World Journal of Environmental Biosciences
Available Online at: **www.environmentaljournals.org**

Volume 13, Issue 2: 36-40

https://doi.org/10.51847/JPYC23upDU

ISSN 2277- 8047

Nigella sativa on the Improvement of Ovarian Dysfunctions in Polycystic Ovary Syndrome (PCOS): A Short Review

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a multifactorial endocrine disorder that is commonly diagnosed in women of reproductive age. The reported incidents of PCOS are drastically increasing every year worldwide, however, the etiology of PCOS is still not fully comprehended. A traditional herb such as Nigella sativa is being consumed as an alternative to modern medications to manage the signs of PCOS. The effectiveness of N. sativa against PCOS signs and symptoms is being widely published, but studies focusing on its effect on ovarian dysregulations are limited. Hence, this review was written to provide an updated summary of N. sativa and the ovaries of PCOS subjects. This review gathered publications from studies conducted in an in vivo and clinical trial settings and is anticipated to be a reference for future research involving N. sativa and PCOS subjects.

Keywords: *Environment, Change, Ecosystem, Destruction, Sustainable development goals (SDGs)*

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Received: 03 March 2024
Accepted: 18 June 2024

INTRODUCTION

Polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women. It was reported that PCOS had affected around 20% of women globally (Rao *et al*., 2020). The exact causes of PCOS are still not defined but hyperandrogenism is one of the most reported possible causes of PCOS. Hyperandrogenism results from the imbalance of the hypothalamic-pituitary-ovarian axis (HPO) and oxidative stress (OS) (Ashraf *et al*., 2019; Sun *et al*., 2021) which may lead to impaired follicular development (Bertoldo *et al*., 2019). An imbalance of the HPO axis occurs when there is an increase of gonadotrophin-releasing hormone (GnRH) from the hypothalamus, favoring the production of luteinizing hormone (LH) instead of follicular stimulating hormone (FSH) (Ashraf *et al*., 2019).

In normal conditions, the development of primordial follicles to primary follicles and subsequently to secondary follicles are gonadotropin-independent while further maturation of preantral follicles to antral follicles is FSH-dependent (Rimon-Dahari *et al*., 2016; Cox & Takov, 2018). The LH receptors will be formed on the antral follicles as the further development will be LH-dependence. LH will be responsible for stimulating antral follicles into Graafian follicles (Franks & Hardy, 2018). Then, the matured oocyte will be released, and follicles will be further developed into corpus luteum. In PCOS conditions, the excessive level of androgen will block the development of follicles and a low level of FSH will cause the accumulation of preantral and antral follicles that cannot develop into corpus luteum **(Figure 1)** (John & Michael, 2021). Other than that, many atretic follicles will also be formed due to the excessive amounts of androgen. This is because androgen can go into the layer of granulosa cells of preantral follicles and bind to their cell receptors, resulting in cell death (Zhang *et al*., 2019; Aburawi *et al*., 2021).

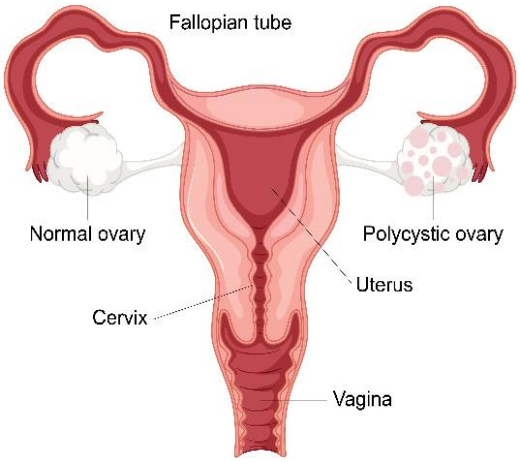

Figure 1. A normal and polycystic ovary (HealthDirect Australia Limited, 2024).

Nigella sativa – The black seeds

N. sativa is a widely used medicinal plant. It is an annual herbaceous flowering plant **(Figure 2)** from the family of Ranunculaceae and is mostly grown or cultivated in South and Southwest Asia (Ramadan, 2016). Its seeds **(Figure 3)** and oil have been used for centuries to treat various ailments (Tavakkoli *et al*., 2017), and its efficiency is reported to be due to the different contained constituents. These include terpenes (thymoquinone, dithymoquinone, p-cymene, α-pinene, limonene, carvone, anethol, etc.), steroids (α-hederin), alkaloids (nigellicine, negillidine, nigellicimine, nigellicimine-N-oxide), flavonoids (quercetin), saponins, fixed oil, coumarins, amino acids, and many others (Rajabian & Hosseinzadeh, 2020; Ahmad *et al*., 2021). Thymoquinone is the major constituent of the *N. sativa* oil contributing to its therapeutic potential as an antimicrobial, anti-inflammatory, and antioxidant.

Figure 2. The *N. sativa* flowers (Rayhanah Group Sdn Bhd, 2024).

Figure 3. The *N. sativa* seeds (Melissa, 2024).

The effectiveness of *N. sativa* against PCOS signs and symptoms is being widely published, but studies focusing on its effect on ovarian dysregulations are limited. Hence, this review was written to provide an updated summary of *N. sativa* and the ovaries of PCOS subjects. This review gathered publications from studies conducted in an in vivo and clinical trial settings and is anticipated to be a reference for future research involving *N. sativa* and PCOS subjects.

RESULTS AND DISCUSSION

N. sativa in PCOS: The reported works

The available reports on the effects of *N. sativa* on the improvisation of PCOS symptoms are limited. The study reports are mainly on hormonal changes, redox disturbances, histological analysis, and improvement of the menstrual cycle. For instance, a laboratory animal-based study was conducted to observe the protective effect of *N. sativa* on the number of cystic follicles in letrozole-induced PCOS mice. In this study, both *N. sativa* seeds powder (10 g/kg body weight) and *N. sativa* oil (4 ml/kg body weight) were used. The results showed that both forms of *N. sativa* have a similar protective effect which decreased the number of ovarian cystic follicles (Anwar *et al*., 2016). The same research group also published a study on the ameliorative impact of *N. sativa* on serum testosterone levels in letrozole-induced PCOS mice, reporting that *N. sativa* in both liquid and solid states improved serum testosterone levels (Anwar *et al*., 2021). Other studies on the improvement of *N. sativa* on body weight (Arivoli, 2019; Nafiu *et al*., 2019; Ammar & Salem, 2021; Anwar *et al*., 2021; Naghsh *et al*., 2023), and the weight, volume, and gross appearance of ovaries in PCOS mice were also reported (Anwar *et al*., 2021).

Supplementation with *N. sativa* oil to letrozole-induced rats reported a significant increase in the number of rats undergoing regular cycles, the average number of regular cycles, the appearance of corpus luteum, and the reduced number of cystic follicles (Nafiu *et al*., 2019). This study also reported on the improved levels of circulating gonadotropins, and the increased activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx) (Nafiu *et al*., 2019). A double-blinded controlled clinical trial conducted on PCOS patients with oligo-amenorrhea, with the intervention of *N. sativa* oil also indicated that *N. sativa* has the potential against menstrual irregularities as it shortens the menstrual interval and increases the frequency of the menstrual cycle in PCOS patients (Naeimi *et al*., 2018; Naeimi *et al*., 2020). These findings were also supported by a report of a non-randomized clinical trial on 40 PCOS women that showed that a 60-day intake of *N. sativa* (powder form) resulted in a normal 28-day menstrual cycle in 50% of the women, a normal 3-5 days cycle duration in 85% of the women, and a completely cleared cysts in 15% of the women (Arivoli, 2019). The improving body weight, ovarian morphology, ovulation, and serum LH and FSH following thymoquinone intervention in PCOS-induced Wistar rats were also reported (Javanshir *et al*., 2018).

The potentials of *N. sativa* are being continuously reported with the addition of a report on the synergistic effects of *N. sativa* hydro-alcoholic extract and honey on the hormonal regulations in PCOS-induced rats (Naseran *et al*., 2020). This laboratory-based study on Wistar rats reported a significant decrease in LH, estrogen, and testosterone; and an increase in FSH level following supplementation with 600 mg/kg *N. sativa* extract and 2400 mg/kg honey for 28 days. An increase in the progesterone level also was reported following the intake of 300mg/kg *N. sativa* extract and 1200mg/kg honey. Similarly, a study by Khani *et al*. (2021) reported that *N. sativa* hydro-alcoholic extract declined the levels of LH, estrogen, testosterone, and malondialdehyde (MDA) and elevated the levels of progesterone and antioxidant enzymes including SOD, GPx, and catalase (CAT) in PCOS-induced rats. *N. sativa* hydro-

alcoholic extract also improved the ovarian histological structure in which the number of Graafian follicles was increased while the number of cystic and atretic follicles decreased (Khani *et al*., 2021).

Another study (Eini *et al*., 2020) using *N. sativa* hydro-alcoholic extract on the quality of oocytes retrieved from PCOS-induced mice during *in vitro* maturation was also reported and indicated that *N. sativa* extract improves oocyte maturation, oxidative status, and epigenetic modifications. A significant increase was observed in the expression of the *Dnmt1*, *Hdac1*, *Cdk1*, *Mapk*, and *Gpx1* genes with a significant decrease in *Cox2* gene expression of the mature oocytes. These important genes play roles during fertilization and embryonic development (Eini *et al*., 2020). Improved ovarian antioxidant activity was also shown through the increase of total antioxidant capacity (TAC) and decline of malondialdehyde (MDA) level following supplementation with *N. sativa* hydro-alcoholic extract in PCOS-induced rats (Kohzadi *et al*., 2017).

Combined supplementation of 500mg of metformin and 500 mg thymoquinone (*N. sativa* oil, capsule) showed that *N. sativa* capsule intake added the improvising effect to metformin as it resumed menstrual regularity, reduced body weight, and regained oxidative balance in the overweight and obese PCOS patients (Jahromi *et al*., 2023). Another randomized double-blind clinical trial on combined supplementation using *N. sativa* and black pepper showed an increase in the pregnancy rates, size of dominant follicles, number of follicles, and endometrial thickness compared to the control group which was treated with letrozole and tamoxifen (Jahromi *et al*., 2023).

The possible effects of N. sativa

Various beneficial effects of *N. sativa* have been suggested as an antimicrobial, cardioprotective, gastroprotective, neuroprotective, anticancer, anti-diabetic, anti-dyslipidemia, anti-obesity, immunomodulatory, anti-inflammatory, nephroprotective, and anti-arthritic activities (Ahmad *et al*., 2021). *N. sativa* as an anti-infertility agent has been reported previously, however the particular reports on ovarian function are limited. From the reports discussed above, *N. sativa* of different forms such as extract, oil, and powder exerted promising effects towards improvisation of the PCOS-induced ovarian dysregulation including folliculogenesis (follicular growth), hormonal levels, structural histology, and oxidative stress. Both experimental studies and clinical trials reported on the enhanced outcomes of the studied parameters, suggesting the promising effects of *N. sativa* in PCOS patients.

The mechanism of action of *N. sativa* towards the managing of PCOS-induced reproductive disorders is not fully established, but it was reported to be possibly due to its phytoestrogen effects. Phytoestrogens are derived from plants and possess structures similar to endogenous estradiol (Desmawati & Sulastri, 2019). They can bind to the alpha and beta estrogen receptors (Paterni *et al*., 2014). Alpha estrogen receptors promote cell proliferation, while beta receptors are responsible for cell apoptosis (Sirotkin & Harrath, 2014). Once the receptor binds to the ligand, it moves from the cytoplasm to the cell nucleus. There, it binds to and influences the area that controls the DNA transcription process or small RNA, which in turn affects the expression of certain genes. Therefore, phytoestrogens have the potential to regulate all processes influenced by estrogen, including the induction of sex hormones (Sirotkin & Harrath, 2014).

Reports on the phytoestrogen effect of *N. sativa* have been reported earlier in a study conducted to evaluate *N. sativa*'s estrogenic activity using ovariectomized rats (Parhizkar *et al*., 2011). The study findings showed a significant increase in uterine weight. *N. sativa* also improved the endometrial histological structure through the increase of luminal and glandular epithelium height, increase of endometrial and myometrial diameters, and increase the number of endometrial glands (Parhizkar *et al*., 2011). The effect of *N. sativa* on the uterus was also reported by Sabrina *et al*. (2023) where co-supplementation of vitamin E and *N. sativa* resulted in a significantly higher endometrial thickness and the other uterine structures were not disrupted. Other effects of *N. sativa* were *N. sativa* oil reported to help remove uterine content of missed abortion through the reduction of human chorionic gonadotropin (hCG) hormone and facilitation of cervix dilation (Mohammadi *et al*., 2024). Another review also reported that *N. sativa* treatment had improved the follicle count, corpus luteum, and level of testosterone and progesterone in infertile women (Darand *et al*., 2019).

CONCLUSION

The effects of *N. sativa* supplementation on PCOS-induced ovarian dysfunctions have been continuously reported, despite the molecular mechanism regulating the effects remains unknown. Other than its phytoestrogen effects, the promising effects of *N. sativa* have been attributed to its potential as an antioxidant, anti-androgenic, anticancer, and anti-inflammatory agent (Ahmad *et al*., 2013), which is due to the presence of thymoquinone, the primary bioactive compound (Amalia *et al*., 2022; Alaee *et al*., 2023). The next research focus should be on finding and understanding the mechanism of action of *N. sativa*, which might require a larger scale of laboratory experiments and clinical trials, as well as determining the optimal dose and duration of intake to achieve effective results.

ACKNOWLEDGMENTS: A special thanks to all staff and members of the Faculty of Pharmacy, UiTM Selangor, Puncak Alam Campus, Malaysia for all the assistance and support provided in completing this study. The authors declare no conflict of interest.

CONFLICT OF INTEREST: None.

FINANCIAL SUPPORT: None.

ETHICS STATEMENT: None.

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