialdehyde Concentrations in Athletes Engaged in Certain Sports. *Thamar University Journal of Natural & Applied Sciences*, *9*(1), 39-42. https://doi.org/10.59167/tujnas.v9i1.2053.
9. Pizzino, G., Irrera, N., Cucinotta, M., Pallio, G., Mannino, F., Arcoraci, V., ... & Bitto, A. (2017). Oxidative stress: harms and benefits for human health. *Oxidative medicine and cellular longevity, 1*, 8416763. https://doi.org/10.1155/2017/8416763.
10. Christodoulakos, G., Augoulea, A., Lambrinoudaki, I., Sioulas, V., & Creatsas, G. (2007). Pathogenesis of endometriosis: the role of defective 'immunosurveillance'. *The European Journal of Contraception & Reproductive Health Care, 12*(3), 194-202. https://doi.org/10.1080/13625180701387266.
11. Agarwal, A., Aponte-Mellado, A., Premkumar, B. J., Shaman, A., & Gupta, S. (2012). The effects of oxidative stress on female reproduction: a review. *Reproductive biology and endocrinology, 10*, 1-31. https://doi.org/10.1186/1477-7827-10-49.
12. Barrea, L., Marzullo, P., Muscogiuri, G., Di Somma, C., Scacchi, M., Orio, F., ... & Savastano, S. (2018). Source and amount of carbohydrate in the diet and inflammation in women with polycystic ovary syndrome. *Nutrition research reviews, 31*(2), 291-301. https://doi.org/10.1017/S0954422418000136.
13. Shukla, P., & Mukherjee, S. (2020). Mitochondrial dysfunction: an emerging link in the pathophysiology of polycystic ovary syndrome. *Mitochondrion, 52*, 24-39. https://doi.org/10.1016/j.mito.2020.02.006.
14. Razavi, M., Jamilian, M., Kashan, Z. F., Heidar, Z., Mohseni, M., Ghandi, Y., ... & Asemi, Z. (2016). Selenium supplementation and the effects on reproductive outcomes, biomarkers of inflammation, and oxidative stress in women with polycystic ovary syndrome. *Hormone and Metabolic Research, 48*(03), 185-190. https://doi.org/10.1055/s-0035-1559604.
15. Afshar Ebrahimi, F., Foroozanfard, F., Aghadavod, E., Bahmani, F., & Asemi, Z. (2018). The effects of magnesium and zinc co-supplementation on biomarkers of inflammation and oxidative stress, and gene expression related to inflammation in polycystic ovary syndrome: a randomized controlled clinical trial. *Biological trace element research, 184*, 300-307. https://doi.org/10.1007/s12011-017-1198-5.
16. Ding, Y., Jiang, Z., Xia, B., Zhang, L., Zhang, C., & Leng, J. (2019). Mitochondria-targeted antioxidant therapy for an animal model of PCOS-IR. *International Journal of Molecular Medicine*, *43*(1), 316-324. https://doi.org/10.3892/ijmm.2018.3977.
17. Lu, J., Wang, Z., Cao, J., Chen, Y., & Dong, Y. (2018). A novel and compact review on the role of oxidative stress in female reproduction. *Reproductive Biology and Endocrinology, 16*, 1-18. https://doi.org/10.1186/s12958-018-0391-5.
18. Allen, R. G., & Tresini, M. (2000). Oxidative stress and gene regulation. *Free Radical Biology and Medicine*, *28*(3), 463-499. https://doi.org/10.1016/S0891-5849(99)00242-7.
19. Di Meo, S., Reed, T. T., Venditti, P., & Victor, V. M. (2016). Role of ROS and RNS sources in physiological and pathological conditions. *Oxidative medicine and cellular longevity, 2016*(1), 1245049. https://doi.org/10.1155/2016/1245049.
20. Valko, M., Rhodes, C. J. B., Moncol, J., Izakovic, M. M., & Mazur, M. (2006). Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chemico-biological interactions, 160*(1), 1-40. https://doi.org/10.1016/j.cbi.2005.12.009.
21. Sies, H., & Jones, D. P. (2020). Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. *Nature reviews Molecular cell biology*, *21*(7), 363-383. https://doi.org/10.1038/s41580-020-0230-3.
22. Agarwal, A., Aponte-Mellado, A., Premkumar, B. J., Shaman, A., & Gupta, S. (2012). The effects of oxidative stress on female reproduction: a review. *Reproductive biology and endocrinology*, *10*, 1-31. https://doi.org/10.1186/1477-7827-10-49.
23. Li, W., Liu, C., Yang, Q., Zhou, Y., Liu, M., & Shan, H. (2022). Oxidative stress and antioxidant imbalance in ovulation disorder in patients with polycystic ovary syndrome. *Frontiers in Nutrition*, *9*, 1018674. https://doi.org/10.3389/fnut.2022.1018674.
24. Moloney, J. N., & Cotter, T. G. (2018, August). ROS signalling in the biology of cancer. In Seminars in cell & developmental biology (Vol. 80, pp. 50-64). Academic Press. https://doi.org/10.1016/j.semcdb.2017.05.023.
25. Papalou, O., M. Victor, V., & Diamanti-Kandarakis, E. (2016). Oxidative stress in polycystic ovary syndrome. *Current pharmaceutical design*, *22*(18), 2709-2722. https://doi.org/10.2174/1381612822666160216151852.
26. Uyanikoglu, H., Sabuncu, T., Dursun, H., Sezen, H., & Aksoy, N. (2017). Circulating levels of apoptotic markers and oxidative stress parameters in women with polycystic ovary syndrome: a case-controlled descriptive study. *Biomarkers*, *22*(7), 643-647. https://doi.org/10.1080/1354750X.2016.1265004.
27. Murri, M., Luque-Ramírez, M., Insenser, M., Ojeda-Ojeda, M., & Escobar-Morreale, H. F. (2013). Circulating markers of oxidative stress and

polycystic ovary syndrome (PCOS): a systematic review and meta-analysis. *Human reproduction update*, *19*(3), 268-288. https://doi.org/10.1093/humupd/dms059.

28. Sengupta, P., Dutta, S., & Hassan, M. F. (2024). Polycystic ovary syndrome (PCOS) and oxidative stress. *Journal of Integrated Science and Technology*, *12*(3), 752-752. https://doi.org/10.62110/sciencein.jist.2024.v12.752.
29. Uçkan, K., Demir, H., Turan, K., Sarıkaya, E., & Demir, C. (2022). Role of oxidative stress in obese and nonobese PCOS patients. *International journal of clinical practice*, *2022*(1), 4579831. https://doi.org/10.1155/2022/4579831.
30. Duleba, A. J., & Dokras, A. (2012). Is PCOS an inflammatory process?. *Fertility and sterility*, *97*(1), 7-12. https://doi.org/10.1016/j.fertnstert.2011.11.023.
31. Gharaei, R., Mahdavinezhad, F., Samadian, E., Asadi, J., Ashrafnezhad, Z., Kashani, L., & Amidi, F. (2021). Antioxidant supplementations ameliorate PCOS complications: a review of RCTs and insights into the underlying mechanisms. *Journal of Assisted Reproduction and Genetics*, 1-15. https://doi.org/10.1007/s10815-021-02342-7.
32. Jamilian, M., Samimi, M., Mirhosseini, N., Ebrahimi, F. A., Aghadavod, E., Talaee, R., ... & Asemi, Z. (2018). The influences of vitamin D and omega-3 co-supplementation on clinical, metabolic and genetic parameters in women with polycystic ovary syndrome. *Journal of affective disorders*, *238*, 32-38. https://doi.org/10.1016/j.jad.2018.05.027.
33. Jamilian, M., Shojaei, A., Samimi, M., Ebrahimi, F. A., Aghadavod, E., Karamali, M., ... & Asemi, Z. (2018). The effects of omega-3 and vitamin E co-supplementation on parameters of mental health and gene expression related to insulin and inflammation in subjects with polycystic ovary syndrome. *Journal of affective disorders*, *229*, 41-47. https://doi.org/10.1016/j.jad.2017.12.049.
34. Afshar Ebrahimi, F., Foroozanfard, F., Aghadavod, E., Bahmani, F., & Asemi, Z. (2018). The effects of magnesium and zinc co-supplementation on biomarkers of inflammation and oxidative stress, and gene expression related to inflammation in polycystic ovary syndrome: a randomized controlled clinical trial. *Biological trace element research*, *184*, 300-307. https://doi.org/10.1007/s12011-017-1198-5.
35. Mousavi, R., Alizadeh, M., Asghari Jafarabadi, M., Heidari, L., Nikbakht, R., Babaahmadi Rezaei, H., & Karandish, M. (2022). Effects of melatonin and/or magnesium supplementation on biomarkers of inflammation and oxidative stress in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. *Biological trace element research*, *200*(3), 1010-1019. https://doi.org/10.1007/s12011-021-02725-y.
36. Shokrpour, M., & Asemi, Z. (2019). The effects of magnesium and vitamin E co-supplementation on hormonal status and biomarkers of inflammation and oxidative stress in women with polycystic ovary syndrome. *Biological trace element research*, *191*, 54-60. https://doi.org/10.1007/s12011-018-1602-9.
37. Gharaei, R., Alyasin, A., Mahdavinezhad, F., Samadian, E., Ashrafnezhad, Z., & Amidi, F. (2022). Randomized controlled trial of astaxanthin impacts on antioxidant status and assisted reproductive technology outcomes in women with polycystic ovarian syndrome. *Journal of Assisted Reproduction and Genetics*, *39*(4), 995-1008. https://doi.org/10.1007/s10815-022-02432-0.
38. Tauqir, S., Israr, M., Rauf, B., Malik, M. O., Habib, S. H., Shah, F. A., ... & Shah, M. (2021). Acetyl-L-carnitine ameliorates metabolic and endocrine alterations in women with PCOS: a double-blind randomized clinical trial. *Advances in Therapy*, *38*(7), 3842-3856. https://doi.org/10.1007/s12325-021-01789-5.
39. Kazemi, M., Lalooha, F., Nooshabadi, M. R., Dashti, F., Kavianpour, M., & Haghighian, H. K. (2021). Randomized double blind clinical trial evaluating the Ellagic acid effects on insulin resistance, oxidative stress and sex hormones levels in women with polycystic ovarian syndrome. *Journal of ovarian research*, *14*, 1-12. https://doi.org/10.1186/s13048-021-00849-2.
40. Khorshidi, M., Moini, A., Alipoor, E., Rezvan, N., Gorgani-Firuzjaee, S., Yaseri, M., & Hosseinzadeh-Attar, M. J. (2018). The effects of quercetin supplementation on metabolic and hormonal parameters as well as plasma concentration and gene expression of resistin in overweight or obese women with polycystic ovary syndrome. *Phytotherapy Research*, *32*(11), 2282-2289. https://doi.org/10.1002/ptr.6166.
41. Artimani, T. K. J. M. M. Y. M. K. E. G. M., Karimi, J., Mehdizadeh, M., Yavangi, M., Khanlarzadeh, E., Ghorbani, M., ... & Kheiripour, N. (2018). Evaluation of pro-oxidant-antioxidant balance (PAB) and its association with inflammatory cytokines in polycystic ovary syndrome (PCOS). *Gynecological endocrinology*, *34*(2), 148-152. https://doi.org/10.1080/09513590.2017.1371691.
42. Ruder, E. H., Hartman, T. J., & Goldman, M. B. (2009). Impact of oxidative stress on female fertility. *Current opinion in obstetrics and gynecology*, *21*(3), 219-222. https://doi.org/10.1097/GCO.0b013e32832924ba.
43. Jana, S. K., Babu, N., Chattopadhyay, R., Chakravarty, B., & Chaudhury, K. (2010). Upper control limit of reactive oxygen species in follicular fluid beyond which viable embryo formation is not favorable. *Reproductive Toxicology*, *29*(4), 447-451. https://doi.org/10.1016/j.reprotox.2010.04.002.
44. Mukerjee, N. (2020). Polycystic Ovary Syndrome (PCOS) symptoms, causes & treatments-a review.

International Journal of Science and Research, *9*(7), 1949-1957.

45. Meczekalski, B., Szeliga, A., Maciejewska-Jeske, M., Podfigurna, A., Cornetti, P., Bala, G., & Adashi, E. Y. (2021). Hyperthecosis: an underestimated nontumorous cause of hyperandrogenism. *Gynecological Endocrinology, 37*(8), 677-682. https://doi.org/10.1080/09513590.2021.1903419.
46. Erickson, G. F., & Shimasaki, S. (2000). The role of the oocyte in folliculogenesis. *Trends in Endocrinology & Metabolism, 11*(5), 193-198.
47. Sander, V. A., Hapon, M. B., Sícaro, L., Lombardi, E. P., Jahn, G. A., & Motta, A. B. (2011). Alterations of folliculogenesis in women with polycystic ovary syndrome. *The Journal of Steroid Biochemistry and Molecular Biology, 124*(1-2), 58-64. https://doi.org/10.1016/j.jsbmb.2011.01.008.
48. Hanukoglu, I. (2006). Antioxidant protective mechanisms against reactive oxygen species (ROS) generated by mitochondrial P450 systems in steroidogenic cells. *Drug metabolism reviews*, *38*(1-2), 171-196. https://doi.org/10.1080/03602530600570040.
49. Garg, D., & Merhi, Z. (2016). Relationship between advanced glycation end products and steroidogenesis in PCOS. *Reproductive Biology and Endocrinology*, *14*, 1-13. https://doi.org/10.1186/s12958-016-0205-6.
50. Masjedi, F., Keshtgar, S., Zal, F., Talaei-Khozani, T., Sameti, S., Fallahi, S., & Kazeroni, M. (2020). Effects of vitamin D on steroidogenesis, reactive oxygen species production, and enzymatic antioxidant defense in human granulosa cells of normal and polycystic ovaries. *The Journal of steroid biochemistry and molecular biology*, *197*, 105521. https://doi.org/10.1016/j.jsbmb.2019.105521.
51. Zeeshan, H. M. A., Lee, G. H., Kim, H. R., & Chae, H. J. (2016). Endoplasmic reticulum stress and associated ROS. *International journal of molecular sciences, 17*(3), 327. https://doi.org/10.3390/ijms17030327.
52. Li, D., You, Y., Bi, F. F., Zhang, T. N., Jiao, J., Wang, T. R., ... & Yang, Q. (2018). Autophagy is activated in the ovarian tissue of polycystic ovary syndrome. *Reproduction, 155*(1), 85-92. https://doi.org/10.1530/REP-17-0499.
53. Darling, A. M., Chavarro, J. E., Malspeis, S., Harris, H. R., & Missmer, S. A. (2013). A prospective cohort study of Vitamins B, C, E, and multivitamin intake and endometriosis. *Journal of Endometriosis and Pelvic Pain Disorders, 5*(1), 17-26. https://doi.org/10.5301/JE.5000151.
54. Heidari, H., Hajhashemy, Z., & Saneei, P. (2022). A meta-analysis of effects of vitamin E supplementation alone and in combination with omega-3 or magnesium on polycystic ovary syndrome. *Scientific reports, 12*(1), 19927. https://doi.org/10.1038/s41598-022-24467-0.
55. Olaniyan, O. T., Femi, A., Iliya, G., Ayobami, D., Godam, E., Olugbenga, E., & Mali, P. C. (2019). Vitamin C suppresses ovarian pathophysiology in experimental polycystic ovarian syndrome. *Pathophysiology, 26*(3-4), 331-341. https://doi.org/10.1016/j.pathophys.2019.08.003.
56. Wong, S. K., Chin, K. Y., & Ima-Nirwana, S. (2020). Vitamin C: a review on its role in the management of metabolic syndrome. *International journal of medical sciences, 17*(11), 1625. https://doi.org/10.7150/ijms.47103.
57. Mumford, S. L., Browne, R. W., Schliep, K. C., Schmelzer, J., Plowden, T. C., Michels, K. A., ... & Schisterman, E. F. (2016). Serum antioxidants are associated with serum reproductive hormones and ovulation among healthy women. *The Journal of nutrition*, *146*(1), 98-106. https://doi.org/10.3945/jn.115.217620.
58. Tenório, M. C. D. S., Graciliano, N. G., Moura, F. A., Oliveira, A. C. M. D., & Goulart, M. O. F. (2021). N-acetylcysteine (NAC): impacts on human health. *Antioxidants*, *10*(6), 967. https://doi.org/10.3390/antiox10060967.
59. Nemati, M., Nemati, S., Taheri, A. M., & Heidari, B. (2017). Comparison of metformin and N-acetyl cysteine, as an adjuvant to clomiphene citrate, in clomiphene-resistant women with polycystic ovary syndrome. *Journal of gynecology obstetrics and human reproduction, 46*(7), 579-585. https://doi.org/10.1016/j.jogoh.2017.07.004.
60. Thakker, D., Raval, A., Patel, I., & Walia, R. (2015). N-acetylcysteine for polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled clinical trials. *Obstetrics and gynecology international, 2015*(1), 817849. https://doi.org/10.1155/2015/817849.
61. Gayatri, K., Kumar, J. S., & Kumar, B. B. (2010). Metformin and N-acetyl cysteine in polycystic ovarian syndrome–-a comparative study. *Indian Journal of clinical medicine*, 1, 117739361000100002. https://doi.org/10.1177/117739361000100002.
62. Lak, T. B., Hajshafiha, M., Nanbakhsh, F., & Oshnouei, S. (2017). N-acetyl cysteine in ovulation induction of PCOS women underwent intrauterine insemination: An RCT. *International Journal of Reproductive BioMedicine, 15*(4), 203.
63. Asl, Z. S., Parastouei, K., & Eskandari, E. (2023). The effects of N-acetylcysteine on ovulation and sex hormones profile in women with polycystic ovary syndrome: a systematic review and meta-analysis. *British Journal of Nutrition, 130*(2), 202-210. https://doi.org/10.1017/S0007114522003270.
64. Hasan, S. R., Junaid, F. M., Mahdi, B. M., & Hussein, F. K. (2025). Therapeutic applications of medicinal plants for the treatment of human intestinal diarrhea: Review article. S. *Asian J. Life Sci*, *13*, 20-24. https://dx.doi.org/10.17582/journal.sajls/2025/13.20.24.

65. Zeber-Lubecka, N., Ciebiera, M., & Hennig, E. E. (2023). Polycystic ovary syndrome and oxidative stress—from bench to bedside. *International journal of molecular sciences*, *24*(18), 14126. https://doi.org/10.3390/ijms241814126.
66. Zhang, J., Xing, C., Zhao, H., & He, B. (2021). The effectiveness of coenzyme Q10, vitamin E, inositols, and vitamin D in improving the endocrine and metabolic profiles in women with polycystic ovary syndrome: a network meta-analysis. *Gynecological Endocrinology*, *37*(12), 1063-1071. https://doi.org/10.1080/09513590.2021.1926975.
67. Menichini, D., Ughetti, C., Monari, F., Di Vinci, P. L., Neri, I., & Facchinetti, F. (2022). Nutraceuticals and polycystic ovary syndrome: a systematic review of the literature. *Gynecological Endocrinology*, *38*(8), 623-631. https://doi.org/10.1080/09513590.2022.2089106.