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Review Article

The Effect of Vitamin E on Hormonal Regulations in Polycystic Ovary Syndrome (PCOS): A Review

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ABSTRACT

Polycystic ovary syndrome (PCOS) is an endocrine disorder that affects women of reproductive age. It is commonly linked to abnormal secretion of sex hormones, leading to disruptions in normal ovarian function. Vitamin E, a powerful lipid-soluble vitamin, has been extensively reported to have numerous positive health effects on the female reproductive system. Despite the existing studies, specific reports on the effects of vitamin E on hormonal regulations in PCOS are limited. Therefore, this paper aims to review the available reports on this topic, providing a reference for future studies on vitamin E and PCOS.

Keywords: Female reproduction, Polycystic ovary syndrome, Tocotrienols, Tocopherols.

Introduction

Polycystic ovary syndrome (PCOS) is among women's most common endocrine disorders. It can be defined as a combination of signs and symptoms of androgen excess, ovarian dysfunction, and polycystic ovarian morphology (Figure 1).[1] PCOS involves hormonal imbalances, which can cause an increased risk of infertility. This is because a woman with PCOS has rising levels of luteinizing hormone (LH) and reduced levels of follicle-stimulating hormone (FSH). As a result of these imbalances, oligomenorrhea or amenorrhea (lack of menstruation) may occur.[2]

Vitamin E

Vitamin E ($C_{29}H_{50}O_2$; mol. weight: 472.7 g/mol) was first discovered in 1922 by Evans and Bishop.[4] This natural lipid-soluble vitamin is found in various fruits and vegetables;[5] and is reported to possess antioxidant properties, specifically as a peroxyl radical scavenger for the body's defense system. Vitamin E is present in eight different forms which are the four forms of tocopherols (TOCs) and tocotrienols (TCTs) respectively. These forms are the alpha-, beta-, gamma- and delta-TOCs and TCTs. Structurally both TOCs and TCTs differ in the presence of double bonds and the number of methyl groups in the structure (Figure 2). Study reports on the benefits of vitamin E are widely available, however, reports on its role in hormonal regulations, particularly in PCOS conditions are lacking. Hence, this review was done to provide an analyzed report on the effects of vitamin E in PCOS subjects.

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Methods

In this review, several databases such as 'NCBI', 'Elsevier', 'PubMed', 'MDPI', and 'Google Scholar' were browsed to retrieve articles related to vitamin E, PCOS and hormonal studies. The search keywords used were 'vitamin E', 'PCOS', 'hormones', 'hyperandrogenism', 'steroidogenesis', and 'female reproductive system'.

Results and Discussion

Vitamin E and PCOS

Vitamin E has been suggested as one of the micronutrient supplements to improve PCOS symptoms due to the study reports that supported its potential. Reports are available on the effects of vitamin E on metabolic effects, inflammation and oxidative stress biomarkers, and histological structures in PCOS. For instance, a single-blind randomized control trial (RCT) was conducted on patients who underwent ovulation induction with clomiphene citrate (CC) and followed up for 6 months.[7] Findings from this study reported that antioxidant supplementation including vitamin E significantly improved the pregnancy rate, live births, and menstrual regularization in PCOS patients.[7]

Another randomized double-blind, placebo-controlled trial on the effects of omega-3 fatty acids and vitamin E co-supplementation reported a significant improvement of gene expression of lipoprotein(a) (Lp[a]) and oxidized low-density lipoprotein (Ox-LDL), lipid profiles and oxidative stress (OS) biomarkers in PCOS women.[8] These findings were also supported by a study that reported the addition of vitamin E (of various concentrations) into the culture media increased the rate of *in vitro* fertilization (IVF), quality and morphology of embryos, and reduced rate of embryonic lysis, fragmentation, and vacuolation.[9] A review report also documented that co-supplementation of coenzyme Q10 (CoQ10) and vitamin E in PCOS patients exerted a more promising result than supplementation with either CoQ10 or vitamin E alone, due to the antioxidant nature possessed by both of them.[10]

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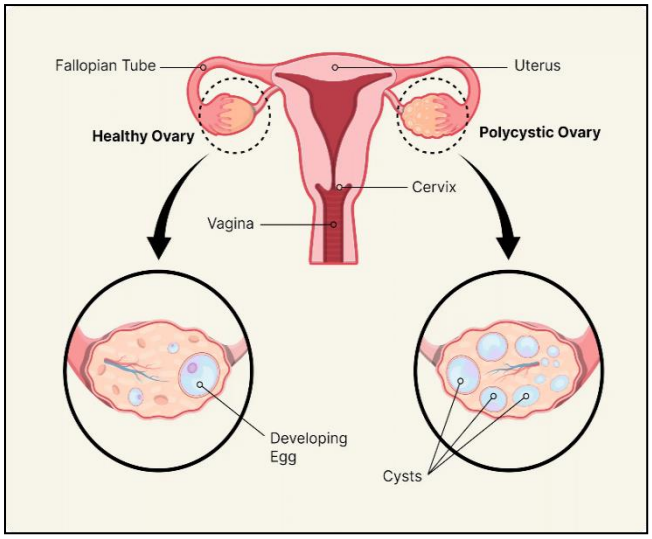
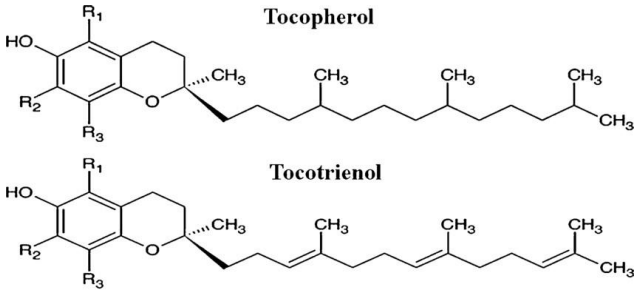


Figure 1: Comparison between the ovarian anatomy in normal and PCOS patients.[3]

In addition, a study by Begum and Mohan[11] on the therapeutic effect of vitamin E in combination with combined oral contraceptive (COC) against PCOS using both *in silico* and *in vivo* approaches reported that supplementation of vitamin E combined with COC could be effective against PCOS. Another recent study conducted using the Mendelian randomization approach reported that genetically presented higher values of vitamin E correlated with a lower risk of PCOS.[12] Vitamin E also has been reported to outperform some common clinical medications such as clomiphene citrate and metformin through the improvisation of the ovulatory and pregnancy rates, as well as improved endometrial conditions.[13] The use of vitamin E in combination with other substances such as ethinyl estradiol, cyproterone, and metformin showed a more promising approach to promote ovulation and increase the possibility of pregnancy compared to individual usage of those substances.[13] To conclude, the discussed studies above present evidence that the inclusion of vitamin E in the dietary and/or treatment has the potential to improve the signs of PCOS.



	R_1	R_2	R_3
α	CH_3	CH_3	CH_3
β	H	CH_3	CH_3
γ	CH_3	H	CH_3
δ	H	H	CH_3

Figure 2: The structural differences between TOCs and TCTs.[6]

Vitamin E and PCOS: Reports on hormonal regulations and ovarian cycles

Evidence-based reports on the effects of vitamin E on hormonal regulations in PCOS patients have been increasingly reported. For example, a study by Hager *et al*.[14] showed that 3 months of continuous intake of multi-nutrient supplementation that contains vitamin E improved PCOS-specific signs such as the LH: FSH ratio, serum testosterone, and serum anti-Mullerian hormone (AMH). The ability of vitamin E to balance the LH: FSH ratio and reduce the level of testosterone in PCOS patients was also reported in another study.[15] An earlier study suggested that multiple micronutrient supplementation containing vitamin E is adjuvant therapy to a standard ovulation induction treatment in women undergoing anovulatory treatment, which resulted in improved ovulation and pregnancy rate.[16]

Tefagh *et al*.[17] in a systematic review reported that vitamin E supplementation decreases LH and testosterone levels, and increases FSH and progesterone levels, suggesting intake of supplementation containing vitamin E can positively affect hormonal parameters in women with PCOS. Consumption of vitamin E is also reported to help antagonize oxidative stress and antioxidant imbalance which can help reduce hyperandrogenism in PCOS patients.[15] Other reported studies on vitamin E on the hormonal regulations and ovarian cycle are summarized in Table 1.

PCOS: Oxidative stress (OS) and vitamin E as the antioxidant

Polycystic ovary syndrome (PCOS) has been extensively studied to understand its etiology and pathophysiology. PCOS is categorized as a chronic systemic disorder associated with a high level of OS marked by markers such as malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GPx).[26] The high level of OS has been widely reported to be linked to the individual differences between the oxidant and antioxidant levels as well as other genetics, environment, and lifestyle factors like obesity, hyperandrogenism, insulin resistance, and chronic inflammation (Figure 3).[26-29]

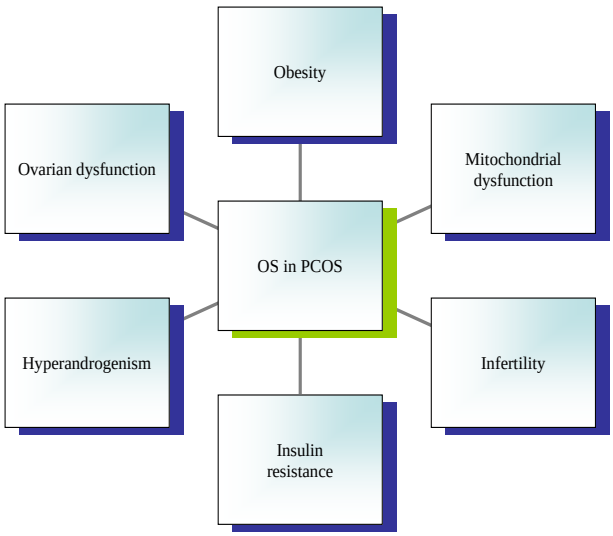


Figure 3: Effects of oxidative stress (OS) on PCOS

Vitamin E is one of the exogenous vitamins that are well-known as an antioxidant. Its lipid-soluble nature makes it a great choice of micronutrient to combat any form of OS-induced disorders including PCOS. The presence of low levels of vitamin E has been reported decades ago as one of the possible factors in PCOS patients. For instance, Mohan and Vishnu[30] reported that serum vitamin E concentration was lower in patients with PCOS. Low levels of vitamin E may interfere with normal ovarian functioning such as folliculogenesis, ovulation, and embryonic development.[31] A study by Fatima et al.[32] reported significantly low levels of vitamin E, vitamin C, and glutathione in PCOS patients and these findings were also supported by other reports.[28,29,33]

Vitamin E was discovered as a vitamin for reproduction. Due to its lipid-soluble ability, vitamin E protects cell membrane damage from oxidation. Its effects on the female reproductive system have been documented before[34,35] including its effects on hormonal changes[36] and embryonic development.[37,38] Vitamin E's presence in the ovarian follicles, uterine secretions, and placenta is essential for oocyte and embryonic growth.[39]

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The beneficial effects of vitamin E supplementation in PCOS patients through dietary and/or treatments are being increasingly reported, however, its mechanisms of action are poorly understood. As an antioxidant, the effects of vitamin E are commonly associated with the changes in the activities of the antioxidant enzymes such as superoxide dismutase (SOD) and malonaldehyde (MDA)[28,32,40] and not many reports specifically on its molecular pathway are available.

In terms of the molecular study, the effects of vitamin E were reported on the expressions of certain genes including the tumor necrosis factor-α (TNF-α), peroxisome proliferator-activated receptors (PPARs), interleukin-8 (IL-8) and interleukin (IL)-1β. TNF-α is a cytokine that regulates numerous cellular processes such as immune and inflammatory responses, cell proliferation and apoptosis.[41] In the female reproductive system, TNF-α also modulates ovarian granulose cell proliferation, follicular development, and ovulation[42] and it is also a proinflammatory cytokine that plays a role in the pathogenesis of PCOS.

PPARs are present in ovaries and have vital roles in the functioning of the female reproductive system[43] with PPAR-α are mainly found in the ovarian theca and stromal cells, PPAR-β and PPAR-δ are present in the entire ovaries and PPAR-γ are vital for the folliculogenesis process.[44,45] PPAR-γ was also reported to be associated with the possibilities of PCOS through the low concentration of estradiol.[46]

Interleukin 8 (IL-8) and interleukin 1β (IL-1β) is a proinflammatory cytokine involved in cell proliferation and inflammation. An earlier study has reported that in PCOS patients, the expression of the IL-8 gene was up-regulated in the granulosa cells.[47] Interventions with vitamin E have been reported to change the expressions of these genes in PCOS patients. Omega-3 and vitamin E co-supplementation were shown to up-regulate PPAR-gamma (PPAR-γ) and down-regulate the IL-8 and TNF-α expressions in peripheral blood mononuclear cells (PBMC),[40] suggesting the improved parameters of gene expression of PPAR-γ, IL-8, and TNF-α of PCOS women. Another recent study reported that the regression analysis of the results of 8-week treatment with vitamin E showed a decrease of IL-1β as the predictor of ovarian diameter decrease and a decrease of serum levels of IL-1β as the predictor of decreased serum testosterone level.[28] This study concluded that vitamin E showed an improvising ability in the hormonal disorders in PCOS patients.

Table 1: Reported effects of vitamin E on the reproductive changes in PCOS subjects

Type of Study	Main Finding	Reference
Retrospective study	Patients who received treatment with vitamin E during the follicular phase had the highest estradiol level and reported lower oxidative stress biomarkers compared to the other groups.	15
Randomized, double-blind, placebo-controlled trial	This study was done on 68 PCOS patients. The patient who received omega-3 fatty acids and vitamin E co-supplementation showed a significant reduction in serum total testosterone, a decrease in insulin, and an increase in the quantitative insulin sensitivity check index compared to the placebo group.	18
Randomized, double-blind, placebo-controlled clinical trial	CoQ10, vitamin E, and co-supplementation of both in PCOS patients reduced the serum total testosterone levels (P<0.001) compared to the placebo group.	19
Randomized, double-blind, placebo-controlled trial	Magnesium and vitamin E co-supplementation resulted in a significant reduction in biomarkers of inflammation, oxidative stress and hirsutism which is caused by hyperandrogenism.	20
Intervention study (case study)	Vitamin E supplementation resulted in an eminent relief in acne, hirsutism, menstrual cycle. There were also increase in FSH hormone level, and reduction in LH and total serum testosterone levels.	21
Randomized, controlled, open-label study on clomiphene citrate (CC) – resistant PCOS patients	Supplementation of vitamin E (1500 IU/day) in addition to metformin and CC resulted in higher clinical pregnancy rates, ovulation rates, and endometrial thickness, but did not show a significant increase in ovulation and pregnancy rates.	22

Randomized, double-blind, placebo-controlled trial	This study was done on 43 PCOS patients who were divided into 2 groups. Patients in one group were given 400 IU/day of vitamin E as alpha-tocopheryl acetate and another group was given cellulose capsules for eight weeks. Findings suggest an improvement in ovarian blood circulation as well as in folliculogenesis and ovulation.	23
***In vivo* study**	Vitamin E showed marked recovery of the ovarian tissue with the presence of many follicles in the various stages of development, indicating normal oogenesis. Follicles showed normal granulosa layers with defined thecal layers. The presence of corpora lutea was also seen, indicating that vitamin E treatment restored the normal estrous cycle.	24
Review	Antioxidants (including vitamin E) can significantly alleviate the symptoms of PCOS and prevent/treat long-term complications.	25

PCOS: Is vitamin E supplementation effective?

Supplementation with natural molecules such as vitamin C, vitamin E, vitamin D, and omega-3 fatty acids has been reported to contribute to overcoming PCOS features.[48] However, some clinical data reports contradict this theory. A double-blinded RCT study on PCOS infertile women scheduled for intracytoplasmic sperm injection (ICSI), given 8 weeks of treatment with vitamin E (400 mg/day) and vitamin D3 (50,000 IU/one in two weeks) reported no added clinical support to the evidence that vitamins E and D3 may play a role in the success rate of IVF through the antioxidant mechanism.[49]Another recent retrospective case-control study on the role of vitamin E supplementation during cycles in CC-induced ovulation also found that vitamin E supplementation was not effective in increasing the number of dominant follicles, ovulation rates, and pregnancy rates in infertile women with PCOS.[50] On top of that, a similar report that documents the benefits of vitamin E following a retrospective analysis as discussed above[15] also reported that short-term supplementation with vitamin E in PCOS patients treated with CC had no effects on the pregnancy rate in the ovulation induction cycle. Another report on meta-analysis found that supplementation with vitamin E alone or in combination with omega-3 or magnesium showed no significant effect on the hormonal profile of testosterone, FSH, LH, and sex hormone-binding globulin (SHB), and OS biomarkers such as MDA, glutathione (GSH) and total antioxidant capacity (TAC) in PCOS patients.[51]

Conclusion

Vitamin E can improve the symptoms of PCOS as reported in many studies.[52] However, some clinical trials have shown the opposite results, which warrants further studies to confirm the effects and regulation of vitamin E, perhaps at the molecular level that controls the changes in PCOS symptoms. This is important to understand whether there are different effects of the roles of vitamin E in different approaches to treatments.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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References

1. Escobar-Morreale HF. Polycystic ovary syndrome: Definition, aetiology, diagnosis and treatment. In: Nature Reviews Endocrinology (vol.14). Nature Publishing Group; 2018. 270–284 p.
2. Bulsara J, Patel P, Soni A, Acharya S. A review: Brief insight into polycystic ovarian syndrome. In: Endocrine and Metabolic Science 2021. (vol.3) . 100085 Elsevier Ltd;
3. Berry Fertility. PCOS and Fertility: Everything You Need to Know. [Online]. 2022[cited 2024 Apr 5]. Available from: https://www.berryfertility.com/articles/pcos-and-fertility-everything-you-need-to-know
4. Evans HM and Bishop KS. On the existence of a hitherto unrecognized dietary factor essential for reproduction. Sci. 1922; 56: 650–651.
5. Udoh BE, Erim AE, Paulinus SO, Eru EM, Ukpong EV, Efanga I, Archibong BE, Egong AE, Udo EE,Egbe NO. Effects of *Cyperus esculentus*(Tiger Nut) Extract on the Irradiated Testes of Wistar Rats. Trop J Nat Prod Res. 2020; 4(11): 966-969.
6. Alqahtani S, Kaddoumi A. Vitamin E Transporters in Cancer Therapy.AAPS J. 2015; 17: 313–322.
7. Panti A, Shehu C, Saidu Y, Tunau K, Nwobodo E, Jimoh A, Bilbis L, Umar A, Hassan M. Oxidative stress and outcome of antioxidant supplementation in patients with polycystic ovarian syndrome (PCOS). Int J Reprod Contracept Obstet Gynecol. 2018;7:1667–1672.
8. Rahmani E, Samimi M, Ebrahimi FA, Foroozanfard F, Ahmadi S, Rahimi M, Jamilian M, Aghadavod E, Bahmani

F, Taghizadeh M, Memarzadeh MR, Asemi Z. The effects of omega-3 fatty acids and vitamin E co-supplementation on gene expression of lipoprotein(a) and oxidized low-density lipoprotein, lipid profiles and biomarkers of oxidative stress in patients with polycystic ovary syndrome. Mol Cell Endocrinol. 2017; 439:247-255.
9. Poshdar M, Ahmadi A, Imani M. Investigation of the effect of experimental polycystic ovarian syndrome induced by stradiolvalerate on oocyte quality and in vitro fertilization potential and evaluation of vitamin E supplementation to embryo culture in mouse model. Stud Med Sci. 2018; 29(7):539-549.
10. Irianto CB and Prasetyadi EG. Coenzyme Q10 and/or vitamin E supplementation for Polycystic Ovarian Syndrome. CDK-298. 2021; 48(11):361-364.
11. Begum RF and Mohan S. Insights into vitamin E with combined oral contraceptive on INSR gene in PCOS by integrating *in silico* and *in vivo* approaches. Appl Biochem Biotechnol. 2024; 196(6):2990–3009.
12. Shen JY, Xu L, Ding Y, Wu XY. Effect of vitamin supplementation on polycystic ovary syndrome and key pathways implicated in its development: A Mendelian randomization study. World J Clin Cases. 2023; 11(23):5468-5478.
13. Bhattacharya K, Dey R, Sen D, Paul N, Basak A, Purkait M, Shukla N, Chaudhuri G, Bhattacharya A, Maiti R, Adhikary K, Chatterjee P, Karak P, Syamal A. Polycystic ovary syndrome and its management: In view of oxidative stress. Biomol Concepts. 2024; 15(1):20220038.
14. Hager M, Nouri K, Imhof M, Egarter C, Ott J. The impact of a standardized micronutrient supplementation on PCOS-typical parameters: a randomized controlled trial. Arch Gynecol Obstet. 2019; 300: 455–460.
15. Chen J, Guo Q, Pei YH, Ren QL, Chi L, Hu RK, Tan Y. Effect of a short-term Vitamin E supplementation on oxidative stress in infertile PCOS women under ovulation induction: A retrospective cohort study. BMC Women's Health. 2020; 20(69):1-9.
16. Banu J, Deeba F, Sultana P, Chowdhury AA, Khan MAH. Effects of multiple micronutrients (MMN) on ovulation inductionin subfertile women with PCOS. J Paediatr Surg Bangladesh. 2015; 4(2):50-53.
17. Tefagh G, Payab M, Qorbani M, Sharifi F, Sharifi Y, Sadat M, Shirvani E, Pourghazi F, Atlasi R, Shadman Z, Rezaei N, Erfan MV, Larijani B, Ebrahimpur M. Effect of vitamin E supplementation on cardiometabolic risk factors, inflammatory and oxidative markers and hormonal functions in PCOS (polycystic ovary syndrome): A systematic review and meta-analysis. Sci Rep. 2022; 12:5770.
18. Ebrahimi FA, Samimi M, Foroozanfard F, Jamilian M, Akbari H, Rahmani E, Ahmadi S, Taghizadeh M, Memarzadeh MR, Asemi Z. The effects of omega-3 fatty acids and vitamin E co-supplementation on indices of insulin resistance and hormonal parameters in patients with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. Exp Clin Endocrinol Diabetes. 2017; 125(6):353–359.
19. Izadi A, Ebrahimi S, Shirzai S, Taghizadeh S, Parizad M, Farzadi L, Gargari BP. Hormonal and metabolic effects of coenzyme Q10 and/or vitamin E in patients with polycystic ovary syndrome. J Clin Endocrinol Metab. 2018; 104(2): 319-327.
20. Shokrpour M and Asemi Z. The effects of magnesium and vitamin E co-supplementation on hormonal status and biomarkers of inflammation and oxidative stress in women with polycystic ovary syndrome. Biol Trace Elem Res. 2019; 191(1):54–60.
21. Atheena MV and Jayakumari S. Can vitamin E be a key supplementation in polycystic ovary syndrome. Indian J Pharm Pract. 2019; 12(2):145-147.
22. Morsy AA, Sabri NA, Mourad AM, Mojahed EM, Shawki MA. Randomized controlled open-label study of the effect of vitamin E supplementation on fertility in clomiphene citrate-resistant polycystic ovary syndrome. J Obstet Gynaecol Res. 2020; 46(11):2375–2382.
23. Shirazi SH, Gargari PB, Izadi A, Taghizadeh SH, Parizad M. Effect of vitamin E on serum levels of vascular endothelial growth factor and angiopoietin-1 in women with polycystic ovary syndrome: A pilot randomized, placebo-controlled trial. Int J Fertil Steril. 2021; 15(1): 44–50.
24. Aburawi MS, Treesh SA, El Jaafari HA, El Ghedamsi MT, Nafati NA, Benmahmoud OA, Marwa A, Shebani N. Effect of vitamin E on polycystic ovary syndrome induced by dehydroepiandrosterone in female albino mice: Histological study. Malay J Pharm Sci. 2021; 19(2):111–130.
25. Cheng X and He B. Clinical and biochemical potential of antioxidants in treating polycystic ovary syndrome. Int J Womens Health. 2022; 14:467-479
26. Mohammadi M. Oxidative stress and polycystic ovary syndrome: A brief review. Int J Prev Med. 2019; 10(1):86.
27. Uçkan K, Demir H, Turan K, Sarıkaya E, Demir C. Role of oxidative stress in obese and nonobese PCOS patients. Int J Clin Pract. 2022; 2022:4579831.
28. Wagdy MA and Hamasat AA. Vitamin D & E supplemental therapy could reduce insulin resistance and control PCOS-specific inflammatory and oxidative stresses. Evid Based Women Health J. 2023; 13(4):348-356.
29. Pallav S, Sulagna D, Muhjah FH. Polycystic ovary syndrome (PCOS) and oxidative stress. J Integr Sci Technol. 2024; 12(3):752.
30. Mohan S and Priya V. Lipid peroxidation, glutathione, ascorbic acid, vitamin E, antioxidant enzyme and serum homocysteine status in patients with polycystic ovary syndrome. Biol Med. 2009; 1:44–49.
31. .Brigelius-Flohé R and Galli F. Vitamin E: a vitamin still awaiting the detection of its biological function. Mol Nutr Food Res. 2010; 54(5): 583-587.
32. Fatima Q, Shajrul A, Kawa IA, Jeelani H, Manzoor S, Masuma SR, Rashid F. Evaluation of antioxidant defense markers in relation to hormonal and insulin parameters in women with polycystic ovary syndrome (PCOS): A case-control study. Diabetes Metab Syndr: Clin Res Rev. 2019; 13(3):1957-1961.
33. Sulagna D, Pallav S, Emmanuel I, Ifeanyi M, Uchenna N. Oxidative and nitrosative stress and female reproduction: Roles of oxidants and antioxidants. J Integr Sci Technol. 2024; 12(3):754.
34. Syairah SSM, Ab-Rahim S, Rajikin MH. Vitamin E as an Antioxidant in Female Reproductive Health. Antioxidants. 2018; 7(2):22.
35. Syairah SMM. Vitamin E and reproductive health. In: Vinood B. Patel (Eds.). Molecular Nutrition. Elsevier Inc. (Online); 2020. 543-559 p.
36. Awatif NMN, Hidayah WNWI, Massita N, Ruzianisra M, Syairah SMM. Effect of delta (δ)-tocotrienol supplementation on the blood follicle stimulating hormone (FSH) and luteinising hormone (LH) levels in female mice: a preliminary study. Int J Pharm Nutraceut Cosmet Sci. 2023; 6(1):1-5.
37. Syairah SMM, Rajikin MH, Ab-Rahim S. Supplementation of annatto (*Bixa orellana*)-derived δ-tocotrienol produced high number of morula through increased expression of 3-phosphoinositide- dependent protein kinase-1 (pdk1) in mice. Int J Med Health Sci. 2015; 9(7):786-790.
38. Syairah SMM, Ab-Rahim S, Rajikin MH. Annatto (*Bixa orellana*) δ-TCT supplementation protection against embryonic malformations through alterations in PI3K/AKT-Cyclin D1 pathway. Biomolecules. 2019; 9(1):19.
39. Amin NAM, Sheikh AKSH, Arshad AH, Aziz NA, Nasir NAA, Latip NA. Are vitamin supplementation beneficial for

female gynaecology health and diseases? Molecules. 2022; 27(6):1896.
40. Jamilian M, Shojaei A, Samimi M, Afshar Ebrahimi F, Aghadavod E, Karamali M, Taghizadeh M, Jamilian H, Alaeinasab S, Jafarnejad S, Asemi Z. The effects of omega-3 and vitamin E co-supplementation on parameters of mental health and gene expression related to insulin and inflammation in subjects with polycystic ovary syndrome. J Affect Disord. 2018; 229:41-47.
41. Mac ED. TNF receptor subtype signaling: differences and cellular consequences. Cell Signal. 2002; 14:472–477.
42. Gonzalez-Navarrete F, Eisner V, Morales P, Castro O, Pommer R, Quiroga C, Lavandro S, Devoto L. Tumor necrosis factor-alpha activates nuclear factor-kappaB but does not regulate progesterone production in cultured human granulosa luteal cells. Gynecol Endocrinol. 2007; 23(7):377–384.
43. Komar CM. Peroxisome proliferator-activated receptors (PPARs) and ovarian function-implications for regulating steroidogenesis, differentiation, and tissue remodeling. Reprod Biol Endocrinol. 2005; 3:41.
44. Froment P, Fabre S, Dupont J, Pisselet C, Chesneau D, Staels B, Monget P. Expression and functional role of peroxisome proliferator-activated receptor-gamma in ovarian folliculogenesis in the sheep. Biol Reprod. 2003; 69:1665–1674.
45. Long MJ, Sairam MR, Komar CM. Initiation of the expression of peroxisome proliferator-activated receptor gamma (PPAR gamma) in the rat ovary and the role of FSH. Reprod Biol Endocrinol. 2009; 7:145.
46. Rahimi Z, Chamaie-Nejad F, Saeidi S, Rahimi Z, Ebrahimi A, Shakiba E, Vaisi-Raygani A. The association of PPARgamma Pro12Ala and C161T polymorphisms with polycystic ovary syndrome and their influence on lipid and lipoprotein profiles. Int J Fertil Steril. 2018;12:147–151.
47. Schmidt J, Weijdegard B, Mikkelsen AL, Lindenberg S, Nilsson L, Brännström M. Differential expression of inflammation-related genes in the ovarian stroma and granulosa cells of PCOS women. Mol Hum Reprod. 2014; 20(1): 49-58
48. Iervolino M, Lepore E, Forte G, Laganà AS, Buzzaccarini G, Unfer V. Natural molecules in the management of polycystic ovary syndrome (PCOS): An analytical review. Nutrients. 2021; 13(5):1677.
49. Fatemi F, Mohammadzadeh A, Sadeghi MR, Akhondi MM, Mohammadmoradi S, Kamali K, Lackpour N, Jouhari S, Zafadoust S, Mokhtar S, Giahi L. Role of vitamin E and D3 supplementation in Intra-Cytoplasmic Sperm Injection outcomes of women with polycystic ovarian syndrome: A double blinded randomized placebo-controlled trial. Clin Nutr ESPEN. 2017; 18:23-30.
50. Kanza GD and Şolt A. The effect of vitamin E supplements added to clomiphene citrate treatment on fertility in polycystic ovary syndrome. CBU-SBED: Celal Bayar Univ Health Sci Inst J. 2021; 8(3): 443-448.
51. 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. Sci Rep. 2022; 12:19927
52. Simon A, Carolyn E, Lisa JM, Vibhuti R, Aya M. Nutritional supplements and complementary therapies in polycystic ovary syndrome. Adv Nutr. 2022; 13(4):1243-1266.