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Epigenetic Regulation of Ferroptosis in Polycystic Ovary Syndrome: Emerging Molecular Insights

Vithika
Amity Institute of Biotechnology, Amity University Uttar Pradesh, Lucknow Campus, Gomti Nagar Extension, Lucknow (INDIA).

Abhineet Pratap Singh
Amity Institute of Biotechnology, Amity University Uttar Pradesh, Lucknow Campus, Gomti Nagar Extension, Lucknow (INDIA).

Somali Sanyal *
Amity Institute of Biotechnology, Amity University Uttar Pradesh, Lucknow Campus, Gomti Nagar Extension, Lucknow (INDIA).

***Corresponding author:** ssanyal@lko.amity.edu*

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Abstract

Polycystic ovary syndrome (PCOS) is a complex endocrine–metabolic disorder characterized by hyperandrogenism, ovulatory dysfunction, insulin resistance, and chronic low-grade inflammation. Although genetic predisposition contributes to disease susceptibility, accumulating evidence suggests that epigenetic modifications play a critical role in modulating gene expression in PCOS without altering the underlying DNA sequence. DNA methylation, histone modifications, and microRNA dysregulation have been implicated in abnormal steroidogenesis, impaired insulin signaling, and disrupted folliculogenesis. Concurrently, ferroptosis—an iron-dependent, lipid peroxidation-driven form of regulated cell death—has emerged as a potential contributor to ovarian dysfunction. Increased oxidative stress, altered iron metabolism, and reduced antioxidant defense mechanisms observed in PCOS create a cellular environment conducive to ferroptotic damage, particularly within granulosa cells essential for follicular maturation.

Recent studies suggest that epigenetic alterations may influence the expression of key ferroptosis-regulating genes, including GPX4, SLC7A11, and iron-handling proteins, thereby enhancing cellular susceptibility to oxidative injury. This integrated perspective proposes that epigenetic dysregulation may serve as an upstream mechanism that sensitizes ovarian tissue to ferroptosis, linking metabolic stress and reproductive dysfunction in PCOS. Understanding this epigenetic–ferroptotic interplay may provide novel insights into disease pathogenesis and identify potential biomarkers and therapeutic targets. This review synthesizes current evidence on epigenetic mechanisms and ferroptotic signaling in PCOS and highlights future research directions to clarify their mechanistic crosstalk.

Keywords: Polycystic Ovary Syndrome, Epigenetics, Ferroptosis, Oxidative Stress, Granulosa Cells.

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1. Introduction

The polycystic ovary syndrome is one of the leading endocrine disorders of women in the reproductive period, and it has a high prevalence rate between 6% and 20%, depending on the population and diagnostic criteria used (Azziz et al., 2016). The main clinical manifestations of this disorder include hyperandrogenism, anovulation, polycystic ovarian morphological changes, insulin resistance, and infertility. Along with its impact on the female reproductive system, PCOS usually includes some other metabolic disorders, including obesity, type 2 diabetes mellitus, and chronic inflammation (Teede et al., 2023).

Although the disturbances of hormonal and metabolic pathways appear to be a necessary condition for PCOS development, their detailed molecular mechanisms remain unclear. Recently, the importance of epigenetic regulations in PCOS has been recognized due to the involvement of different regulatory processes, such as DNA methylation, histone modification, and RNA regulation, that disrupt the ovarian metabolism in PCOS patients (Li et al., 2021). Additionally, cell death regulations are currently gaining increased attention.

Out of these pathways, ferroptosis – an iron-dependent cell death pathway, mediated by lipid peroxides and oxidative stress, recently emerged, garnering much attention for its role in cellular damage. Recent studies suggest that oxidative stress, mitochondrial dysfunction and iron accumulation in PCOS can induce ferroptosis-mediated damage in granulosa cells and follicle dysfunctions (Stockwell, 2022).

Therefore, the aim of this paper is to highlight the existing literature on epigenetic changes and ferroptosis in PCOS and their possible connection.

2. Overview of PCOS Pathophysiology

Polycystic ovary syndrome is among the multitude of multifactorial diseases with different abnormalities in the endocrine system and metabolism, which lead to disorders in the normal functioning of ovaries. The excess production of LH hormone and a high LH/FSH ratio promote the production of androgens by the ovarian theca cells, causing hyperandrogenism, anovulation, and follicular dysmaturity (Escobar-Morreale, 2018). FSH deficiency results in a disturbance in granulosa cell activity and ovarian dysfunction.

Furthermore, metabolic disorders in the form of insulin resistance and hyperinsulinemia have an important role in the formation of the disease. Increased insulin secretion promotes hormonal disorders due to the increased production of androgens; however, obesity can cause exacerbated metabolic disorders and inflammation in addition (Teede et al., 2023).

In addition to this, the development of PCOS is related to inflammation, excessive ROS production, mitochondrial disorders, and apoptosis of granulosa cells. All these factors result in oxidative stress, impairing the activity of antioxidants and promoting the appearance of favorable conditions for the process of ferroptosis (Shen et al., 2021).

3. Epigenetic Mechanisms Involved in PCOS:

3.1 Changes in DNA Methylation

Changes in DNA methylation have been investigated extensively in women with PCOS, which entails alterations in the methylation of cytosine in the CpG islands of promoters of specific genes. DNA methylation is an epigenetic process that enables transcription regulation without changing the sequence of nucleotides. Studies show that hypermethylation or hypomethylation of genes associated with the insulin pathway, steroidogenesis, and inflammation is common among patients with PCOS (Li et al., 2021). The modifications in the methylation of CYP19A1, LHCGR, and INSR result in hormonal imbalances, insulin resistance, and ovulatory dysfunction, making DNA methylation an integral part of PCOS pathogenesis.

3.2 Histone Modifications

Histone modifications should be considered when regulating gene transcription because they affect chromatin structure and the expression levels of particular genes. In PCOS, changes in histone modifications cause abnormalities in follicular development, steroidogenesis, and inflammatory signaling processes (Wang et al., 2022). Acetylated histones increase transcription levels, but the influence of methylated histones is dependent on their position. (Fig. 1 summarizes the mechanisms discussed in the literature.)

3.3 Dysregulated MicroRNA Expression

MicroRNAs (miRNAs) are a class of small non-coding RNAs that regulate gene expression at the post-transcriptional level. Deregulation of several miRNAs like miR-93, miR-21, miR-27a, and miR-320 has been observed in ovarian tissues and granulosa cells of women with PCOS (Jiang et al., 2020). These deregulated miRNAs are involved in insulin resistance, apoptosis, proliferation of granulosa cells, inflammation and oxidative stress response. In particular, miR-93 is related to insulin resistance, whereas miR-21 is involved in the regulation of inflammation and granulosa cell survival. (Fig. 1 summarizes the mechanisms discussed in the literature.)

3.4 Epigenetics as a Bridge between Environmental and Genetic Causes

Epigenetics is an important link between environment and genetics in PCOS. Environmental factors like obesity, bad eating habits, stress, exposure to endocrine disruptors, and high prenatal androgen levels can lead to epigenetic modifications in ovarian tissue and metabolism, resulting in the development of PCOS (Azziz et al., 2019). These environmentally induced epigenetic modifications have the capacity to be maintained for a prolonged duration and are likely to be involved in the heterogeneity and transgenerational inheritance observed in PCOS .(Fig. 1 summarizes the mechanisms discussed in the literature.)

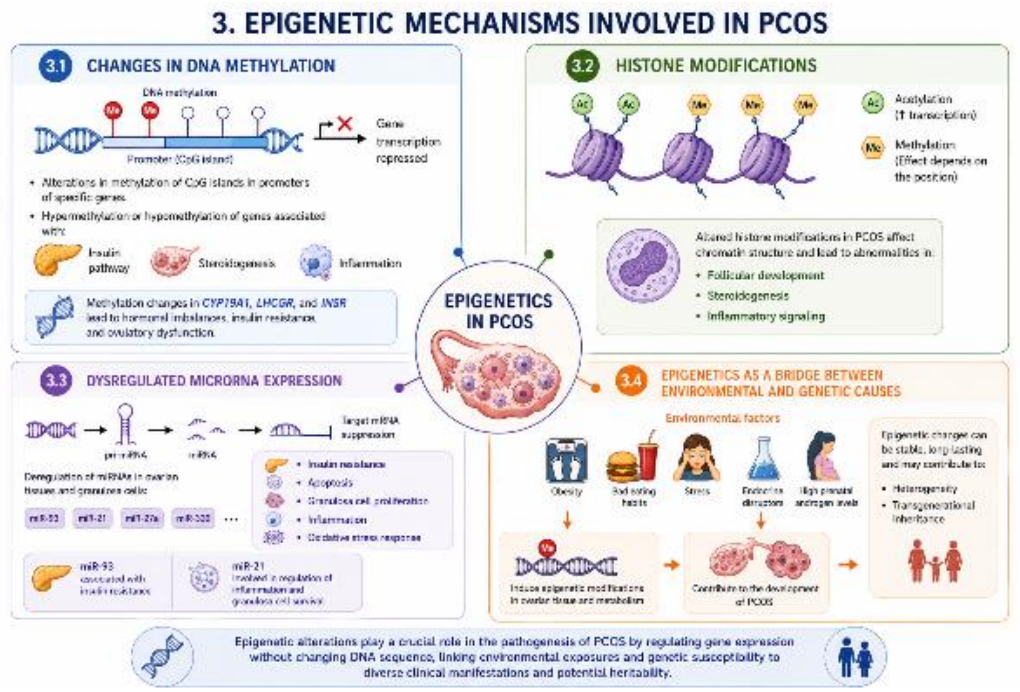

Fig 1. Epigenetic mechanisms involved in PCOS, including altered DNA methylation, histone modifications, microRNA dysregulation, and environmental influences contributing to ovarian dysfunction.

4. Ferroptosis: Mechanism and Biological Basis

Ferroptosis is a recently identified programmed cell death process that depends on iron overload and lipid peroxidation. This form of cell death is characterized by increased lipid ROS production, impaired cell membrane integrity, and depletion of cellular glutathione, leading to oxidative damage (Stockwell, 2022). Unlike apoptosis and necroptosis, the major trigger for ferroptosis is the metabolic dysfunction caused by iron imbalance. (Fig. 2 provides a summary of the literature discussed.)

4.1 Molecular Regulators of Ferroptosis That Are of Importance

Glutathione peroxidase 4 (GPX4) is an essential antioxidant responsible for protecting cells from the effects of lipid peroxidation. GPX4 transforms dangerous lipid hydroperoxides into safe lipid alcohols.

Reduced activity of GPX4 leads to ferroptosis occurrence. One of the primary functions of System Xc−, namely, of SLC7A11, is involved in the transport of cystine for the formation of glutathione. Inhibition of SLC7A11 decreases the concentration of glutathione and provokes ferroptosis onset (Jiang et al., 2021).

The enzyme acyl-coenzyme A synthetase long-chain family member 4 (ACSL4) is engaged in the synthesis of polyunsaturated fatty acids that are highly susceptible to lipid peroxidation. The transferrin receptor 1 (TFR1) assists in cellular iron absorption, whereas ferritin participates in the cellular iron retention. Increased levels of free iron result in increased ROS synthesis by means of the Fenton reaction and quick deterioration of the lipid membrane. Ferroptosis suppressor protein 1 (FSP1) acts without GPX4 involvement and prevents ferroptosis through decreasing oxidative stress.

4.2 Ovarian Cell Ferroptosis

Since granulosa cells have a significant role in follicular maturation and steroid hormones production, they are susceptible to oxidative stress. Research has demonstrated that iron overload and elevated levels of ROS can affect follicular development and functioning because of disrupted mitochondrial activity and impaired steroidogenesis in ovaries (Zhang et al., 2023). Considering that granulosa cells facilitate developing oocytes, any damages sustained because of cell ferroptosis can cause decreased quality of oocytes.

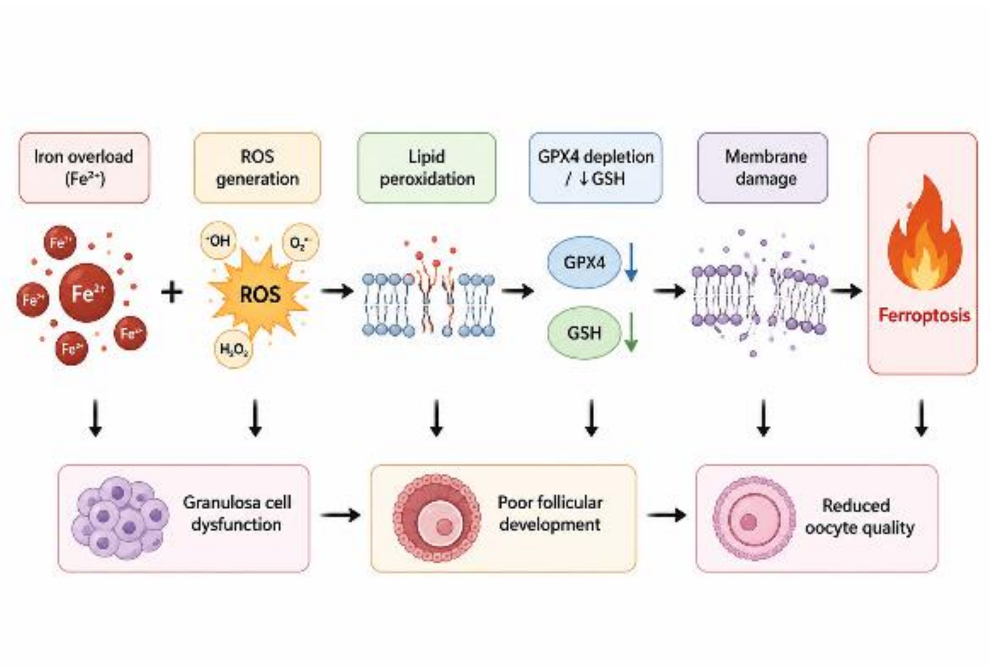

Fig. 2 Simplified ferroptosis pathway illustrating iron overload, ROS generation, lipid peroxidation, GPX4/GSH depletion, and membrane damage leading to granulosa cell dysfunction and poor oocyte quality.

5. Evidence of Ferroptosis in Polycystic Ovary Syndrome

There exists a large amount of evidence in support of the role played by ferroptosis in PCOS disease pathology in connection with oxidative stress, iron homeostasis, and granulosa cell damage. Specifically, it has been established that there is increased oxidative stress, iron accumulation, ferritin accumulation, ROS production, and decreased glutathione concentration in the ovarian tissues of females with PCOS. Given that ferroptosis includes iron-mediated lipid peroxidation, these changes in the ovarian microenvironment would lead to the onset of ferroptosis (Wang et al., 2024).

In addition, ferroptosis markers were detected in the granulosa cells of PCOS patients. Such ferroptosis markers include iron accumulation, high MDA content, mitochondrial atrophy, and reduced GPX4 expression, all of which are considered to be common features of ferroptosis (Li et al., 2024). Besides, ferroptosis could be even more pronounced because of GPX4 degradation, weak antioxidant activity, ROS overproduction, glutathione imbalance, and lipid peroxidation within the ovarian follicle (Tang et al., 2023; Zhang et al., 2021).

The experimental application of the ferroptosis inhibitors provides further evidence that ferroptosis serves as a mechanism of disease. Indeed, administration of Ferrostatin-1 resulted in decreased ovarian damage, inhibition of lipid peroxidation, and restoration of follicles in PCOS models. Thus, inhibition of ferroptosis may be a potential effective treatment for ovarian disorders associated with PCOS (Li et al., 2024). (Fig. 3 provides a summary of the literature discussed.)

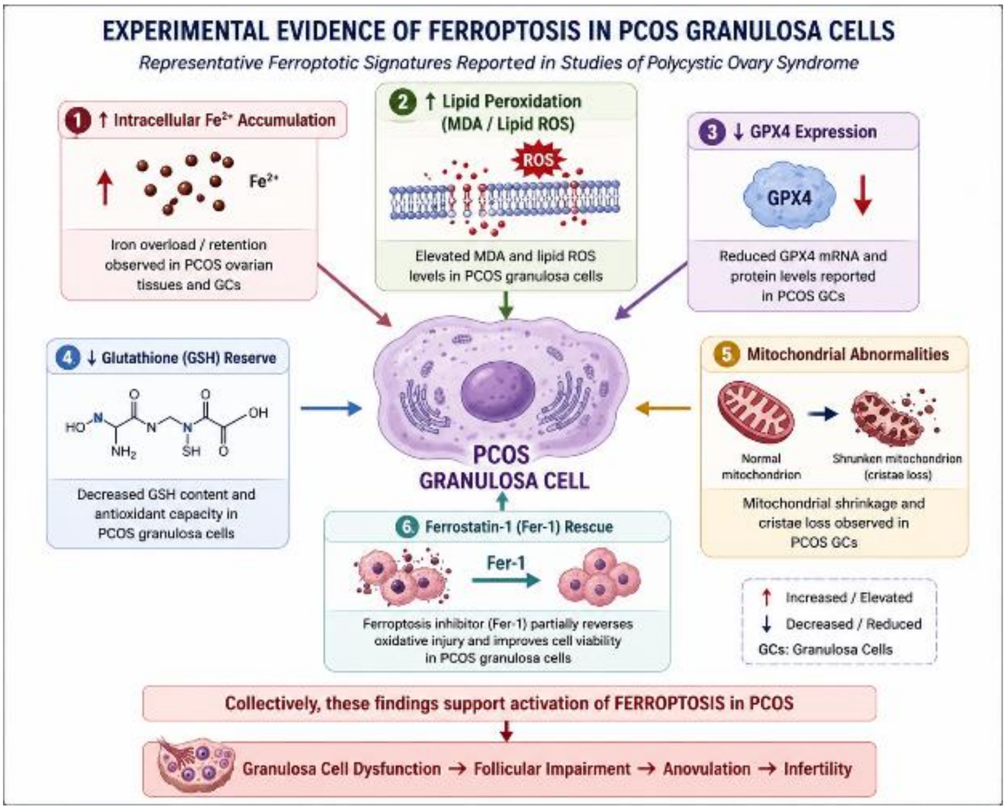

Fig 3. *Experimental evidence supporting ferroptotic activation in ovarian granulosa cells under Polycystic Ovary Syndrome conditions.*

6. Epigenetic Regulation of Ferroptosis in Polycystic Ovary Syndrome: Molecular Crosstalk

The alterations in epigenetics play a vital role in regulating ferroptosis signaling pathways in PCOS. Through the DNA methylation process, there arises a suppression of gene expression for antioxidants such as GPX4 resulting in oxidative stress and lipid peroxidation in granulosa cells. Reduced enzymatic activity of GPX4 results in the inability of lipid ROS detoxification. Consequently, there is a decline in the mitochondrial functions followed by ferroptosis (Yang et al., 2025). Similarly, epigenetic alteration of SLC7A11 gene leads to the low cystine uptake, thus hindering glutathione production and lowering the cell antioxidative defense against ferroptosis (Lv et al., 2025).

Additionally, the epigenetic changes of histone acetylation and methylation have negative impacts on iron homeostasis and lipids regulation, hence causing the increase in intracellular iron, formation of ROS by Fenton reaction, and damage to the lipids in ovarian cells (Zhou et al., 2024). Furthermore, alterations in noncoding RNAs such as microRNAs (miRNAs), circular RNAs (circRNAs), and RNA in exosomes are responsible for the regulation of ferroptosis signaling pathways through the targeting of antioxidants such as GPX4, NRF2, and SLC7A11 (Tan et al., 2022). Thus, the epigenetic modifications of RNAs promote oxidative stress and make granulosa cells susceptible to ferroptosis.

Metabolic disorders that commonly occur with PCOS, such as hyperandrogenemia, insulin resistance, and inflammation, may also play a role in the epigenetic changes of granulosa cells. Enzyme activity increases due to oxidative stress include DNA methyltransferase, histone deacetylase, and transcription factors, resulting in reduced antioxidant production and promoting pro-oxidants (An et al., 2025). These epigenetic changes lead to higher iron content, lower glutathione levels, lipid peroxide formation, and mitochondrial dysfunction, leading to granulosa cell death through ferroptosis (Wang et al., 2024). (Fig. 4 summarizes the mechanisms discussed in the literature.)

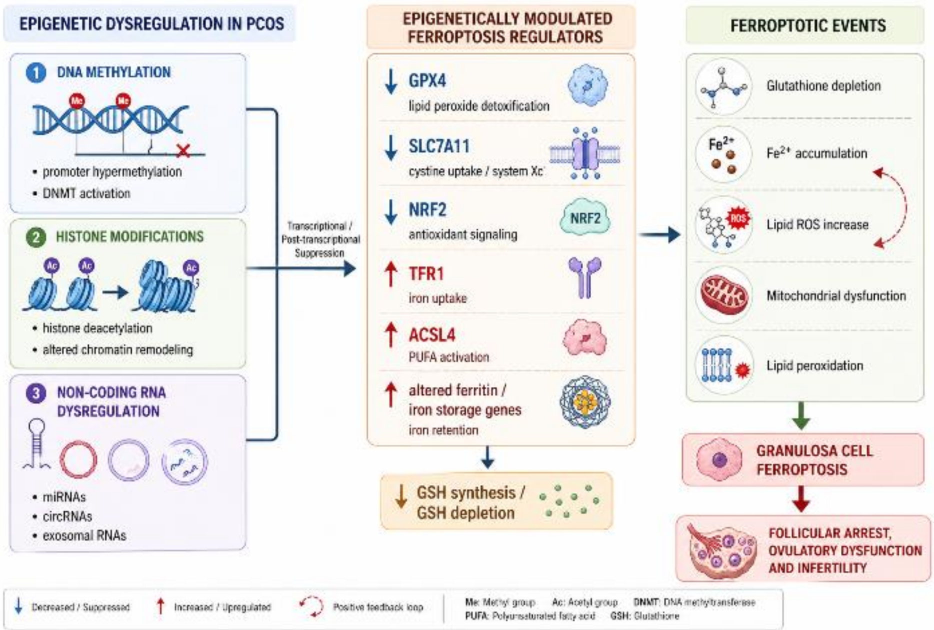

Fig 4. *Proposed molecular crosstalk between epigenetic dysregulation and ferroptosis in ovarian granulosa cells during Polycystic Ovary Syndrome.*

7. Therapeutic and Diagnostic Implications

7.1 Diagnostic Importance

Increased serum ferritin, high malondialdehyde level, reduced glutathione concentration, decreased GPX4 levels, DNA methylation, and microRNA expression could possibly act as diagnostic markers for the oxidative stress-induced damage caused by granulosa cells in patients suffering from PCOS (Zhang et al., 2024; Lin et al., 2025).

7.2 Therapeutic Implications

The modulation of ferroptosis might have considerable clinical utility in patients having PCOS, as pharmacological drugs like Ferrostatin-1 have proven their potential to inhibit the oxidative damage of lipids and improve follicular health in animal experiments. The use of epigenetic modulators, metformin, and antioxidants could help minimize ferroptosis-induced damage (Shi et al., 2022; Yang et al., 2025; Jamilian et al., 2023).

7.3 Translational Potential

Even though these findings are quite promising, most of the scientific research has been conducted using in vitro studies and laboratory animals. Clinical validation would be necessary before implementing ferroptosis-based diagnostic tests and treatments in actual cases of PCOS.

8. Future Perspectives and Research Gaps

8.1 Validation of Markers for Clinical Applications

Recent scientific reports suggest that ferroptosis occurs in women with PCOS; however, human data are rare. A need exists to validate large-scale data using ovarian tissue and follicular fluid samples from patients.

8.2 Lack of Insights into Epigenetic Control Mechanisms

Ferroptosis is influenced by DNA methylation and other epigenetic marks as well as non-coding RNA molecules. However, little is known about the role of epigenetic control mechanisms in GPX4, SLC7A11, NRF2 and genes associated with iron homeostasis in PCOS patients.

8.3 Possible Targets for Treatment of PCOS

Combination therapy targeting ferroptosis and epigenetic changes seems to offer a perspective for future treatment of PCOS. Further research is needed to explore clinically applicable methods of normalizing the oxidative status in ovaries.

9. Conclusion

Polycystic Ovary Syndrome (PCOS) has been recognized to be more than just a disorder with hormonal and metabolic disturbances but also a disorder of molecular malfunctions within ovarian cells. From the existing literature on the subject matter, ferroptosis has been found to play a very significant part in the damage of granulosa cells owing to excessive iron build-up, oxidative damage due to lipids, depletion of glutathione content, and the inhibition of antioxidative responses. The epigenetic abnormalities that take place here act as the initial triggers for the process of ferroptosis by controlling the expression of genes needed for antioxidative response.

Author Declaration Statements

Declaration: The authors hereby declare that the manuscript submitted for consideration is an original work and has not been published or submitted elsewhere for publication. The authors take full responsibility for the integrity, accuracy, and ethical compliance of the work presented in the manuscript.

Conflict of Interest: All authors confirm that:

- Any potential conflicts of interest, whether financial or non-financial, have been fully disclosed. **– Yes / Not Applicable**√
- All sources of funding and financial support received for the conduct of the study have been appropriately acknowledged. **– Yes / Not Applicable**√
- Necessary ethical approvals have been obtained from the relevant institutional or regulatory bodies for studies involving human participants, animals, or sensitive data, wherever applicable. **– Yes / Not Applicable**√

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