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Effects of antioxidant supplementation for polycystic ovary syndrome

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Abstract

Introduction and purpose: Polycystic ovary syndrome is the most common endocrinopathy in women, with a prevalence ranging from 10% to 13%. Oxidative stress and decreased antioxidant levels contribute to the development of various diseases, and one of them is polycystic ovary syndrome. The aim of this review is to provide an overview of the current knowledge about the effects of antioxidant administration in PCOS treatment.

A brief description of the state of knowledge: Oxidative stress is an imbalance between increased levels of reactive oxygen species and a decreased efficiency of antioxidant mechanisms, which can potentially cause damage. The harmful effects of free radicals might be neutralized by antioxidants obtained from the diet, such as polyphenols, vitamins C, and E. These compounds improve several aspects of the PCOS pathomechanism, including hormonal imbalance, glucose metabolism, lipid profile, and ovarian functionality.

Conclusions: The outcomes of all the reviewed studies in this paper indicate that antioxidants such as resveratrol, curcumin, vitamin C and E, N-acetylcysteine, and melatonin have therapeutic potential in the management of PCOS. However, currently antioxidant therapies cannot be recommended in PCOS therapy since there is a need for more prospective randomized clinical trials on a larger sample to establish a long-term effects of antioxidants supplementation in PCOS, the optimal dosage, and finally to assess which antioxidant is the most efficient in PCOS treatment.

Key words: polycystic ovary syndrome, antioxidant, oxidative stress

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women, with a prevalence ranging from 10% to 13%. It is a main cause of anovulation, infertility, and hyperandrogenism among women of reproductive age [1][2]. PCOS should be diagnosed using the revised consensus Rotterdam criteria, there must be at least two of the following: a) clinical or biochemical hyperandrogenism; b) oligoovulation and/or anovulation; c) polycystic ovaries on ultrasound or increased anti-mullerian hormone (AMH) levels. To confirm the diagnosis, other causes of these features must be excluded [3].

The specific etiology and pathophysiology of PCOS are still unknown due to its heterogeneous and complex nature; however, it includes the interplay between hormones,

genes, and environmental factors [4] [5] . It is assumed that some women possess a genetic predisposition, and certain environmental factors, commonly insulin resistance, trigger the development of PCOS [6] . Hyperandrogenism is the main cause of oligomenorrhea and is also responsible for the typical symptoms of PCOS, such as hirsutism and acne. Moreover, hormonal imbalance leads to the development of cysts in the antral follicles of the ovary, stops ovulation, and disturbs the menstrual cycle, leading to amenorrhea [4] . There is a vicious cycle between hyperandrogenemia and insulin resistance. Excessive androgen synthesis leads to visceral obesity, which in turn intensifies insulin resistance. Consequently, the level of insulin is elevated, and this hyperinsulinemia stimulates theca cells to increase the synthesis of androgens and inhibits the production of sex hormone-binding globulin (SHBG) in the liver, so free testosterone levels are elevated. Furthermore, elevated levels of luteinizing hormone (LH) cause an imbalance in the LH/FSH ratio and exacerbate the dysregulation of follicular development, while also causing the overproduction of androgens by thecal cells [5].

Oxidative stress is characterized by an imbalance between increased levels of reactive oxygen species (ROS) and a decreased effectiveness of antioxidant mechanisms, which can potentially lead to damage [7] . Thus, oxidative stress and decreased antioxidant levels contribute to the development of various diseases, and one of them is polycystic ovary syndrome [8]. Murri et al. conducted a meta-analysis on 4933 PCOS patients, which revealed that circulating markers of oxidative stress are abnormal in women with PCOS. There was an increase in mainly malondialdehyde levels, but also homocysteine and asymmetric dimethylarginine, as well as increased superoxide dismutase activity. However, levels of glutathione and paraoxonase-1 activity decreased [9] . Furthermore, increased oxidative stress in women with PCOS may lead to other health implications, such as cardiovascular disease, hypertension, obesity, or dyslipidemia [8] . The harmful effects of free radicals are neutralized by antioxidant compounds produced in our body, for example, glutathione or melatonin, and the ones obtained from the diet, such as vitamins C, E, and A, and polyphenols [10] [11]. An antioxidant is a stable molecule capable of donating an electron to a highly reactive free radical and neutralizing it, thus limiting its capacity for damage [12].

The aim of this review is to provide an overview of the current knowledge about the effects of antioxidant administration in PCOS treatment.

Material and methods

This article is based on the literature found in the PubMed Database from the period of 2003–2024 with the use of keywords such as “PCOS”; “antioxidants”; “resveratrol”; “curcumin”; “n-acetylcysteine”; “oxidative stress”; “vitamin C”; “vitamin E”; “melatonin”.

Results

1. Polyphenols

1.1. Resveratrol

Resveratrol (3,4',5-trihydroxystilbene) is a bioactive, polyphenolic compound that naturally occurs in a variety of plants, such as grapes, berries, cocoa, and peanuts[13][14]. There is multiple evidence strongly suggesting that resveratrol has anti-oxidative, anti-inflammatory, anticancerous, and immunomodulatory activity. It can also regulate glucose and lipid metabolism. Moreover, it is neuroprotective and cardioprotective [13] . Most of the properties make resveratrol highly promising in PCOS treatment; thus, multiple clinical trials regarding resveratrol intervention were conducted.

An intervention in PCOS patients with 1,500 mg p.o. daily for 3 months, compared with the placebo group, has shown that resveratrol treatment resulted in a major reduction of 23.1% in total testosteron levels and a 22.2% decrease in dehydroepiandrosterone sulfate (DHEAS) levels. In terms of glucose metabolism, there was a noteworthy decrease in fasting insulin levels by 31.8% and a 66.3% increase in the Insulin Sensitivity Index (Matsuda and DeFronzo). It was concluded that the decline in androgen levels was possibly caused by an amelioration of insulin sensitivity and a reduction in insulin levels. [15].

Based on strong evidence, it was found that chronic inflamation is crucial in PCOS pathogenesis. Thus, Brenjian et al. decided to do research on endoplasmic reticulum stress and inflammatory markers in PCOS patients. There was an intervention involving the administration of resveratrol (800 mg/d) and a placebo group. The outcome of the clinical trial revealed that resveratrol decreased serum levels of IL-1β, IL-6, TNF-α, IL-18, NF-κB, and CRP. Additionally, resveratrol has the ability to modulate endoplasmic reticulum stress in granulosa cells by altering the expression of genes that are involved in the unfolded protein response process. [16].

Rencber et al. demonstrated that resveratrol effectively ameliorated the serum levels of testosterone, LH, LH/FSH, TNF-α, and tissue AMH levels in rats with dehydroepiandrosterone-induced PCOS. Treatment with resveratrol and/or metformin ameliorated the excessive number of secondary and atretic follicles, as well as the reduced

number of Graafian follicles in the PCOS group. This showed that the intervention had an effect on maintaining folliculogenesis. [17]. According to other study, resveratrol contributed to the amelioration of some PCOS symptoms, such as menstrual irregularity and hair loss. However, this study found no significant alterations in the levels of androgens, insulin, or lipids [18] .

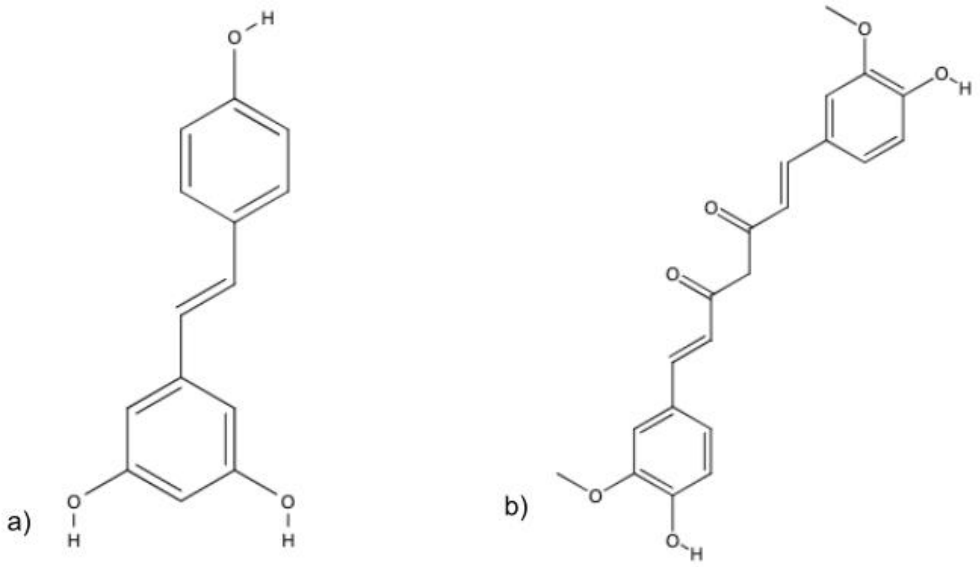

Figure 1. a) Structural formula of resveratrol (3,4',5-trihydroxystilbene); b) Structural formula of curcumin [1,7-bis (4-hydroxy-3- methoxyphenyl)-1,6-heptadiene-3,5-dione]

1.2. Curcumin

One of the most prevalent polyphenols is curcumin. It is derived from Curcuma longa, a plant that belongs to the ginger family, Zingiberaceae [19]. Moreover, curcumin is called a dietary polyphenol since it is a key component of curry powder, which is commonly used worldwide, particularly in Asian cuisine. It is a lipophilic polyphenol, the main curcuminoid found in turmeric [20] [21] – specifically a diferuloyl methane [1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], which has two ferulic acid residues linked by a methylene bridge. Curcumin's antioxidant effect is attributed to the presence of the o-methoxyphenol group and methylenic hydrogen [22]. According to multiple studies, curcumin has antibacterial, antiviral, and antifungal activity. Furthermore, it is claimed to have anti-inflammatory, anti-cancerous, antimutagenic, cardioprotective, and radioprotective features

[20] [23] [24] . For this reason, curcumin was claimed to have therapeutic potential in PCOS treatment [25].

The meta-analysis by Shen et al. aimed to evaluate the therapeutic effect and safety of curcumin in 447 patients with PCOS. Firstable, the level of C-reactive protein (CRP) was assessed by comparing curcumin with a placebo. The meta-analysis demonstrated a substantial decrease after curcumin supplementation. What is crucial in PCOS glucose metabolism was evaluated; fasting blood glucose levels were significantly reduced in patients treated with curcumin. Equally major improvement was displayed in HOMA-IR, insulin level, and insulin sensitivity check index (QUICKI). Moreover, compared with the control group, patients after the curcumin intervention had a reduced body mass index (BMI), which is highly beneficial for PCOS patients [25] . In other study, it was additionaly proven that curcumin effectively reduced total cholesterol levels, LDL-cholesterol levels, and there was a considerable improvement in HDL-cholesterol levels in comparison with the placebo [26] . A recent study has shown that the frequency of typical for PCOS menstrual abnormalities such as amenorrhea and oligomenorrhea was significantly reduced after the curcumin administration, compared to the control group [27] . Overall, curcumin was very well-tolerated and seems to be safe [25].

2. Vitamin C and E

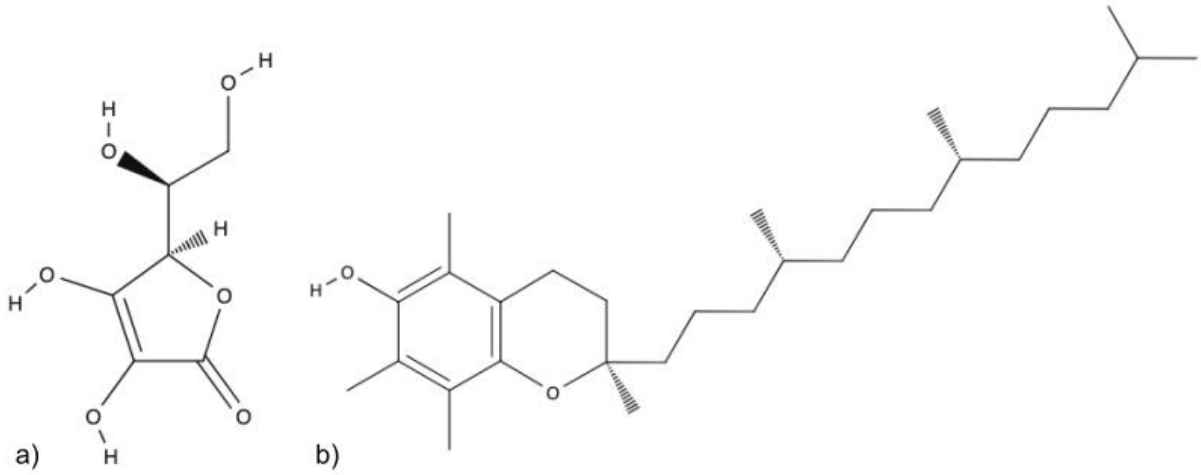

Figure 2. a) Structural formula of Vitamin C (L-Ascorbic Acid); b) Structural formula of Vitamin E (α-Tocopherol)

Vitamin C, or ascorbic acid, is crucial for life and one of the best-known water-soluble compounds. As a vitamin, it is necessary to regularly obtain it through the dietary intake of fruits and vegetables, such as citrus fruits, tomatoes, berries, or green leafy vegetables

[28] [29] . It demonstrates multiple antioxidant properties, like direct scavenging of free radicals, activation of intracellular antioxidant systems, or augmenting the activity of other antioxidants [30].

Vitamin C intervention in female Wistar rats revealed the protective role of vitamin C against DHEA-induced Polycystic Ovary in Wistar rats through antioxidant and anti-apoptotic mechanisms. Vitamin C intervention in Wistar rats with DHEA-Induced PCOS resulted in a major reduction in malondialdehyde, cytokines, and estrogen levels, as well as a substantial increase in antioxidant and metabolic enzymes when compared with the control group. The histopathological evaluation shows a reduction in cystic and atretic ovaries, increased expression of Bcl2 and E-Cadherin, and a reduction in Bax expression in comparison with the control group [31].

Another study compared the therapeutic potential of vitamin C in PCOS with the vitamin E (alpha-tocopherol) intervention in PCOS. Researchers conducted the study on mice, inducing PCOS with either mifepristone or letrozole. Both vitamin C and vitamin E restored reproductive cycling; however, vitamin C was more effective. Moreover, vitamin C reduced testosterone levels, whereas vitamin E led to minor elevations. Both vitamins enhanced total antioxidant capacity and reduced malondialdehyde levels. Ascorbic acid and alpha-tocopherol also reduced ovarian weight, effectively removing cysts in the ovaries and congestion in the uterus [32].

According to Heidari et al., vitamin E supplementation or vitamin E in combination with omega-3 or magnesium had a positive impact on lipid profile (reduced serum levels of triglycerides, VLDL, LDL-c, TC, TC/HDL-c ratio) when compared with placebo. Moreover, the intervention reduced the hs-CRP and hirsutism score. However, there was no difference in HDL-c levels, glycemic indices, hormonal profile, anthropometric measurements, or other biomarkers related to inflammation or oxidative stress. This meta-analysis emphasizes not only the potential anti-oxidant and anti-inflammatory properties of vitamin E but also its significant anti-hyperlipidemic effect on PCOS patients [33].

3. Other antioxidants

3.1. N-acetylcysteine

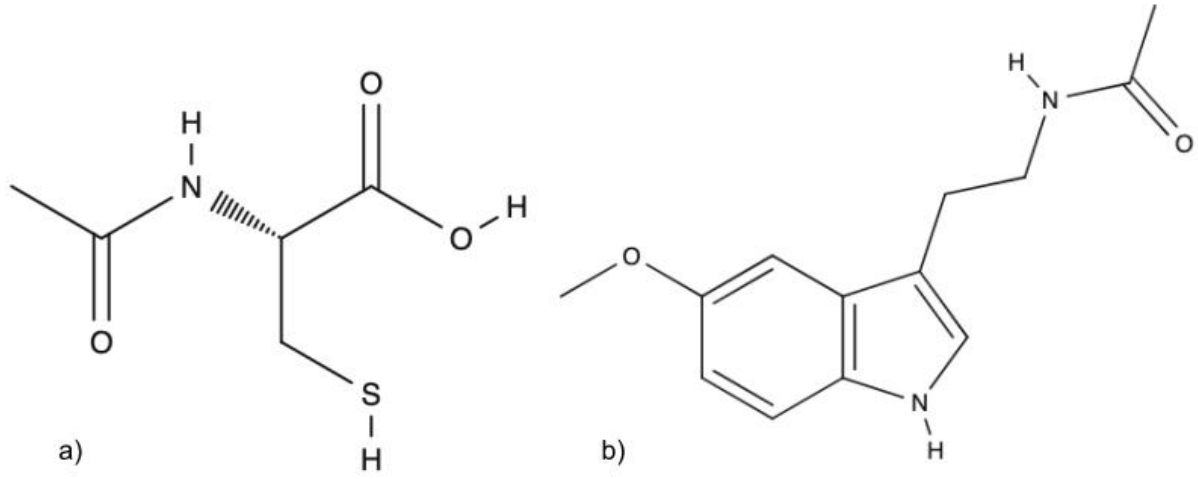

Figure 3. a) Structural formula of NAC (N-Acetyl-L-cysteine); b) Structural formula of Melatonin (N-acetyl-5-methoxytryptamine)

N-acetylcysteine (NAC) is a synthetic sulfur-containing compound derived from the natural amino acid L-cysteine and a precursor of glutathione; a very powerful antioxidant that naturally exists in the human body [34] [35] . NAC is commonly known for being an antidote to paracetamol overdose, but it is also a mucolytic agent [34] . NAC has extraordinary antioxidant, radical scavenging and anti-inflammatory properties. Being a thiol molecule, it exhibits high stability, safety and is commercially available at a low cost. Therefore, it could potentially be used in the treatment of disorders associated with oxidative stress and inflammation [36] [37]. NAC has important direct antioxidant activity as it is able to increase the intracellular concentration of glutathione. Research has revealed that NAC, since it has anti-inflammatory activity, can reduce levels of tumor necrosis factor-alpha (TNF-α) and interleukins (IL-6 and IL-1β) by suppressing the activity of nuclear factor kappa B (NF-κB) [37].

Since sex hormone levels are crucial in PCOS treatment, NAC supplementation has been proven to reduce total testosterone levels and increase FSH (follicle-stimulating hormone) levels [38]. Women diagnosed with PCOS have a high rate of infertility. A meta-

analysis from 2015 by Thakker et al. demonstrated that PCOS patients after NAC intervention had higher chances of ovulation, pregnancy, and giving birth in comparison with placebo [39]. Another meta-analysis, involving 869 women with PCOS, demonstrated that NAC treatment had a positive impact on their metabolic parameters, such as: body mass index, body weight, fasting insulin, ratio of fasting blood glucose to fasting insulin, total cholesterol, triglycerides, and low-density lipoprotein comparing with metformin. Moreover, in comparison with metformin or placebo, NAC highly decreased fasting blood-glucose levels [40].

Unfortunately, the results of clinical studies on NAC supplementation in women with PCOS are ambiguous; other meta-analyses found no significant difference in pregnancy rate, serum LH level, fasting insulin, and LH/FSH ratio compared with the placebo group, whereas the previously mentioned study demonstrated a relevant difference in most of those parameters [41].

3.2. Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone that is synthesized by the pineal gland from a precursor, which is the amino acid tryptophan [42][43]. While this compound plays a vital role in regulating the sleep-wake cycle, it is also a highly effective antioxidant [42] [44]. The reduction in oxidative stress caused by melatonin seems to be far more effective than in vitamins C and E, as well as glutathione. A single molecule of melatonin is able to capture up to 10 ROS (reactive oxygen species), while the classic antioxidants neutralize one or less ROS [43]. Furthermore, melatonin increases the effectiveness of mitochondrial oxidative phosphorylation and reduces electron leakage, thus lowering free radical generation [45]. The pituitary gland's hormone can also stimulate antioxidant enzymes such as SOD, CAT, GPx. Moreover, melatonin protects cells from lipid peroxidation by reducing levels of MDA (malondialdehyde) and decreasing TBARS (thiobarbituric acid reactive substances). The metabolites of melatonin also possess antioxidant properties [43]. Li et al. proved in their clinical trial that women with PCOS have decreased melatonin concentrations in follicular fluid and mild sleep disturbances [46]. Another study found that patients with PCOS after 12 weeks of melatonin intervention (5 mg twice a day) had a major reduction in hirsutism, total testosterone, highly-sensitive CRP, and plasma malondialdehyde levels. Additionally, their plasma total antioxidant capacity and total glutathione levels significantly increased. Melatonin supplementation also reduced the gene expression of IL-1 and TNF-α [47]. Weight loss is usually a first-line treatment for PCOS.

Melatonin seems to be beneficial in this process since it has been demonstrated that administration of 3 mg of melatonin daily for 2 months reduces LH levels and BMI in PCOS patients in comparison with the control group [48].

Discussion

Polycystic ovary syndrome is one of the most frequent endocrinopathies in women of reproductive age. PCOS patients present heterogeneous clinical manifestations with several phenotypes of the disorder. However, usually women with PCOS suffer from anovulation, infertility, and symptoms of hyperandrogenism such as acne, hirsutism, or female androgenetic alopecia [1][2]. The precise etiology and pathophysiology of PCOS are still not clear because of the multifactorial and complex nature of the disease [4] . Nevertheless, oxidative stress and reduced levels of antioxidants play a significant role in the development of PCOS [8]. Taking this into consideration, in this review, we have presented the effects of six antioxidants: resveratrol, curcumin, vitamin C and E, N-acetylcysteine, and melatonin in PCOS treatment.

Resveratrol has an impact on two main components of PCOS: hormonal imbalance and metabolic abnormalities, reducing testosterone and DHEAS, and fasting insulin levels. It also demonstrated improvement in the insulin sensitivity index [15] . Since it seems that chronic low-grade inflammation plays an important role in PCOS pathogenesis, resveratrol has huge potential in this field [49] . It reduces chronic inflammation; it was proven that resveratrol reduces inflammatory markers. Moreover, the anti-inflammatory and antioxidant effects of resveratrol can modulate ER stress in patients with PCOS, and it is a promising therapeutic target in PCOS treatment [16]. The combination of resveratrol and metformin has shown efficacy in maintaining folliculogenesis. This study has shown not only the potential of resveratrol in PCOS treatment, but the authors have also suggested that it could be highly effective as a complementary therapy with metformin [17] . Moreover, it was proven that resveratrol works not only on the molecular level but also on the clinical level, alleviating the symptoms of PCOS like menstrual irregularity and hair loss [18] . Resveratrol has therapeutic potential for patients with PCOS. However, the results of the studies are not fully consistent. Therefore, more high-quality randomized clinical trials on a larger sample are necessary. Also, there is a need for studies evaluating the effects of long-term supplementation with resveratrol and assessing the most efficient dosage of resveratrol for PCOS patients.

Curcumin, just like reveratrol, effectively reduced CRP levels. It also had a positive influence on glucose metabolism by reducing fasting blood glucose levels, and improving HOMA-IR, insulin level, and insulin sensitivity check index (QUICKI). What's crucial in PCOS treatment, curcumin contribiuted to BMI reduction and ameliorated lipid profile in PCOS patients [25] [26] . Moreover, their menstruation was more frequent after the curcumin administration [27] . According to current studies, curcumin is very promising in terms of PCOS treatment; however, prospective randomized clinical trials on a larger sample are needed to establish a final conclusion.

Vitamin C and E might have positive effects on PCOS; however, most of the presented studies were conducted on animal models. Vitamin C reduced testosterone levels and oxidative stress marker levels. Both vitamins restored reproductive cycling and reduced ovarian weight, effectively removing cysts [31][32]. Vitamin E in combination with omega-3 or magnesium had a positive impact on lipid profile, inflammation marker, and hirsutism score [33] . Vitamin C and E seem to be beneficial in the therapy of PCOS; however, well-designed clinical trials are necessary to confirm these findings.

Administration of N-acetylcysteine in PCOS reduced total testosterone levels and increased FSH levels; it also increased the chances of ovulation, pregnancy, and giving birth [38] [39] . In comparison with metformin, NAC presented was efficient in terms of improving metabolic parameters, lipid profile, and BMI [40] . Thus, NAC might be considered as an alternative to metformin. Even though NAC administration is surely beneficial, safe, and effective for PCOS patients, prospective, high-quality randomized clinical trials on a large sample are necessary for a clear-cut conclusion.

Melatonin significantly reduces testosterone and LH levels, BMI, hirsutism, as well as levels of oxidative stress and inflammation markers [43] [47] [48] . Therefore, patients with PCOS may benefit from melatonin through several mechanisms regulating their hormones, glucose metabolism, and combating oxidative stress and chronic inflammation.

Conclusion

The results of all the reviewed studies in this paper indicate that antioxidants such as resveratrol, curcumin, vitamin C and E, N-acetylcysteine, and melatonin have therapeutic potential in the management of PCOS. These compounds improve several aspects of the PCOS pathomechanism, including hormonal imbalance, glucose metabolism, lipid profile, ovarian functionality, chronic inflammation, and oxidative stress. However, currently antioxidant therapies cannot be recommended in PCOS therapy since there is a need for more

prospective randomized clinical trials on a larger sample to establish a long-term effects of antioxidants supplementation in PCOS, the optimal dosage, and finally to assess which antioxidant is the most efficient in PCOS treatment.

Author's contribution:

Conceptualization, OŁ, and KS; methodology, EW; software, KC; check, KC, AMK, AK and KB; formal analysis, EO; investigation, EW; resources, OS, KC, EW; data curation, OŁ, KS, AMK, KC, AK, JJ, OS, EO, EW, KB; writing – rough preparation, OŁ, KS, EW, AK, JJ; writing – review and editing, OŁ, KS, AMK, KC, AK, JJ, OS, EO, EW, KB; visualization, JJ and AMK; supervision, OŁ and KS; project administration, OŁ, KS, AK, OS;

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References

1. Teede, H.J., Tay, C.T., Laven, J.J.E., Dokras, A., Moran, L.J., Piltonen, T.T., Costello, M.F., Boivin, J., Redman, L.M., Boyle, J.A., Norman, R.J., Mousa, A., Joham, A.E., Network, on behalf of the I.P.: Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 108, 2447–2469 (2023). https://doi.org/10.1210/CLINEM/DGAD463
2. Dennett, C.C., Simon, J.: The Role of Polycystic Ovary Syndrome in Reproductive and Metabolic Health: Overview and Approaches for Treatment. Diabetes Spectr. 28, 116 (2015). https://doi.org/10.2337/DIASPECT.28.2.116
3. Teede, H.J., Tay, C.T., Laven, J., Dokras, A., Moran, L.J., Piltonen, T.T., Costello, M.F., Boivin, J., M Redman, L., A Boyle, J., Norman, R.J., Mousa, A., Joham, A.E., International PCOS Network: Recommendations from the 2023 International Evidence-based Guideline for

the Assessment and Management of Polycystic Ovary Syndrome. Fertil Steril. 120, 767–793 (2023). https://doi.org/10.1016/j.fertnstert.2023.07.025

4. Hajam, Y.A., Rather, H.A., Neelam, Kumar, R., Basheer, M., Reshi, M.S.: A review on critical appraisal and pathogenesis of polycystic ovarian syndrome. Endocrine and Metabolic Science. 14, 100162 (2024). https://doi.org/10.1016/J.ENDMTS.2024.100162
5. Harada, M.: Pathophysiology of polycystic ovary syndrome revisited: Current understanding and perspectives regarding future research. Reprod Med Biol. 21, (2022). https://doi.org/10.1002/RMB2.12487
6. Rasquin, L.I., Anastasopoulou, C., Mayrin, J. V.: Polycystic Ovarian Disease. Encyclopedia of Genetics, Genomics, Proteomics and Informatics. 1528–1528 (2022). https://doi.org/10.1007/978-1-4020-6754-9_13178
7. Preiser, J.C.: Oxidative stress. JPEN J Parenter Enteral Nutr. 36, 147–154 (2012). https://doi.org/10.1177/0148607111434963
8. Fenkci, V., Fenkci, S., Yilmazer, M., Serteser, M.: Decreased total antioxidant status and increased oxidative stress in women with polycystic ovary syndrome may contribute to the risk of cardiovascular disease. Fertil Steril. 80, 123–127 (2003). https://doi.org/10.1016/S0015-0282(03)00571-5
9. Murri, M., Luque-ramírez, M., Insenser, M., Ojeda-ojeda, M., Escobar-morreale, H.F.: Circulating markers of oxidative stress and polycystic ovary syndrome (PCOS): a systematic review and meta-analysis. Hum Reprod Update. 19, 268–288 (2013). https://doi.org/10.1093/HUMUPD/DMS059
10. Janciauskiene, S.: The Beneficial Effects of Antioxidants in Health and Diseases. Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation. 7, 182 (2020). https://doi.org/10.15326/JCOPDF.7.3.2019.0152
11. Tan, D.X., Manchester, L.C., Esteban-Zubero, E., Zhou, Z., Reiter, R.J.: Melatonin as a Potent and Inducible Endogenous Antioxidant: Synthesis and Metabolism. Molecules. 20, 18886 (2015). https://doi.org/10.3390/MOLECULES201018886
12. Lobo, V., Patil, A., Phatak, A., Chandra, N.: Free radicals, antioxidants and functional foods: Impact on human health. Pharmacogn Rev. 4, 118 (2010). https://doi.org/10.4103/0973-7847.70902
13. Meng, X., Zhou, J., Zhao, C.N., Gan, R.Y., Li, H. Bin: Health Benefits and Molecular Mechanisms of Resveratrol: A Narrative Review. Foods 2020, Vol. 9, Page 340. 9, 340 (2020). https://doi.org/10.3390/FOODS9030340

14. Hurst, W.J., Glinski, J.A., Miller, K.B., Apgar, J., Davey, M.H., Stuart, D.A.: Survey of the trans-resveratrol and trans-piceid content of cocoa-containing and chocolate products. J Agric Food Chem. 56, 8374–8378 (2008). https://doi.org/10.1021/JF801297W
15. Banaszewska, B., Wrotyńska-Barczyńska, J., Spaczynski, R.Z., Pawelczyk, L., Duleba, A.J.: Effects of Resveratrol on Polycystic Ovary Syndrome: A Double-blind, Randomized, Placebo-controlled Trial. J Clin Endocrinol Metab. 101, 4322–4328 (2016). https://doi.org/10.1210/JC.2016-1858
16. Brenjian, S., Moini, A., Yamini, N., Kashani, L., Faridmojtahedi, M., Bahramrezaie, M., Khodarahmian, M., Amidi, F.: Resveratrol treatment in patients with polycystic ovary syndrome decreased pro-inflammatory and endoplasmic reticulum stress markers. American Journal of Reproductive Immunology. 83, e13186 (2020). https://doi.org/10.1111/AJI.13186
17. Furat Rencber, S., Kurnaz Ozbek, S., Eraldemlr, C., Sezer, Z., Kum, T., Ceylan, S., Guzel, E.: Effect of resveratrol and metformin on ovarian reserve and ultrastructure in PCOS: An experimental study. J Ovarian Res. 11, 1–16 (2018). https://doi.org/10.1186/S13048-018-0427-7/FIGURES/6
18. Mansour, A., Samadi, M., Sanginabadi, M., Gerami, H., Karimi, S., Hosseini, S., Shirzad, N., Hekmatdoost, A., Mahdavi-Gorabi, A., Mohajeri-Tehrani, M.R., Qorbani, M.: Effect of resveratrol on menstrual cyclicity, hyperandrogenism and metabolic profile in women with PCOS. Clinical Nutrition. 40, 4106–4112 (2021). https://doi.org/10.1016/J.CLNU.2021.02.004
19. Prasad, S., Aggarwal, B.B.: Turmeric, the Golden Spice. Herbal Medicine: Biomolecular and Clinical Aspects: Second Edition. 263–288 (2011)
20. Jin, T.R.: Curcumin and dietary polyphenol research: beyond drug discovery. Acta Pharmacologica Sinica 2018 39:5. 39, 779–786 (2018). https://doi.org/10.1038/aps.2017.179
21. Wang, W., Trung, K., Nguyen, K., Zhao, C., Hung, H.-C.: A N T H R O P O LO G Y Earliest curry in Southeast Asia and the global spice trade 2000 years ago. (2023)
22. Indira Priyadarsini, K.: Chemical and structural features influencing the biological activity of curcumin. Curr Pharm Des. 19, 2093–2100 (2013). https://doi.org/10.2174/138161213805289228
23. Ardebili, A., Pouriayevali, M.H., Aleshikh, S., Zahani, M., Ajorloo, M., Izanloo, A., Siyadatpanah, A., Nikoo, H.R., Wilairatana, P., Coutinho, H.D.M.: Antiviral Therapeutic Potential of Curcumin: An Update. Molecules. 26, (2021). https://doi.org/10.3390/MOLECULES26226994

24. Martins, C.V.B., Da Silva, D.L., Neres, A.T.M., Magalhães, T.F.F., Watanabe, G.A., Modolo, L. V., Sabino, A.A., De Fátima, Â., De Resende, M.A.: Curcumin as a promising antifungal of clinical interest. J Antimicrob Chemother. 63, 337–339 (2009). https://doi.org/10.1093/JAC/DKN488
25. Shen, W., Qu, Y., Jiang, H., Wang, H., Pan, Y., Zhang, Y., Wu, X., Han, Y., Zhang, Y.: Therapeutic effect and safety of curcumin in women with PCOS: A systematic review and meta-analysis. Front Endocrinol (Lausanne). 13, 1051111 (2022). https://doi.org/10.3389/FENDO.2022.1051111/BIBTEX
26. Jamilian, M., Foroozanfard, F., Kavossian, E., Aghadavod, E., Shafabakhsh, R., Hoseini, A., Asemi, Z.: Effects of curcumin on body weight, glycemic control and serum lipids in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. Clin Nutr ESPEN. 36, 128–133 (2020). https://doi.org/10.1016/J.CLNESP.2020.01.005
27. Ghanbarzadeh-Ghashti, N., Ghanbari-Homaie, S., Shaseb, E., Abbasalizadeh, S., Mirghafourvand, M.: The effect of Curcumin on metabolic parameters and androgen level in women with polycystic ovary syndrome: a randomized controlled trial. BMC Endocr Disord. 23, 1–10 (2023). https://doi.org/10.1186/S12902-023-01295-5/TABLES/4
28. Abdullah, M., Jamil, R.T., Attia, F.N.: Vitamin C (Ascorbic Acid). Encyclopedia of Toxicology: Third Edition. 962–963 (2023). https://doi.org/10.1016/B978-0-12-386454-3.01250-1
29. Padayatty, S.J., Katz, A., Wang, Y., Eck, P., Kwon, O., Lee, J.H., Chen, S., Corpe, C., Levine, M., Dutta, A., Dutta, S.K.: Vitamin C as an Antioxidant: Evaluation of Its Role in Disease Prevention. J Am Coll Nutr. 22, 18–35 (2003). https://doi.org/10.1080/07315724.2003.10719272
30. Gęgotek, A., Skrzydlewska, E.: Ascorbic acid as antioxidant. Vitam Horm. 121, 247–270 (2023). https://doi.org/10.1016/BS.VH.2022.10.008
31. Olaniyan, O.T., Femi, A., Iliya, G., Ayobami, D., Godam, E., Olugbenga, E., Bamidele, O., Chand Mali, P.: Vitamin C suppresses ovarian pathophysiology in experimental polycystic ovarian syndrome. Pathophysiology. 26, 331–341 (2019). https://doi.org/10.1016/J.PATHOPHYS.2019.08.003
32. Bafor, E.E., Uchendu, A.P., Osayande, O.E., Omoruyi, O., Omogiade, U.G., Panama, E.E., Elekofehinti, O.O., Oragwuncha, E.L., Momodu, A.: Ascorbic Acid and Alpha-Tocopherol Contribute to the Therapy of Polycystic Ovarian Syndrome in Mouse Models. Reproductive Sciences. 28, 102–120 (2021). https://doi.org/10.1007/S43032-020-00273-9/TABLES/2

33. Heidari, H., Hajhashemy, Z., Saneei, P.: A meta-analysis of effects of vitamin E supplementation alone and in combination with omega-3 or magnesium on polycystic ovary syndrome. Scientific Reports 2022 12:1. 12, 1–13 (2022). https://doi.org/10.1038/s41598-022-24467-0
34. Raghu, G., Berk, M., Campochiaro, P.A., Jaeschke, H., Marenzi, G., Richeldi, L., Wen, F.-Q., Nicoletti, F., Calverley, P.M.A.: The Multifaceted Therapeutic Role of N-Acetylcysteine (NAC) in Disorders Characterized by Oxidative Stress. Curr Neuropharmacol. 19, 1202–1224 (2021). https://doi.org/10.2174/1570159X19666201230144109
35. Hristov, B.D.: The Role of Glutathione Metabolism in Chronic Illness Development and Its Potential Use as a Novel Therapeutic Target. Cureus. 14, (2022). https://doi.org/10.7759/CUREUS.29696
36. Aldini, G., Altomare, A., Baron, G., Vistoli, G., Carini, M., Borsani, L., Sergio, F.: N-Acetylcysteine as an antioxidant and disulphide breaking agent: the reasons why. Free Radic Res. 52, 751–762 (2018). https://doi.org/10.1080/10715762.2018.1468564
37. Tenório, M.C.D.S., Graciliano, N.G., Moura, F.A., de Oliveira, A.C.M., Goulart, M.O.F.: N-Acetylcysteine (NAC): Impacts on Human Health. Antioxidants 2021, Vol. 10, Page 967. 10, 967 (2021). https://doi.org/10.3390/ANTIOX10060967
38. Shahveghar Asl, Z., Parastouei, K., Eskandari, E.: 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, 202–210 (2023). https://doi.org/10.1017/S0007114522003270
39. Thakker, D., Raval, A., Patel, I., Walia, R.: N-Acetylcysteine for Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Clinical Trials. Obstet Gynecol Int. 2015, 1–13 (2015). https://doi.org/10.1155/2015/817849
40. Liu, J., Su, H., Jin, X., Wang, L., Huang, J.: The effects of N-acetylcysteine supplement on metabolic parameters in women with polycystic ovary syndrome: a systematic review and meta-analysis. Front Nutr. 10, 1209614 (2023). https://doi.org/10.3389/FNUT.2023.1209614/FULL
41. Song, Y., Wang, H., Huang, H., Zhu, Z.: Comparison of the efficacy between NAC and metformin in treating PCOS patients: a meta-analysis. Gynecol Endocrinol. 36, 204–210 (2020). https://doi.org/10.1080/09513590.2019.1689553
42. Pereira, J.C., Pradella Hallinan, M., Alves, R.C.: Secondary to excessive melatonin synthesis, the consumption of tryptophan from outside the blood-brain barrier and melatonin over-

signaling in the pars tuberalis may be central to the pathophysiology of winter depression. Med Hypotheses. 98, 69–75 (2017). https://doi.org/10.1016/J.MEHY.2016.11.020

43. Chrustek, A., Olszewska-Słonina, D.: Melatonin as a powerful antioxidant. Acta Pharmaceutica. 71, 335–354 (2021). https://doi.org/10.2478/ACPH-2021-0027
44. Reiter, R.J., Mayo, J.C., Tan, D.X., Sainz, R.M., Alatorre-Jimenez, M., Qin, L.: Melatonin as an antioxidant: under promises but over delivers. J Pineal Res. 61, 253–278 (2016). https://doi.org/10.1111/JPI.12360
45. Reiter, R.J., Tan, D.X., Mayo, J.C., Sainz, R.M., Leon, J., Czarnocki, Z.: Melatonin as an antioxidant: Biochemical mechanisms and pathophysiological implications in humans, (2003)
46. Li, H., Liu, M., Zhang, C.: Women with polycystic ovary syndrome (PCOS) have reduced melatonin concentrations in their follicles and have mild sleep disturbances. BMC Womens Health. 22, 1–9 (2022). https://doi.org/10.1186/S12905-022-01661-W/TABLES/4
47. Jamilian, M., Foroozanfard, F., Mirhosseini, N., Kavossian, E., Aghadavod, E., Bahmani, F., Ostadmohammadi, V., Kia, M., Eftekhar, T., Ayati, E., Mahdavinia, M., Asemi, Z.: Effects of Melatonin Supplementation on Hormonal, Inflammatory, Genetic, and Oxidative Stress Parameters in Women With Polycystic Ovary Syndrome. Front Endocrinol (Lausanne). 10, 273 (2019). https://doi.org/10.3389/FENDO.2019.00273
48. Al-Qadhi, H.I.: Effect of Melatonin Supplementation on Serum LH Level and BMI in Women with Polycystic Ovarian Syndrome.
49. Rudnicka, E., Suchta, K., Grymowicz, M., Calik-ksepka, A., Smolarczyk, K., Duszewska, A.M., Smolarczyk, R., Meczekalski, B.: Chronic Low Grade Inflammation in Pathogenesis of PCOS. International Journal of Molecular Sciences 2021, Vol. 22, Page 3789. 22, 3789 (2021). https://doi.org/10.3390/IJMS22073789