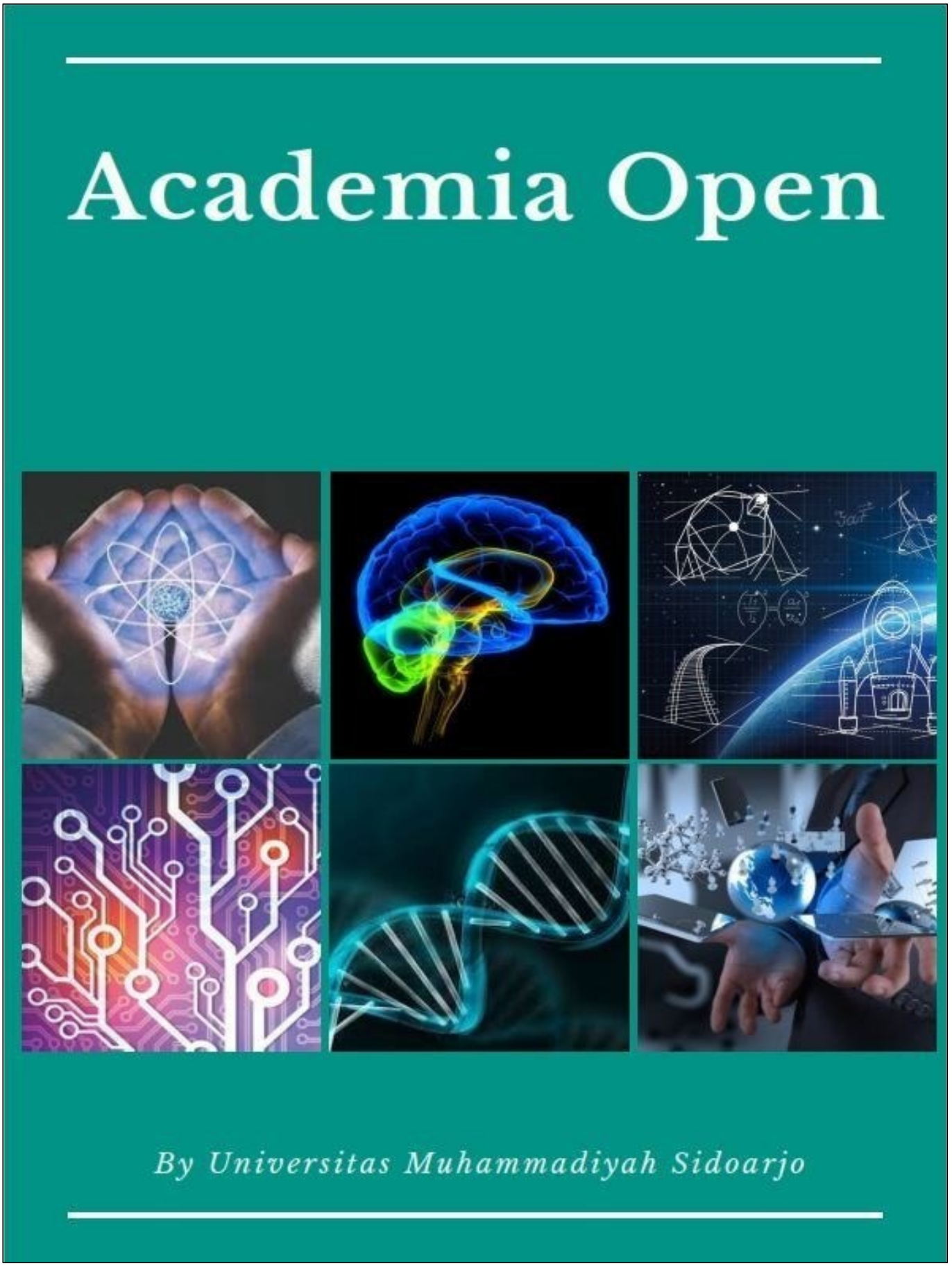
Academia Open

Vol. 10 No. 2 (2025): December DOI: 10.21070/acopen.10.2025.12842



ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open

Vol. 10 No. 2 (2025): December DOI: 10.21070/acopen.10.2025.12842

Table Of Contents

Journal Cover 1
Author[s] Statement 3
Editorial Team 4
Article information 5
Check this article update (crossmark) 5
Check this article impact 5
Cite this article 5
Title page 6
Article Title 6
Author information 6
Abstract 6
Article content 6

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open

Vol. 10 No. 2 (2025): December DOI: 10.21070/acopen.10.2025.12842

Originality Statement

The author[s] declare that this article is their own work and to the best of their knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the published of any other published materials, except where due acknowledgement is made in the article. Any contribution made to the research by others, with whom author[s] have work, is explicitly acknowledged in the article.

Conflict of Interest Statement

The author[s] declare that this article was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright Statement

Academia Open

Vol. 10 No. 2 (2025): December DOI: 10.21070/acopen.10.2025.12842

EDITORIAL TEAM

Academia Open

Vol. 10 No. 2 (2025): December DOI: 10.21070/acopen.10.2025.12842

Article information

Check this article update (crossmark)

Check this article impact (*)

Save this article to Mendeley

(*) Time for indexing process is various, depends on indexing database platform

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

Antioxidants and Their Relationship with Polycystic Ovary Syndrome: a Review Study

Israa Ali Abdul Kareem Al-Samarai, israa.a@uosamarra.edu.iq (1)

Department of Applied Chemistry, College of Applied Science, University of Samarra, Saleh Aden, Iraq

Hanan N. Mohammed, hananalabasy92@gmail.com (0)

Department of Biotechnology, College of Applied Science, University of Samarra, Saleh Aden, Iraq

(1) Corresponding author

Abstract

General Background: Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine disorder among women of reproductive age, characterized by hormonal and metabolic imbalances that impair fertility and overall health. **Specific Background:** Recent studies have emphasized the crucial role of oxidative stress in PCOS pathogenesis, where excessive reactive oxygen species (ROS) and reduced antioxidant capacity lead to cellular and molecular damage. **Knowledge Gap:** Despite extensive research on PCOS, the mechanistic link between oxidative imbalance and PCOS progression, particularly the interplay between endogenous and exogenous antioxidants, remains insufficiently understood. **Aims:** This review aims to elucidate the relationship between oxidative stress and antioxidant systems in PCOS and to identify potential therapeutic roles of antioxidants in mitigating PCOS symptoms. **Results:** The synthesis of current findings demonstrates that antioxidant deficiency correlates with increased insulin resistance, ovulatory dysfunction, and chronic inflammation in PCOS patients. Supplementation with vitamins C and E, selenium, and metformin enhances oxidative balance, improves ovarian function, and reduces metabolic risks. **Novelty:** This study integrates biochemical, metabolic, and therapeutic perspectives on antioxidant-mediated modulation of PCOS. **Implications:** Strengthening antioxidant defenses presents a promising adjunctive strategy to traditional PCOS management, potentially improving reproductive outcomes and reducing long-term comorbidities.

Highlights:

- Oxidative imbalance contributes significantly to PCOS pathogenesis.
- Antioxidant therapy improves hormonal and metabolic regulation.
- Combining antioxidants with lifestyle changes enhances treatment outcomes.

Keywords: Polycystic Ovary Syndrome, Oxidative Stress, Antioxidants, Insulin Resistance, Reproductive Health

Published date: 2025-10-30

Introduction

Many chemical reactions take place in the human body that are basically required to maintain the continuity of life, including oxidation that occurs during some biochemical processes inside the body, such as respiration, and by the action of a group of reactive oxygen species derived from oxygen, such as hydrogen peroxide and the hydroxyl radical OH, or derived from nitrogen, reactive nitrogen species, such as the nitroxyl

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

radical and the peroxy radical [1]. Reactive species are divided into two forms depending on the arrangement of electrons in the outer shell, one of which is free radicals, most of which are derived from oxygen, as 1-3% of the oxygen used in the respiration process in the mitochondria is converted into free radicals, in addition to what results from diseases and the stage of aging [2].In addition to the other non-free radical form, which is similar to free radicals in terms of the unsaturation of its outer shell with electrons, and differs from it in terms of the way these electrons spread, as they are distributed here in a double manner and do not exist in a single form like free radicals, so they are less affinity for interacting with neighboring molecules [3]. Reactive species contribute at low levels to many physiological roles and are normally generated as by-products of oxygen metabolism, but their overproduction results from exposure of the body to environmental stressors (i.e., UV and ionizing radiation, pollutants, heavy metals, and xenobiotics) [1]. As a result of the accumulation of free radicals and other oxidizing agents beyond the capacity of cellular antioxidant defenses, the oxidation and reduction signals are disrupted [4] or the cell structure and protein synthesis are disrupted, and even the genetic material is damaged [5]. Oxidizing agents are produced from two sources: one is exogenous sources, such as cigarette smoke and air pollution, and the other is endogenous sources through the electron transport chain in mitochondria, macrophages, and the endothelium of blood vessels. Under normal conditions, reactive species (ROS) and RNA act as signaling molecules to regulate physiological activities. However, in the case of chronic inflammation, excessive generation of reactive species occurs, leading to oxidative damage and destruction of many organelles and cellular processes, ultimately causing various diseases [6]. The term reactive oxygen species is a general concept that refers to a diverse group of oxidant molecules or pro-oxidants with largely different biological properties and functions, ranging from sending signals that regulate almost all biological processes within certain levels to increasing them beyond these levels, causing cell damage and the occurrence of various diseases [4]. The term ROS includes all molecules derived from oxygen, such as the superoxide radical, which is mainly produced during cellular respiration in the mitochondria, the hydroxyl radical, and hydrogen peroxide, which are also produced from several other sources, including inflammation, and cause damage to DNA as well as damage to vital molecules such as proteins and lipids [7].

1. Reactive Oxygen Species Sources

Reactive oxygen species can be divided into two groups according to their origin and source of formation:

a. Endogenous Sources

Reactive oxygen species are produced as a byproduct of metabolic processes that proceed in conjunction with oxidation-reduction reactions [8]. All living organisms have specific cellular systems capable of producing ROS, which are found in the mitochondrial membrane, cytosol, peroxisomes, and endoplasmic reticulum. The cytosol is composed of compounds such as thiols, catecholamines, and flavins, which undergo oxidation-reduction reactions and thus produce free radicals. In addition, the cytosol contains enzymes that produce ROS during their catalytic activity. Regardless of the cytosol [9]. In addition to the

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

above, free radicals can be produced from other sources, including the activity of macrophages, which increases in the presence of diseases such as diabetes [10].

b. Exogenous Sources

External sources of free radicals are related to lifestyle and exposure to various environmental factors that can increase ROS generation or reduce the capacity of endogenous antioxidants. External environmental factors include polluted air and water, cigarette smoke, medical radiation, industrial waste, sunlight, alcohol, polyunsaturated fats , and some medications. In addition to other factors such as mutagens (Xenobiotic microorganisms), Nutrient overdose, and ionizing radiation, the entry of foreign bodies through polluted air and water stimulates the immune system cells to attack them and produce free radicals to eliminate them. This leads to the accumulation of free radicals in the body. Also, the foods we eat contain chemicals similar to those used in the manufacture of pesticides and fertilizers. Some of them contain free radicals, while others can generate free radicals [11].

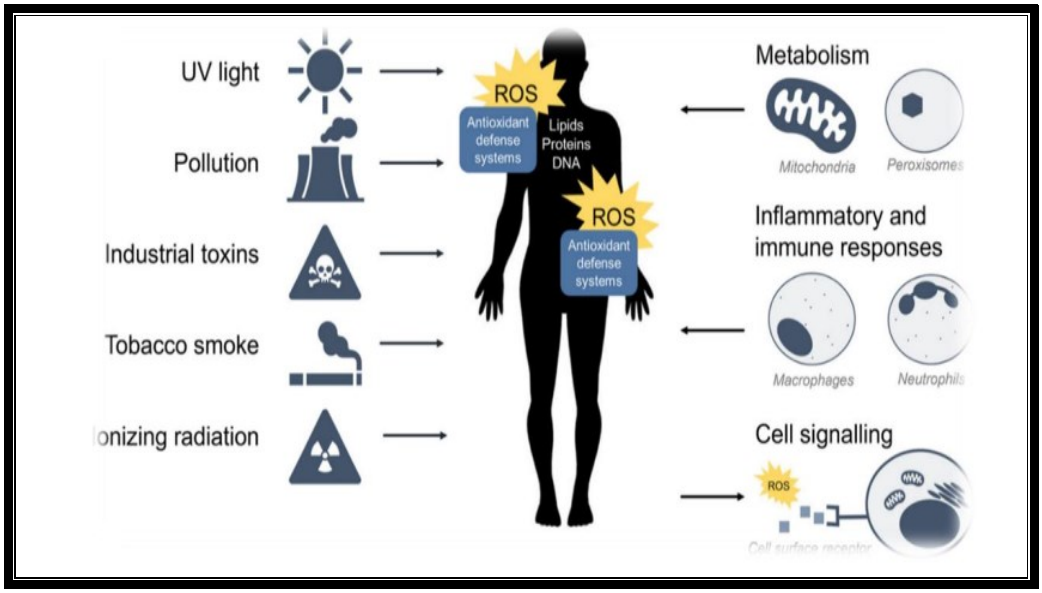


Figure 1. Some endogenous and exogenous sources of reactive oxygen species and their role in cellular signaling [12].

2. Benefits of Free Radicals

Free radicals are highly reactive and unstable molecules that can be generated in various ways and are harmful and threatening to humans through their effect on various vital molecules in the body body, including playing an important role in the human body's immune system, helping macrophage cells engulf and destroy invading pathogens, participating in energy production, cell growth, and stimulating cell division [13]. Free radicals also contribute to the mechanism of radiotherapy for some diseases, such as cancer, by attacking cancer cells and stimulating the programmed death mechanism of these cells [14].

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

a. Free Radical Damage

It is characterized by its ability to chemically modify the surrounding compounds through the oxidation of proteins and changes in amino acids, the collapse of peptide chains, enzyme inhibition, protein denaturation that leads to the loss of proteins' activity, and the auto-oxidation of glucose. DNA fragmentation, alteration of cell membrane functions, base mutation, and lipid peroxidation lead to damage to biomolecules and to cell and tissue damage with subsequent pathological effects and disorders[15]. The accumulation of free radicals plays an important role in the pathophysiology of many diseases, including Alzheimer's disease, cancer, arteriosclerosis, atherosclerosis, and retinal damage. It performs this role through two main mechanisms, one of which is the increased production of types of oxidizing agents, especially OH, ONOO, and HOCl. It works directly on the oxidation of large molecules such as membrane lipids, structural proteins, enzymes, and nucleic acids, which leads to encouraging abnormal functions and activating programmed cell death. The second mechanism occurs through its effect on redox signals, and thus the occurrence of several diseases [7] [16].

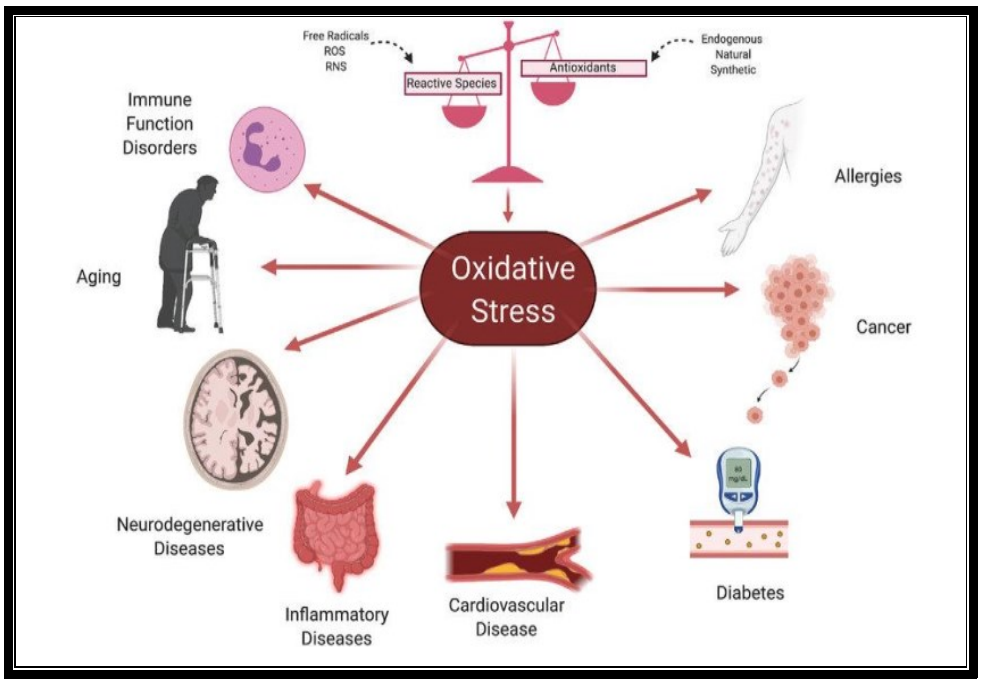


Figure 2. Some diseases resulting from oxidative stress [17]

3. Antioxidant

Antioxidant research has recently become increasingly active in various fields [18]. It examines the two types of natural antioxidants and synthetic antioxidants due to their use as nutritional supplements and functional ingredients [19]. In addition to its preventive and therapeutic role against the negative effects and diseases resulting from oxidative stress, which has greatly increased interest in it, especially in food, pharmaceutical, and cosmetic products [20] [21]. Antioxidants are defined as molecules or compounds that inhibit or delay the oxidation of biomolecules and operate at low concentrations compared to the

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

concentrations of the protected molecules [22]. By inhibiting the formation of free radicals and their ability to interact with biological targets by donating electrons, primary antioxidants achieve this, producing stable, non-reactive radical and non-radical species that can be later decomposed by enzymes and other processes [23]. Secondary antioxidants work to inhibit the activity of singlet oxygen and prevent the formation of some free radicals by inhibiting the decomposition of peroxides. They also work to bind transition metal ions and prevent them from transforming into their oxidized forms, in addition to inhibiting oxidative enzymes that can produce free radicals [24].

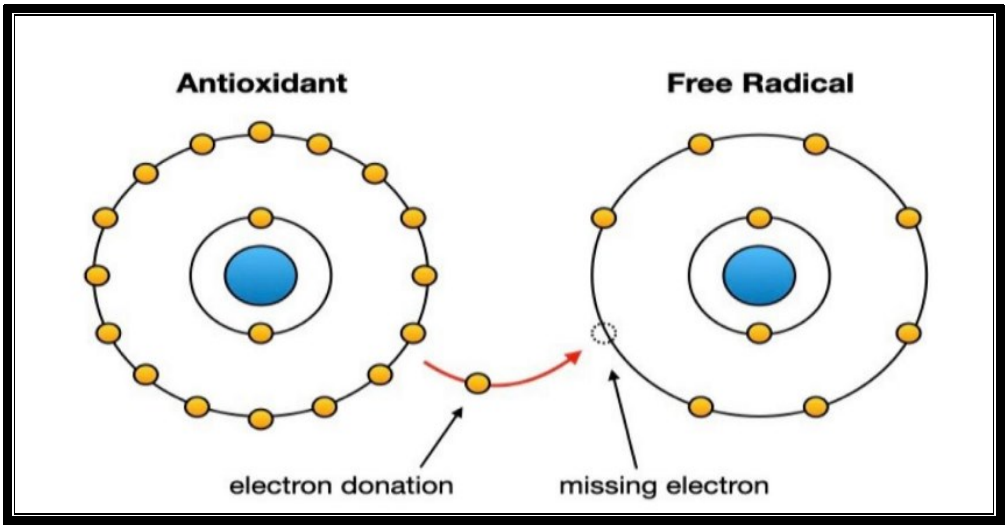


Figure 3. Antioxidants and free radicals [25]

Antioxidants are classified according to their mechanism of action as follows:

Preventive antioxidant: These antioxidants prevent or reduce the formation of free radicals. Some of them are metal-binding proteins, such as ceruloplasmin [26]. Transferrin, which prevents several minerals from participating in the formation of free radicals [27]. In addition to folic acid, which plays an important role in the chemoprevention of gastric cancer by promoting programmed death of gastric epithelial cells in patients with precancerous lesions by increasing the expression of the P53 protein, which is the main suppressor of cancerous tumors, and by protecting the genome from mutations [28]. Chain-breaking or scavenging antioxidants, also called primary antioxidants, work by scavenging unstable free radicals and converting them into more stable compounds [23]. Before causing oxidative damage, some enzymes include natural Superoxide Dismutase, Catalase, Glutathione Peroxidase, and some similar synthetic enzymes, such as Co\PMCS, which can eliminate reactive species ROS and RNS to mitigate sepsis [29].Repair antioxidant: works to repair damage caused by free radicals, such as DNA ligase enzymes [30]. RNA polymerase, which works to repair DNA from oxidative damage caused by free radicals [31]. In addition to melatonin, which works to repair mitochondrial function in bone marrow-derived stem cells by increasing mitochondrial membrane potential, increasing ATP production, and increasing the expression of respiratory chain proteins [32].

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

a. Classification of Antioxidants Depending On Origin

1) Exogenous Antioxidant

Substances that the body obtains from an external source through the diet. They act as reducing compounds that complement the work of the body's internal antioxidant systems[33]. It includes many nutrients such as vitamins and carotenes [34] and flavonoids that show distinctive biological capabilities, the most important of which is their ability as antioxidants. This is attributed to their chemical structure, which enables them to get rid of them. Plants are the main source of them, in addition to fungi and other types of living organisms[35]. It is worth noting here that the health effectiveness of external antioxidants is still in doubt due to several reasons, the most important of which is the lack of a basic understanding of the interaction of external antioxidants within the body and the lack of special measuring tools and tests to link the effectiveness of external antioxidants to health outcomes[36].

2) Endogenous Antioxidant

They are molecules produced by the body that help protect cells from damage resulting from exposure to reactive oxygen species [37]. It constitutes 80% of the total antioxidant activity in the body, although this percentage varies depending on a group of factors, the most important of which are the patient's age, gender, health condition, or comorbidity, especially among smokers, diabetics, and obese patients [38]. It plays an important role in protecting against oxidative stress through its ability to activate many antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and heme oxygenase 1, which remove reactive oxygen species and prevent oxidative damage [39].

3) Non-Enzymatic Antioxidant

They are divided into two groups, one of which is endogenous non-enzymatic antioxidants, which are known to be scavenging molecules that are formed internally and are characterized by their ability to quickly disable radicals and oxidants. The most important of these are glutathione, albumin, mineral-binding proteins, uric acid, melatonin, and polyamines. They are considered part of the internal defense mechanisms that protect cells and tissues from ROS [40]. The second group is available from external sources such as food and nutritional supplements [41]. It includes ascorbic acid, phenols, flavonoids, tocopherol, carotenoids, and carotenes [42].

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

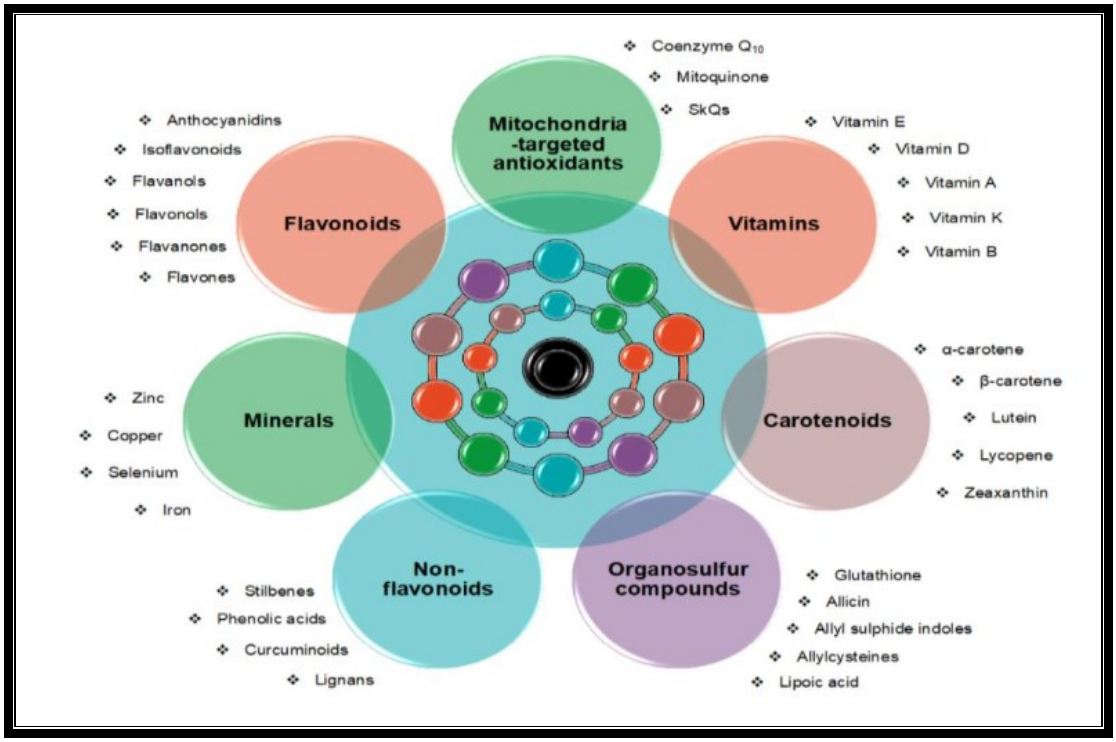


Figure 4. Non-enzymatic antioxidants [43]

Result and Discussion

A. Internal Genital Organs Polycystic Ovarian Syndrome

Polycystic ovary syndrome is known as the most common endocrine disorder. It affects women of reproductive age and is characterized by excess androgen production, affecting up to 13% of women of reproductive age. [44] PCOS is a complex multifactorial disorder caused by environmental factors in addition to genetic, hormonal, and metabolic background[45]. It is characterized by decreased ovulation, hyperandrogenism, and the presence of ovarian cysts [46]. It is associated with insulin resistance, obesity, hyperinsulinemia, high blood pressure, and dyslipidemia[47]. Despite diagnostic criteria, the medical and scientific understanding of the etiology of PCOS remains incomplete, although it does involve a complex mix of genetic, environmental, and epigenetic factors [48], with intrauterine growth of the mother possibly contributing to the development of PCOS features [49]. Excessive secretion of androgens by theca and stromal cells of the PCOS leads to the main manifestations of the syndrome [50]. Hypersecretion of LH by the pituitary gland occurs as a result of disturbances in the ovarian response to the pituitary gland and excessive pulses of GnRH from the hypothalamus. It also stimulates the secretion of testosterone by the ovary, and a decrease in FSH levels occurs or may remain constant and unchanged [51]. Insulin is a powerful stimulant for ovarian androgen secretion, which occurs via a different insulin receptor that does not exhibit insulin resistance. Therefore, insulin doubles the effect of LH and also doubles the degree of androgen excess by inhibiting the liver's production of SHBG (a glycoprotein that binds most sex steroids). Thus, free androgen is elevated,

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

excess body weight exacerbates the underlying hormonal disturbances (increased androgen and insulin levels), and clinical manifestations are evident in women with PCOS [52]. The common theories put forward to explain the pathophysiology of PCOS are:

1. Neurondocrine defects
2. Impaired ovarian steroidogenesis
3. Impaired adrenal androgen production
4. Increased sympathetic nervous system activity
5. Genetic defects [53].
6. Insulin resistance with compensatory hyperinsulinemia [53].

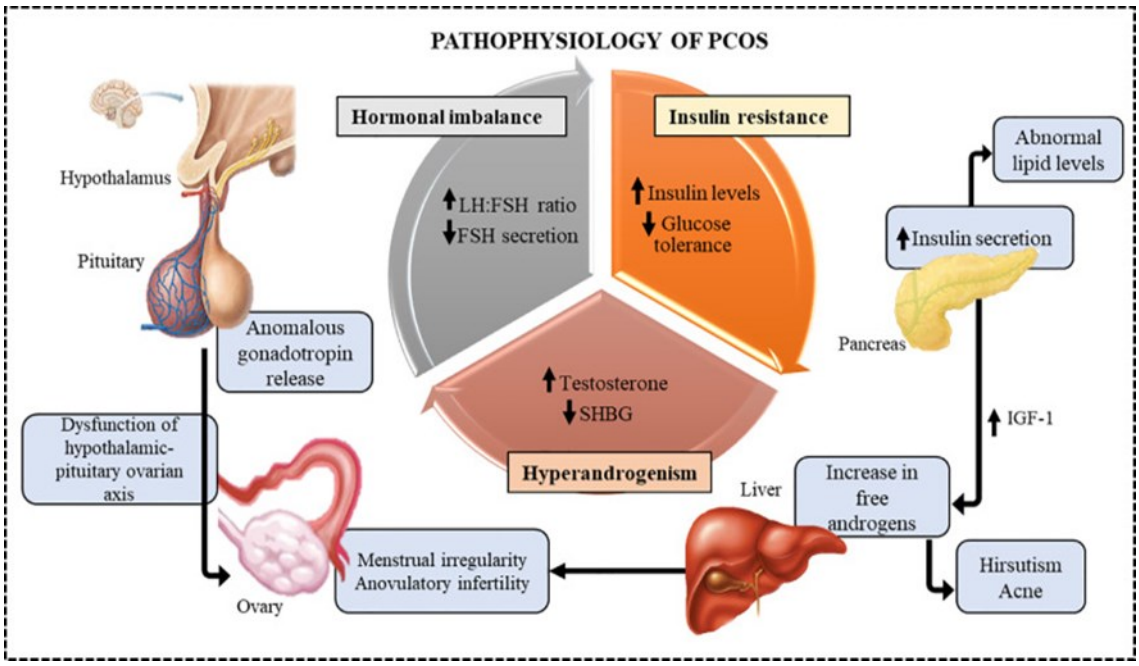


Figure 5. Pathophysiology of PCOS [53]

B. Appearance and Diagnosis of Polycystic Ovary Syndrome

The ovaries in polycystic ovaries are described as having a dilated and taut spherical shape. Histologically, they are characterized by the presence of multiple cysts, rarely larger than 15 mm. These cysts are arranged beneath the layer of enlarged theca cells. It has been noted that the tunica albuginea (the collagen-rich lining located directly beneath the epithelial layer of the ovarian surface) is much wider than in normal ovaries and may be torn [54]. Also, in the case of polycystic ovary syndrome, the ovaries are devoid of the corpus luteum [55], and PCOS can be detected and diagnosed by ultrasound examination (Figure 1-2). For a woman to be considered to have PCOS, it is necessary to have at least one ovary containing 12 or more follicles with a diameter of 2 to 9 mm or an increase in ovarian volume of more than 10 ml [56].

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

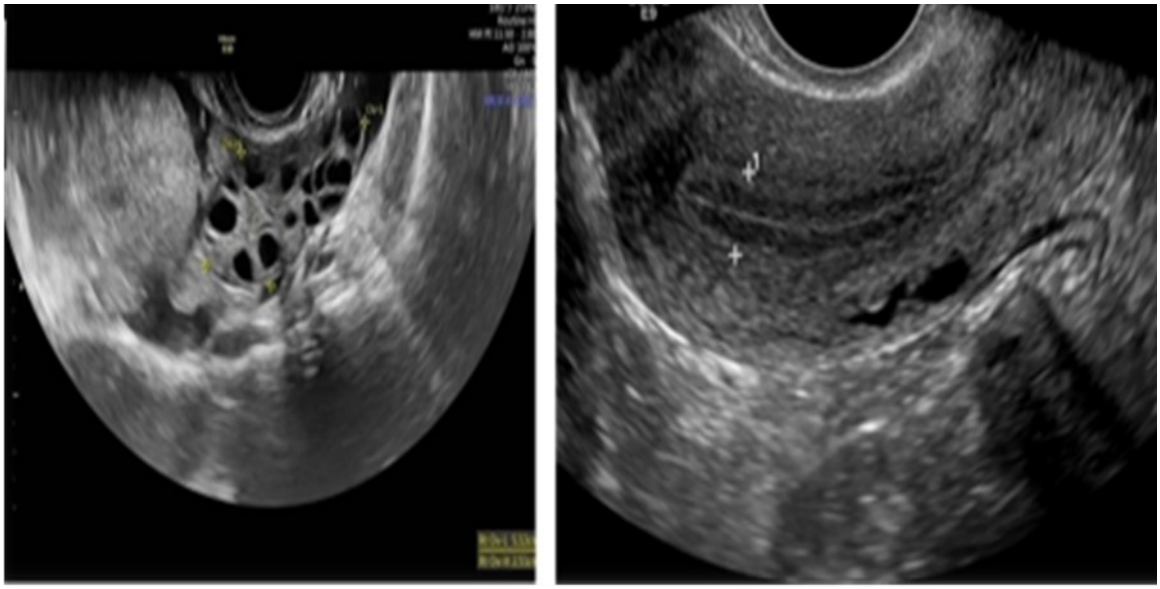


Figure 6. Comparison between a normal ovary and a polycystic ovary using ultrasound [57]

Signs are used as a basis for diagnosing the syndrome: irregular menstrual cycles, ultrasound, and blood tests for reproductive hormones E2 and FSH will be normal or low with PCOS, and LH will be elevated. In addition, there are external symptoms such as acne and hirsutism [58].

C. Treatment of Polycystic Ovary Syndrome

1. Lifestyle changes: Increasing daily activity along with eating a diet rich in fiber and low in sugars will help reduce excess weight and maintain a healthy waist circumference, thus eliminating the syndrome and its symptoms [59].
2. Medical treatment and the most important treatments used below
3. Metformin is a type of drug that helps stimulate ovulation and egg formation. It lowers blood glucose levels by increasing insulin sensitivity without increasing insulin concentration. It also improves and regulates the menstrual cycle and reduces miscarriage in women with polycystic ovary syndrome [60].
4. Clomid (Clomiphene citrate) is one of the ovulation medications and the most common treatment for polycystic ovary syndrome. It helps stimulate the process of egg formation, follicle growth, and doubling their number [61].

D. Oxidative Stress

Oxidative stress is associated with PCOS, as an increase indicates an imbalance between oxidants and antioxidants in women with PCOS [62]. Low antioxidant levels and increased oxidative stress associated with insulin resistance suggest that women with PCOS may be exposed to oxidative stress. This plays a role in the pathophysiology of the syndrome and may therefore be a contributing factor to the risk of cardiovascular disease[63].

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

Oxidative stress is a condition resulting from an imbalance between antioxidants and reactive oxygen species plays a role in a variety of diseases, including polycystic ovary syndrome and endometriosis. Consequently, mitochondrial mutations lead to impaired oxidative phosphorylation, decreased ATP production, and increased production of reactive oxygen species [64]. Unlike nuclear DNA, which is found in the cell nucleus and is inherited from both parents, mitochondrial DNA is inherited from the mother only [65]. Due to its unique genetic pattern, mitochondrial DNA can be used to determine maternal lineages. It is less susceptible to genetic replication and has a higher mutation rate than DNA, making it useful for analyzing the evolution and history of populations [66]. Any defect in the concentration of mitochondrial DNA replication affects the figuration of many mutations, while mitochondrial DNA shows a deficiency in histone protection and DNA damage repair systems [67]. In fact, previous studies have shown that mitochondrial DNA mutations contribute to several diseases, including PCOS [68].

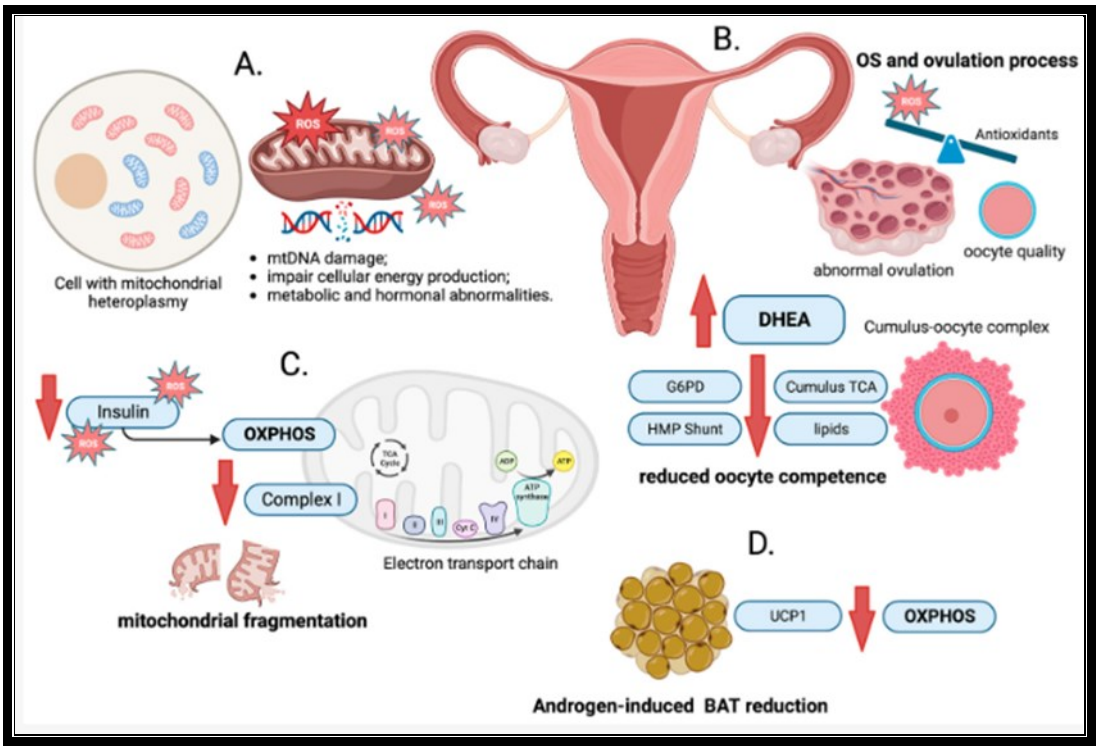


Figure 7. The association between oxidative stress and polycystic ovary syndrome

Menopause has been found to hurt ovarian follicles, disrupting their normal growth and maturation. Excessive levels of reactive oxygen species can damage oocytes and granulosa cells within follicles, negatively impacting their quality and fertility [65]. Almost 20 years ago, data revealed elevated OS concentrations and decreased antioxidant capacity in women with polycystic ovary syndrome [69]. Especially in women with PCOS associated with obesity or metabolic syndrome [70] [71]. A study has shown that oxidative stress enhances the activity of steroidogenic enzymes in the ovary and stimulates the secretion of androgens [72].

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

The regulation of ovulation is influenced by fluctuating concentrations of gonadotropins, particularly FSH and LH, secreted by the pituitary gland [73]. Some researchers have described the role of reactive oxygen species in the ovulation process. The increased secretion of luteinizing hormone before ovulation leads to the Release of inflammatory substances within the ovary [73]. This leads to an overproduction of reactive oxygen species. Elevated concentration of reactive oxygen species plays a crucial role in key aspects of the ovulation process, including cumulus cell expansion, progesterone production, the expression of preovulatory genes, and the activation of ovulatory signals [74]. Antioxidants have been studied for their importance in treating polycystic ovary syndrome[75]. It was found that vitamins C and E work to reduce reactive oxygen species by protecting cells from oxidative damage. [76] [77] These vitamins may support ovarian function and hormonal balance. Vitamin supplements are effective in reducing lipid levels in women with PCOS. [78] [79] Metformin has been shown to have anti-inflammatory effects, contributing to reduced inflammation through its antioxidant properties [80]. Metformin has also been found to have protective effects on endothelial cells due to its antioxidant properties [81]. Selenium can also modulate immune responses and inflammation. Therefore, chronic low-grade inflammation is associated with polycystic ovary syndrome, and selenium's anti-inflammatory effects may contribute to improving its symptoms[82] [83]. Oxidative stress is one of the stress factors that contribute to the pathogenesis of PCOS. It is important to note that oxidative stress in PCOS may be linked to numerous disorders and diseases, including insulin resistance, hyperandrogenism, obesity, chronic inflammation, cardiovascular disease, and cancer. [84]

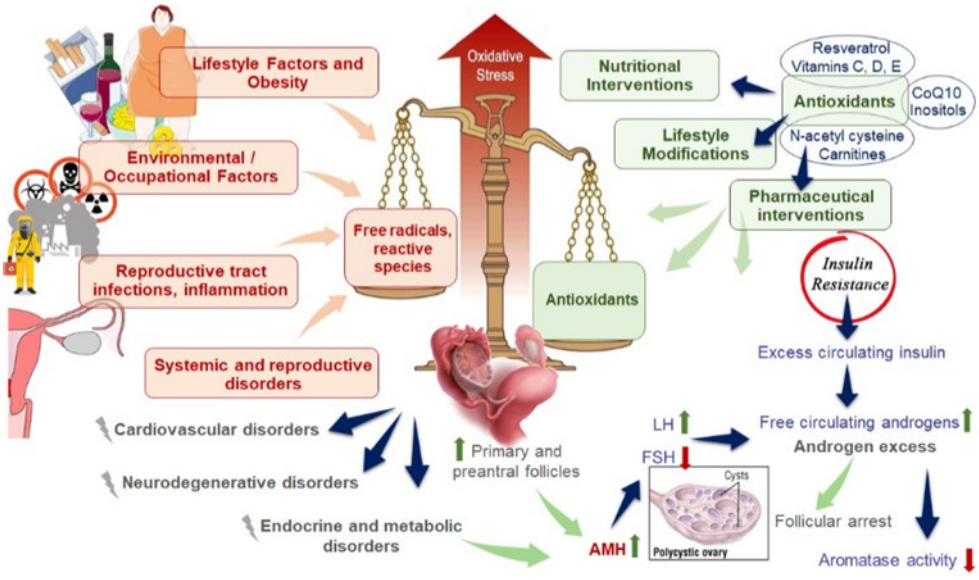


Figure 8. Mechanistic pathophysiology of polycystic ovary syndrome and its relationship to oxidative stress

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

E. Glutathione and Polycystic Ovary Syndrome

Glutathione is the most abundant low molecular weight thiol within cells and body tissues that plays a key role in many cellular processes, including its antioxidant action, its role in regulating protein function and stability, gene expression, cell proliferation, and the regulation of intercellular signaling [85]. It is one of the important non-enzymatic antioxidants that is produced inside the body [86]. It consists of three amino acids: glutamate, cysteine, and glycine. Its antioxidant activity is distinguished by its containing the thiol group of cysteine [87].

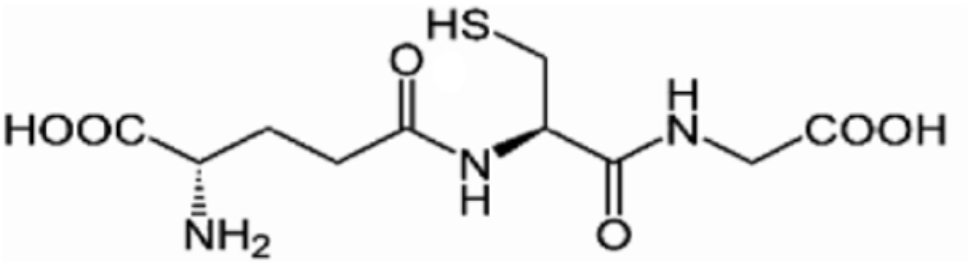


Figure 9. Chemical structure of glutathione [88]

A study has shown that glutathione levels are significantly lower in patients with polycystic ovary syndrome (PCOS). Low levels may be indirectly linked to insulin resistance. Low glutathione levels may also be a result of increased glucose utilization under hyperglycemic conditions. It was reported that the presence of impaired mitochondrial function in patients with PCOS is evident from a decrease in mitochondrial oxygen consumption and, consequently, a decrease in glutathione levels and a weakening of the plasma membrane potential [89].

F. Superoxide Dismutase and Polycystic Ovary Syndrome

It is a functional antioxidant enzyme for physiological defense strategies in animals and plants against free radicals and reactive oxygen species resulting from biotic and abiotic stress [90]. It consists of proteins and mineral cofactors [91] that catalyze the dissociation of superoxide radicals into hydrogen peroxide and oxygen. Superoxide dismutase proteins form the first line of defense against damage caused by reactive oxygen species [92]. A study has shown that SOD enzymes constitute an important antioxidant defense against oxidative stress in the body. The enzyme works as a good therapeutic agent against diseases caused by reactive oxygen species. It describes the therapeutic effects of superoxide dismutase in various physiological and pathological conditions. Such as cancer, inflammatory diseases, cystic fibrosis, stroke, aging, rheumatoid arthritis, diabetes, and polycystic ovary syndrome [93].

The balance between active oxygen radicals and antioxidants greatly affects reproductive activities, such as changes in the endometrium in the different luteal phases, follicle formation, ovulation, fertilization,

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

conception, placental development, and embryogenesis [94]. However, under conditions of oxidative stress, impaired reproduction and fertility may occur. Including ovarian dysfunction, deterioration in the number of eggs, and growth disorders. It is also noted that antioxidants play an important role in the functions of the female reproductive system. Therefore, polycystic ovary syndrome is associated with a decrease in the concentration of antioxidants, which indicates an increase in oxidative stress [95].

Serum SOD activity may be a clinical marker for identifying systemic oxidative stress in PCOS Study [96] indicated an increase in the concentration of SOD in the blood serum of patients with the syndrome, and that the widespread signs of oxidative stress are abnormal in women with polycystic ovary syndrome, regardless of excess weight.

G. Catalase Activity and Polycystic Ovary Syndrome

They are mineral antioxidant enzymes essential for life. They contribute to the process of oxygen metabolism inside cells and regulate hydrogen peroxide by accelerating its decomposition and reduction into water and oxygen [97], as in the figure.

This group of enzymes performs its function in reducing hydrogen peroxide resulting from the activity of SOD into water and lowering its level to the normal level, in cooperation with peroxidase. Antioxidant levels have been linked to polycystic ovary syndrome. Reduced catalase activity has been found in PCOS patients. This decrease is due to increased hydrogen peroxide production and elevated malondialdehyde concentrations, which can disrupt several enzymes associated with the plasma membrane. The increase in the intake of lipid peroxides may be associated with a deficiency of the enzyme superoxide dismutase in the body tissues, and the decrease in the activity of the enzyme catalase may be due to enzyme depletion as a result of oxidative stress [98].

H. Malondialdehyde and Polycystic Ovarian Syndrome

Malondialdehyde (MDA) is one of the end products of unsaturated fatty acid oxidation and lipid peroxidation [99] [100]. Lipids are among the most biomolecules exposed to oxidative stress, and MDA is the main product of lipid peroxidation. It is a toxic molecule and should be considered not only as a marker of lipid peroxidation, but it can also interact with proteins and DNA, leading to oxidative stress [101] [102].MDA levels are a good indicator of the level of lipid peroxidation and a biomarker of some diseases, especially atherosclerosis. The end products of lipid peroxidation were used as the best and easiest way to measure them through their products [103]. Malondialdehyde represents 20% of the end products derived from lipid peroxidation, and it is characterized by stability and a long half-life compared to other peroxidation products, so MDA is considered an indicator of the occurrence of oxidation [104].

Several studies have found a relationship between malondialdehyde levels and polycystic ovary syndrome [105]. Patients with PCOS have been found to have elevated levels, which may be due to fatty tissue. Malondialdehyde is an end product of lipid oxidation and a hallmark of damage resulting from oxidative

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

stress, which increases ROS production in patients with polycystic ovary syndrome [106]. Its concentration may also increase as a result of a decrease in the estrogen hormone, as estrogen acts as an antioxidant by scavenging free radicals due to the presence of the phenol hydroxyl group [107]. In the synthesis of estrogen [108], it has been proven that estradiol regulates the gene expression of antioxidant systems, including superoxide dismutase, by activating the mitogen-activated protein kinase signaling pathway, which is another example of the antioxidant effects of estrogen [109]. A study found that there is a close link between oxidative stress and inflammatory factors. It is difficult to distinguish inflammation from oxidative stress. An elevated level of tumor necrosis factor was found in women with PCOS compared to the normal rate [110]. Inflammation activates reactive oxygen species by activating redox-sensitive transcription factors such as nuclear factor-kappa-B, adaptor protein-1, and hypoxia-inducible factor-1, which regulate the expression of inflammatory cytokines, leading to increased oxidative stress [111].

Reactive oxygen species may negatively affect oocytes by using oxygen to produce energy, causing oxidative phosphorylation of mitochondria and thus damaging them [112]. What increases the oxidation state is that the egg membranes contain high levels of unsaturated fatty acids, which are usually sensitive to oxidation compounds when they are available in the environment, causing damage to the egg through the process of lipid peroxidation. This oxidation can lead to functional and structural changes in the eggs, causing their damage [113]. Reactive oxygen radicals also impede embryonic development in the early stages after fertilization by negatively affecting key cellular organelles required for rapid cell division [114]. It has been observed that reactive oxygen species contribute to the loss of sensitivity of granulosa cells to LH and FSH hormones, thus preventing steroid synthesis and damaging the DNA of ovarian endothelial cells or causing programmed cell death. Also, the increase in MDA levels causes obstruction of the activity of the antioxidant superoxide dismutase system and depletion of glutathione in the eggs. The effect of oxidative stress on the follicles directly harms the defensive role of antioxidants and hinders the eggs, and may lead to damage to the egg DNA, which leads to fertility disorders such as repeated miscarriages and congenital malformations in the living fetus [115]. Physiological levels of reactive oxygen species are required for the proper functioning of various biological pathways and for maintaining balance within the human body. Low levels of free radicals act as modifiers in female reproductive pathways such as egg maturation, physiological follicle atresia, egg fertilization, and the formation and dissolution of the corpus luteum during pregnancy [116]. At puberty, the monthly maturation of the parenchymal follicle into a Graafian follicle occurs, and normal concentration of reactive oxygen species helps in the resumption of meiosis as well as in the development of the dominant oocyte. It has been proven that increased concentrations of antioxidants prevent this process [117].

Conclusion

Oxidative stress has also been found to play a pivotal role in the development of this syndrome. The accumulation of free radicals and low levels of antioxidants leads to an oxidative imbalance, which

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

contributes to insulin resistance, ovulation disorders, poor egg quality, and increased levels of chronic low-grade inflammation. This is also associated with an increased risk of many of the diseases associated with the syndrome. Therefore, high antioxidant levels are the primary line of defense against free radicals and their damage. Therefore, introducing antioxidants, whether enzymatic or non-enzymatic, can improve tissue response to insulin. It reduces markers of inflammation and supports ovarian health by improving the egg environment and maturation. Therefore, enhancing antioxidants is a promising strategy to support conventional treatment for PCOS, especially when combined with lifestyle changes such as physical activity and a balanced diet.

References

[1] G. Pizzino, N. Irrera, M. Cucinotta, et al., “Oxidative Stress: Harms and Benefits for Human Health,” Oxidative Medicine and Cellular Longevity, 2017, Art. no. 8416763.

[2] M. Valko, D. Leibfritz, J. Moncol, et al., “Free Radicals and Antioxidants in Normal Physiological Functions and Human Disease,” International Journal of Biochemistry & Cell Biology, vol. 39, no. 1, pp. 44–84, 2007.

[3] C. E. Ofoedu, L. You, and C. M. Osuji, “Hydrogen Peroxide Effects on Naturally-Sourced Polysaccharides: Free Radical Formation/Production, Degradation Process, and Reaction Mechanism—A Critical Synopsis,” Foods, vol. 10, no. 4, p. 699, 2021.

[4] H. Sies, V. V. Belousov, and N. S. Chandel, “Defining Roles of Specific Reactive Oxygen Species (ROS) in Cell Biology and Physiology,” Nature Reviews Molecular Cell Biology, vol. 23, no. 7, pp. 499–515, 2022.

[5] S. Anand and N. Bharadvaja, “Potential Benefits of Nutraceuticals for Oxidative Stress Management,” Revista Brasileira de Farmacognosia, vol. 32, no. 2, pp. 211–220, 2022.

[6] L. E. de Groot, T. A. van der Veen, and F. O. Martinez, “Oxidative Stress and Macrophages: Driving Forces Behind Exacerbations of Asthma and Chronic Obstructive Pulmonary Disease?,” American Journal of Physiology—Lung Cellular and Molecular Physiology, vol. 316, no. 2, pp. L369–L384, 2021.

[7] H. J. Forman and H. Zhang, “Targeting Oxidative Stress in Disease: Promise and Limitations of Antioxidant Therapy,” Nature Reviews Drug Discovery, vol. 20, no. 9, pp. 689–709, 2021.

[8] A. T. Alahmar, “Role of Oxidative Stress in Male Infertility: An Updated Review,” Journal of Human Reproductive Sciences, vol. 12, no. 1, pp. 4–18, 2019.

[9] S. Di Meo and P. Venditti, “Evolution of the Knowledge of Free Radicals and Other Oxidants,” Oxidative Medicine and Cellular Longevity, vol. 2020, Art. no. 9829176.

[10] I. Marrocco, F. Altieri, and I. Peluso, “Measurement and Clinical Significance of Biomarkers of Oxidative Stress in Humans,” Oxidative Medicine and Cellular Longevity, vol. 2017, Art. no. 8416763.

[11] R. J. Bloomer and A. H. Goldfarb, “Anaerobic Exercise and Oxidative Stress: A Review,” Canadian Journal of Applied Physiology, vol. 29, pp. 245–263, 2004.

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

[12] V. Ngo and M. L. Duennwald, "Nrf2 and Oxidative Stress: A General Overview of Mechanisms and Implications in Human Disease," Antioxidants, vol. 11, no. 12, p. 2345, 2022.

[13] N. Gadoth and H. Göbel, Oxidative Stress and Free Radical Damage in Neurology, in Oxidative Stress in Applied Basic Research and Clinical Practice, Totowa, NJ: Humana Press, 2011, p. 323.

[14] J. L. Martindale and N. J. Holbrook, "Cellular Response to Oxidative Stress: Signaling for Suicide and Survival," Journal of Cellular Physiology, vol. 192, no. 1, pp. 1–15, 2002.

[15] R. Kohen and A. Nyska, "Oxidation of Biological Systems: Oxidative Stress and Antioxidants," Toxicologic Pathology, vol. 30, pp. 620–630, 2002.

[16] B. E. Domènech and G. Marfany, "The Relevance of Oxidative Stress in the Pathogenesis and Therapy of Retinal Dystrophies," Antioxidants, vol. 9, no. 4, p. 347, 2020.

[17] E. Fleming and Y. Luo, "Co-Delivery of Synergistic Antioxidants from Food Sources for the Prevention of Oxidative Stress," Journal of Agriculture and Food Research, vol. 3, p. 100107, 2021.

[18] F. Xiao, T. Xu, and B. Lu, "Guidelines for Antioxidants Assays for Food Components," Food Frontiers, vol. 1, no. 1, pp. 60–69, 2020.

[19] M. Parcheta, R. Świsłocka, and S. Orzechowska, "Recent Developments in Ineffective Antioxidants: The Structure and Antioxidant Properties," Materials, vol. 14, no. 8, p. 1984, 2021.

[20] İ. Gülçin, "Antioxidants and Antioxidant Methods: An Updated Overview," Archives of Toxicology, vol. 94, no. 3, pp. 651–715, 2020.

[21] A. Marino, M. Battaglini, and N. Moles, "Natural Antioxidant Compounds as Potential Pharmaceutical Tools Against Neurodegenerative Diseases," ACS Omega, vol. 7, no. 30, pp. 25974–25990, 2022.

[22] A. M. Pisoschi, A. Pop, and F. Iordache, "Antioxidant Determination with the Use of Carbon-Based Electrodes," Chemosensors, vol. 9, no. 4, p. 72, 2021.

[23] L. P. Calegari, J. Barbosa, and G. A. Marodin, "A Conjoint Analysis to Consumer Choice in Brazil: Defining Device Attributes for Recognizing Customized Foods Characteristics," Food Research International, vol. 109, pp. 1–13, 2018.

[24] A. M. Pisoschi, A. Pop, and F. Iordache, "Oxidative Stress Mitigation by Antioxidants—An Overview on Their Chemistry and Influences on Health Status," European Journal of Medicinal Chemistry, vol. 209, p. 112891, 2021.

[25] F. Inchingolo, A. M. Inchingolo, and G. Latini, "Oxidative Stress and Natural Products in Orthodontic Treatment: A Systematic Review," Nutrients, vol. 16, no. 1, p. 113, 2023.

[26] Z. Liu, M. Wang, and C. Zhang, "Molecular Functions of Ceruloplasmin in Metabolic Disease Pathology," Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, pp. 695–711, 2022.

[27] K. Bigot, P. Gondouin, and R. Bénard, "Transferrin Non-Viral Gene Therapy for Treatment of Retinal Degeneration," Pharmaceutics, vol. 12, no. 9, p. 836, 2020.

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

[28] J. P. Merlin, H. P. Rupasinghe, and G. Dellaire, "Role of Dietary Antioxidants in p53-Mediated Cancer Chemoprevention and Tumor Suppression," Oxidative Medicine and Cellular Longevity, vol. 2021, Art. no. 9924328.

[29] M. Liu, X. Sun, and B. Chen, "Insights into Manganese Superoxide Dismutase and Human Diseases," International Journal of Molecular Sciences, vol. 23, no. 24, p. 15893, 2022.

[30] P. Nguyen-Powanda and B. Robaire, "Aging and Oxidative Stress Alter DNA Repair Mechanisms in Male Germ Cells of Superoxide Dismutase-1-Null Mice," Biology of Reproduction, vol. 105, no. 4, pp. 944–957, 2021.

[31] P. Sykora, S. Kanno, and M. Akbari, "DNA Polymerase Beta Participates in Mitochondrial DNA Repair," Molecular and Cellular Biology, vol. 37, no. 16, e00237, 2017.

[32] C. Gu, Q. Zhou, and X. Hu, "Melatonin Rescues the Mitochondrial Function of Bone Marrow-Derived Mesenchymal Stem Cells and Improves the Repair of Osteoporotic Bone Defect in Ovariectomized Rats," Journal of Pineal Research, vol. 76, no. 1, e12924, 2024.

[33] J. Bouayed and T. Bohn, "Exogenous Antioxidants—Double-Edged Swords in Cellular Redox State: Health Beneficial Effects at Physiologic Doses Versus Deleterious Effects at High Doses," Oxidative Medicine and Cellular Longevity, vol. 3, no. 4, pp. 228–237, 2010.

[34] O. O. Sinbad, A. A. Folorunsho, and O. L. Olabisi, "Vitamins as Antioxidants," Journal of Food Science and Nutrition Research, vol. 2, no. 3, pp. 214–235, 2019.

[35] A. R. Silva, T. C. Finimundy, and L. Barros, "Antioxidant Methodology: Approaches to Activity Determination," in Handbook of Antioxidant Methodology, P. D. Prenzler, D. Ryan, and K. Robards, Eds., Cambridge, UK: Royal Society of Chemistry, 2021, pp. 203–245.

[36] R. R. Kotha, F. S. Tareq, and E. Yildiz, "Oxidative Stress and Antioxidants—A Critical Review on In Vitro Antioxidant Assays," Antioxidants, vol. 11, no. 12, p. 2388, 2022.

[37] Z. Wang, M. Liang, and H. Li, "Methionine Activates Nrf2-ARE Pathway to Induce Endogenous Antioxidant Activity for Depressing ROS-Derived Oxidative Stress in Growing Rats," Journal of the Science of Food and Agriculture, vol. 99, no. 10, pp. 4849–4862, 2019.

[38] B. J. Mathis, H. Kato, and Y. Matsuishi, "Endogenous and Exogenous Protection from Surgically Induced Reactive Oxygen and Nitrogen Species," Surgery Today, vol. 54, no. 1, pp. 1–13, 2024.

[39] L. Han, Q. Yang, and W. Ma, "Protocatechuic Acid Ameliorated Palmitic-Acid-Induced Oxidative Damage in Endothelial Cells through Activating Endogenous Antioxidant Enzymes via an AMPK-Dependent Pathway," Journal of Agricultural and Food Chemistry, vol. 66, no. 40, pp. 10400–10409, 2018.

[40] I. Mironczuk-Chodakowska, A. M. Witkowska, and M. E. Zujko, "Endogenous Non-Enzymatic Antioxidants in the Human Body," Advances in Medical Sciences, vol. 63, no. 1, pp. 68–78, 2018.

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

[41] Z. Moussa, Z. M. Judeh, and S. A. Ahmed, "Nonenzymatic Exogenous and Endogenous Antioxidants," Free Radical Medicine and Biology, vol. 1, pp. 11–22, 2019.

[42] B. P. Kuti and O. A. Oyelami, "Serum Nonenzymatic Antioxidants in Nigerian Children with Severe Pneumonia: Association with Complications and Hospital Outcomes," Pediatric Respirology and Critical Care Medicine, vol. 4, no. 1, p. 2, 2020.

[43] A. Varesi, L. I. M. Campagnoli, and A. Carrara, "Non-Enzymatic Antioxidants Against Alzheimer's Disease: Prevention, Diagnosis and Therapy," Antioxidants, vol. 12, no. 1, p. 180, 2023.

[44] C. E. Pirotta, A. Mousa, and L. Moran, "Providing Lifestyle Advice to Women with PCOS: An Overview of Practical Issues Affecting Success," Nutrients, 2021, pp. 1–12.

[45] G. Creatsas and E. Deligeoroglou, "Polycystic Ovarian Syndrome in Adolescents," Current Opinion in Obstetrics and Gynecology, vol. 19, no. 5, pp. 420–426, 2023.

[46] M. Jaripur, H. Ghasemi-Tehrani, and G. Askari, "The Effects of Magnesium Supplementation on Abnormal Uterine Bleeding, Alopecia, Quality of Life, and Acne in Women with Polycystic Ovary Syndrome: A Randomized Clinical Trial," Reproductive Biology and Endocrinology, vol. 20, no. 1, pp. 1–11, 2022.

[47] I. Kowalska, "Changes in Metabolic Profile in the Women with a History of PCOS — A Long-Term Follow-Up Study," Journal of Clinical Medicine, 2020.

[48] A. Wawrzkiewicz-Jałowiecka, "In Search of New Therapeutics—Molecular Aspects of the PCOS Pathophysiology: Genetics, Hormones, Metabolism and Beyond," International Journal of Molecular Sciences, vol. 21, no. 19, pp. 1–24, 2020.

[49] K. Nahar, "Polycystic Ovary Syndrome in Teenage and Young Women," Journal of Bangladesh College of Physicians and Surgeons, vol. 37, no. 2, pp. 78–82, 2019.

[50] S. Panchal and C. B. Nagori, "Sonographic Panorama of PCOS to Explain Its Endocrinal Orchestra," International Journal of Human Reproduction Research and Development, vol. 1, no. 1, pp. 27–38, 2021.

[51] G. Bozdag, S. Mumusoglu, and D. Zengin, "The Prevalence and Phenotypic Features of Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis," Human Reproduction, vol. 31, no. 12, pp. 2841–2855, 2016.

[52] L. S. S., H. S. K., V. R. E., N. R. J., T. H. J., and M. L. J., "Lifestyle Changes in Women with Polycystic Ovary Syndrome (Review)," Biomedical Reports, 2019.

[53] J. Bulsara, P. Patel, A. Soni, and S. Acharya, "A Review: Brief Insight into Polycystic Ovarian Syndrome," Endocrine and Metabolic Science, vol. 3, no. 2, p. 100085, 2021.

[54] N. Alhalabi, M. M. Alhalabi, S. Alsamawi, and M. Alhalabi, "Ovulation Stigma and Rupture of Ovarian Tunica Albuginea in a Patient with Polycystic Ovary Syndrome (Video)," Journal of Surgical Case Reports, vol. 2021, no. 10, rjab482, 2021.

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

[55] A. Guscott, A. Deslandes, and N. Parange, "Australasian Sonographers' Knowledge, Awareness, and Attitudes Towards the International Evidence-Based Guidelines for the Diagnosis of Polycystic Ovarian Syndrome," Australasian Journal of Ultrasound in Medicine, vol. 26, no. 2, 2023.

[56] A. T. Brinca, "Follicular Fluid: A Powerful Tool for the Understanding and Diagnosis of Polycystic Ovary Syndrome," Biomedicines, vol. 10, no. 6, pp. 1–27, 2022.

[57] A. K. M. Salman Hosain, M. H. K. Mehedi, and I. E. Kabir, "PCONet: A Convolutional Neural Network Architecture to Detect Polycystic Ovary Syndrome (PCOS) from Ovarian Ultrasound Images," in Proc. 8th Int. Conf. Engineering and Emerging Technology (ICEET), pp. 27–28, 2022.

[58] E. Khashchenko, "The Relevant Hormonal Levels and Diagnostic Features of Polycystic Ovary Syndrome in Adolescents," Journal of Clinical Medicine, vol. 9, no. 6, pp. 1–12, 2020.

[59] J. Parker, "Polycystic Ovary Syndrome: An Evolutionary Adaptation to Lifestyle and the Environment," International Journal of Environmental Research and Public Health, vol. 19, no. 3, p. 1336, 2022.

[60] A. S. Chouhan, "Advance Research on Polycystic Ovary Syndrome (PCOS)," Journal of Women's Healthcare and Midwifery Research, vol. 1, no. 2, pp. 1–5, 2022.

[61] T. Girase, "Clomiphene Citrate as Nanomedicine Assistance in Ovulatory Disorders and Its Hyphenated Techniques," Materials Proceedings, vol. 14, 2023.

[62] N. K. Kuscu and A. Var, "Oxidative Stress but Not Endothelial Dysfunction Exists in Non-Obese, Young Group of Patients with Polycystic Ovary Syndrome," Acta Obstetricia et Gynecologica Scandinavica, vol. 88, no. 5, pp. 612–617, 2009.

[63] S. B. Al-Takriti, "The Role of Hepcidin Hormone and Some Biochemical Variables in the Sera of Patients with Polycystic Ovary Syndrome in Kirkuk," Ph.D. dissertation, College of Science, Tikrit Univ., Iraq, 2017.

[64] M. Ciebiera and E. E. Hennig, "Polycystic Ovary Syndrome and Oxidative Stress—From Bench to Bedside," International Journal of Molecular Sciences, vol. 24, no. 18, p. 14126, 2023.

[65] R. Asally, R. Markham, and F. Manconi, "Mitochondrial DNA Haplogroup H Association with Endometriosis and Possible Role in Inflammation and Pain," Journal of Endometriosis and Pelvic Pain Disorders, vol. 12, pp. 158–164, 2020.

[66] P. Kowalczyk, D. Sulejczak, and P. Kleczkowska, "Mitochondrial Oxidative Stress—A Causative Factor and Therapeutic Target in Many Diseases," International Journal of Molecular Sciences, vol. 22, p. 13384, 2021.

[67] G. Hudson, P. Amati-Bonneau, and E. L. Blakely, "Mutation of OPA1 Causes Dominant Optic Atrophy with External Ophthalmoplegia, Ataxia, Deafness and Multiple Mitochondrial DNA Deletions: A Novel Disorder of MtDNA Maintenance," Brain, vol. 131, pp. 329–337, 2008.

[68] N. Zeber-Lubecka, M. Ciebiera, and E. E. Hennig, "Polycystic Ovary Syndrome and Oxidative Stress—From Bench to Bedside," International Journal of Molecular Sciences, vol. 24, no. 18, p. 14126, 2023.

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

[69] A. Stejskalova, "In Vitro Modelling of the Physiological and Diseased Female Reproductive System," Acta Biomaterialia, pp. 1–59, 2021.

[70] T. Sabuncu, H. Vural, and M. Harma, "Oxidative Stress in Polycystic Ovary Syndrome and Its Contribution to the Risk of Cardiovascular Disease," Clinical Biochemistry, vol. 34, pp. 407–413, 2001.

[71] S. Mahalingaiah and E. Diamanti-Kandarakis, "Targets to Treat Metabolic Syndrome in Polycystic Ovary Syndrome," Expert Opinion on Therapeutic Targets, vol. 19, pp. 1561–1574, 2015.

[72] P. C. Piotrowski, I. J. Rzepczynska, and J. Kwintkiewicz, "Oxidative Stress Induces Expression of CYP11A, CYP17, Star and 3β-HSD in Rat Theca-Interstitial Cells," Journal of the Society for Gynecologic Investigation, vol. 12, p. 319A, 2005.

[73] A. M. Kicinska, R. B. Maksym, and M. A. Zabielska-Kaczorowska, "Immunological and Metabolic Causes of Infertility in Polycystic Ovary Syndrome," Biomedicines, vol. 11, p. 1567, 2023.

[74] F. Yan, Q. Zhao, and Y. Li, "The Role of Oxidative Stress in Ovarian Aging: A Review," Journal of Ovarian Research, vol. 15, p. 100, 2022.

[75] A. M. Darling, J. E. Chavarro, and S. Malspeis, "A Prospective Cohort Study of Vitamins B, C, E, and Multivitamin Intake and Endometriosis," Journal of Endometriosis and Pelvic Pain Disorders, vol. 5, pp. 17–26, 2013.

[76] H. Heidari, Z. Hajhashemy, and P. Saneei, "A Meta-Analysis of Effects of Vitamin E Supplementation Alone and in Combination with Omega-3 or Magnesium on Polycystic Ovary Syndrome," Scientific Reports, vol. 12, p. 19927, 2022.

[77] O. T. Olaniyan, A. Femi, and G. Iliya, "Vitamin C Suppresses Ovarian Pathophysiology in Experimental Polycystic Ovarian Syndrome," Pathophysiology, vol. 26, pp. 331–341, 2019.

[78] P. V. Dludla, B. B. Nkambule, and T. M. Nyambuya, "Vitamin C Intake Potentially Lowers Total Cholesterol to Improve Endothelial Function in Diabetic Patients at Increased Risk of Cardiovascular Disease: A Systematic Review of Randomized Controlled Trials," Frontiers in Nutrition, vol. 9, p. 1011002, 2022.

[79] M. P. McRae, "Vitamin C Supplementation Lowers Serum Low-Density Lipoprotein Cholesterol and Triglycerides: A Meta-Analysis of 13 Randomized Controlled Trials," Journal of Chiropractic Medicine, vol. 7, pp. 48–58, 2008.

[80] B. Bai and H. Chen, "Metformin: A Novel Weapon Against Inflammation," Frontiers in Pharmacology, vol. 12, p. 622262, 2021.

[81] T. Salvatore, P. C. Pafundi, and R. Galiero, "Can Metformin Exert as an Active Drug on Endothelial Dysfunction in Diabetic Subjects?," Biomedicines, vol. 9, no. 3, p. 210, 2020.

[82] S. Sam and D. A. Ehrmann, "Metformin Therapy for the Reproductive and Metabolic Consequences of Polycystic Ovary Syndrome," Diabetologia, vol. 60, pp. 1656–1662, 2017.

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

[83] J. Zhao, L. Dong, and Z. Lin, "Effects of Selenium Supplementation on Polycystic Ovarian Syndrome: A Systematic Review and Meta-Analysis on Randomized Clinical Trials," BMC Endocrine Disorders, vol. 23, p. 33, 2023.

[84] M. Jamilian, S. Mansury, and F. Bahmani, "The Effects of Probiotic and Selenium Co-Supplementation on Parameters of Mental Health, Hormonal Profiles, and Biomarkers of Inflammation and Oxidative Stress in Women with Polycystic Ovary Syndrome," Journal of Ovarian Research, vol. 11, p. 80, 2018.

[85] E. R., A. M. D., M. K., and P. T., "Oxidative Stress in Polycystic Ovary Syndrome," Reproduction, vol. 164, no. 6, pp. F145–F154, 2022.

[86] Y. H. Ham, G. Pan, and H. W. Chan, "LC-MS/MS Quantitation of Formaldehyde–Glutathione Conjugates as Biomarkers of Formaldehyde Exposure and Exposure-Induced Antioxidants: A New Look at an Old Topic," Chemical Research in Toxicology, vol. 35, no. 5, pp. 858–866, 2022.

[87] R. Dringen, "Metabolism and Functions of Glutathione in Brain," Progress in Neurobiology, vol. 62, no. 6, pp. 649–671, 2000.

[88] C. Pimson, W. Chatuphonprasert, and K. Jarukamjorn, "Improvement of Antioxidant Balance in Diabetes Mellitus Type 1 Mice by Glutathione Supplement," Pakistan Journal of Pharmaceutical Sciences, vol. 27, no. 6, pp. 1731–1737, 2014.

[89] R. C. Gomez and A. H. Mijares, "Mitochondrial Complex I Impairment in Leukocytes from Polycystic Ovary Syndrome Patients with Insulin Resistance," Journal of Clinical Endocrinology & Metabolism, vol. 94, no. 9, pp. 3505–3512, 2009.

[90] S. Stephenie, Y. P. Chang, A. Gnanasekaran, and N. M. Esa, "An Insight on Superoxide Dismutase (SOD) from Plants for Mammalian Health Enhancement," Journal of Functional Foods, vol. 68, p. 103917, 2020.

[91] Y. Liang, Y. Han, and J. Dan, "A Highly Efficient and Stable Artificial Superoxide Dismutase Based on Functionalized Melanin Nanoparticles from Cuttlefish Ink for Food Preservation," Food Research International, vol. 163, p. 112211, 2023.

[92] H. Younus, "Therapeutic Potentials of Superoxide Dismutase," International Journal of Health Sciences, vol. 12, no. 3, pp. 88–98, 2018.

[93] K. H. Al-Gubory, P. A. Fowler, and J. Garrel, "The Roles of Cellular Reactive Oxygen Species, Oxidative Stress, and Antioxidants in Pregnancy Outcomes," International Journal of Biochemistry & Cell Biology, vol. 42, no. 10, pp. 1634–1650, 2010.

[94] A. Agarwal, A. Aponte-Mellado, B. J. Premkumar, A. Shaman, and S. Gupta, "The Effects of Oxidative Stress on Female Reproduction: A Review," Reproductive Biology and Endocrinology, vol. 10, no. 1, pp. 1–31, 2012.

[95] L. Poston, N. Igosheva, and H. D. Mistry, "Role of Oxidative Stress and Antioxidant Supplementation in Pregnancy Disorders," American Journal of Clinical Nutrition, vol. 94, suppl. 6, pp. 1980S–1985S, 2011.

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

[96] M. Murri, M. Luque-Ramírez, M. Insenser, and M. Ojeda-Ojeda, "Circulating Markers of Oxidative Stress and Polycystic Ovary Syndrome (PCOS): A Systematic Review and Meta-Analysis," Human Reproduction Update, vol. 19, no. 3, pp. 268–288, 2013.

[97] K. Coulibaly, M. Thauvin, and A. Melenbacher, "A Di-Copper Peptidyl Complex Mimics the Activity of Catalase, a Key Antioxidant Metalloenzyme," Inorganic Chemistry, vol. 60, no. 13, pp. 9309–9319, 2021.

[98] S. K. Pandey and R. M. Banik, "Selection and Optimization of Nutritional Constituents for Enhanced Production of Alkaline Phosphatase by Bacillus licheniformis MTCC 1483," Journal of Agricultural Technology, vol. 8, no. 4, pp. 1317–1325, 2012.

[99] L. P. Atip, P. T. Natchai, and S. Charn, "Lipid Peroxidation and Antioxidant Enzyme Activities in Erythrocytes of Type 2 Diabetic Patients," Journal of the Medical Association of Thailand, vol. 93, no. 6, pp. 187–190, 2010.

[100] D. D. Rio, A. J. Stewart, and A. Pellegrini, "A Review of Recent Studies on Malondialdehyde as Toxic Molecule and Biological Marker of Oxidative Stress," Nutrition, Metabolism and Cardiovascular Diseases, vol. 15, no. 4, pp. 316–320, 2005.

[101] R. Buddi, B. Lin, and S. R. Atilano, "Evidence of Oxidative Stress in Human Corneal Diseases," Journal of Histochemistry & Cytochemistry, vol. 50, no. 3, pp. 341–351, 2002.

[102] N. Gopal, A. Selvam, and A. R. Srinivasan, "Serum Gamma Glutamyl Transferase Levels in Obese South Indian Adults with Reference to Atherogenic Lipid Risk Factors and Lipid Peroxides," International Journal of Medical and Health Sciences, vol. 1, no. 1, pp. 2–14, 2012.

[103] J. Cederberg, "Oxidative Stress; Antioxidative Defence and Outcome of Gestation in Experimental Diabetic Pregnancy," Doctoral Dissertation, Acta Universitatis Upsaliensis, Uppsala University, 2001.

[104] H. Esterbauer, R. Schaur, and H. Zollner, "Chemistry and Biochemistry of 4-Hydroxynonenal, Malondialdehyde, and Related Aldehydes," Free Radical Biology and Medicine, vol. 11, pp. 81–128, 1991.

[105] G. Willis, R. Hocking, M. Udiawar, and A. Rees, "Oxidative Stress and Nitric Oxide in Polycystic Ovary Syndrome," Nitric Oxide, vol. 27, Suppl., p. S28, 2012.

[106] M. Murri, M. Luque-Ramírez, M. Insenser, and M. Ojeda-Ojeda, "Circulating Markers of Oxidative Stress and Polycystic Ovary Syndrome (PCOS): A Systematic Review and Meta-Analysis," Human Reproduction Update, vol. 19, no. 3, pp. 268–288, 2013.

[107] J. Barp, A. S. D. R. Araújo, and T. R. G. Fernandes, "Myocardial Antioxidant and Oxidative Stress Changes Due to Sex Hormones," Brazilian Journal of Medical and Biological Research, vol. 35, pp. 1075–1081, 2002.

[108] H. Lee, S. Lee, and J. Y. Baek, "Estrogenic Activity of Ethyl Gallate and Its Potential Use in Hormone Replacement Therapy," Bioorganic & Medicinal Chemistry Letters, vol. 40, p. 127919, 2021.

[109] J. Vina, J. Gambini, and R. Lopez-Grueso, "Females Live Longer than Males: Role of Oxidative Stress," Current Pharmaceutical Design, vol. 17, no. 36, pp. 3959–3965, 2011.

Vol. 10 No. 2 (2025): December
DOI: 10.21070/acopen.10.2025.12842

[110] M. Š. Goldštajn, K. Toljan, and F. Grgić, "Sex Hormone Binding Globulin (SHBG) as a Marker of Clinical Disorders," Collegium Antropologicum, vol. 40, no. 3, pp. 211–218, 2016.

[111] H. N. Y. Siti, Y. Kamisah, and J. Kamsiah, "The Role of Oxidative Stress, Antioxidants and Vascular Inflammation in Cardiovascular Disease: A Review," Vascular Pharmacology, vol. 71, pp. 40–56, 2015.

[112] N. Guo, Y. F. Li, and J. H. Ai, "Two Different Concentrations of Oxygen for Culturing Precompaction Stage Embryos on Human Embryo Development Competence: A Prospective Randomized Sibling-Oocyte Study," International Journal of Clinical and Experimental Pathology, vol. 7, pp. 6191–6198, 2014.

[113] A. Al-Mulla, A. B. E. Fazari, M. Elkhouly, and N. Moghaddam, "Role of Antioxidants in Female Fertility," Open Journal of Obstetrics and Gynecology, vol. 8, pp. 85–91, 2018.

[114] B. Kovačič, "Culture Systems: Low-Oxygen Culture," in Methods in Molecular Biology, vol. 912, Clifton, NJ: Humana Press, 2012, pp. 249–272.

[115] M. S. Hamza, M. S. Raheem, and S. J. Abdurrahman, "Correlation Between Levels of Serum Antioxidants and Numerous Hormones in Primary Infertility of Women," International Journal of Reproductive BioMedicine, vol. 18, no. 10, pp. 1–8, 2020.

[116] J. C. M. Riley and H. R. Behrman, "Oxygen Radicals and Reactive Oxygen Species in Reproduction," Proceedings of the Society for Experimental Biology and Medicine, vol. 198, no. 3, pp. 781–791, 1991.

[117] H. R. Behrman, S. L. Kodaman, S. Preston, and S. Gao, "Oxidative Stress and the Ovary," Journal of the Society for Gynecologic Investigation, vol. 8, no. 1, pp. S40–S42, 2001.