CHAPTER 37

Nigella sativa: Therapeutic Potential in Reproductive Health and Wellness

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SUMMARY

Nigella (*N.*) *sativa* is a flowering plant commonly called black seed and is native to the Southwest Asian and Mediterranean regions. The plant has a long history in traditional medicine and is included within the Ranunculaceae family. It contains oils, proteins, carbohydrates, and fibers. The chemical makeup of *N. sativa* has an ingredient called quinone, which is also called thymoquinone (TQ) which is primarily responsible for the plant's medical usefulness. Significant anti-inflammatory and anti-nociceptive effects are produced by *N. sativa*. Thymoquinone has been shown to have an antioxidant impact on several illnesses, including encephalomyelitis, asthma, diabetes, and a variety of cancers. It has promised anti-carcinogenic, anti-neoplastic, anti-mutagenic, and anti-proliferative effects on a variety of tumor cells. It strengthens both male and female fertility, as well as enhances reproductive health. Its seed extract increases sperm viability, motility, and count. Thymoquinone therapy enhances the quantity, mobility, and shape of sperm. Moreover, *N. sativa* lowers oxidative stress and inflammation in the testes, which can enhance general reproductive health. It improves serum testosterone levels in males and enhances female reproductive health. Additionally, it functions as a potent antioxidant and anti-inflammatory agent, playing an important role in protecting the uterus from oxidative stress or inflammation. It also enhances ovarian function regulates menstruation, and leads to better pregnancy outcomes. It is a safe and effective herbal remedy which can be used to enhance male or female fertility as well as reproductive function. It is a cheaper, more accessible option for people who favor organic and holistic healthcare.

INTRODUCTION

Nigella sativa, a flowering plant commonly called black seed, is native to the Southwest Asian and Mediterranean regions. The plant has a long history in traditional medicine and is included within the *Ranunculaceae* family. Because of its strong scent and flavor, its seeds are used as fragrant condiments in Middle Eastern and Indian cuisine. Traditionally, *N. sativa* was used to treat many illnesses such as rheumatism and gastrointestinal problems, skin disorders (like eczema) as well as infections of the respiratory system (Salem et al., 2010). Everybody knows about *N. sativa* as a kitchen ingredient, but it is also an immune system booster and one of the world's best health tonics. Scientific research shows that it is antioxidant, anti-inflammatory, and immune regulating (Ahmad et al., 2013). The data from this study seems to hold out hope for the treatment of many kinds of medical problems, including cancer, diabetes, high blood pressure as well as hyperlipidemia. *N. sativa* has also shown some promise in improving reproductive health. Studies indicate that the botanical wonder has the potential to increase reproductive performance in males and females alike. This can be achieved by regulating the menstrual cycle, improving sperm quality, and stimulating ovulation. In this way, modern scientific evidence also indicates that *N. sativa* has medical applications in a variety of areas relevant to reproductive health.

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This plant has a deep and glorious religious heritage, deriving from several books of religion and ritual. The following information concerns the metaphysical base of *N. sativa*. The blessed seed or Shabbat al-barakah is the term for *N. sativa* in Islam. With regard to certain sources, the Prophet Muhammad said, "The black seed has curative properties for every disease save death" (Sahih Bukhari). The Bible frequently mentions *N. sativa*, particularly in the book of Isaiah [Isaiah 28: (25–27)], in which it is called by the name "cummin" and praised for its curative properties. Ancient Egyptian civilization exploited it in both cosmetics and medicine. Seeds excavated in the tomb of Tutankhamun were supposedly used as a medicine to treat gastrointestinal and respiratory illnesses. For centuries in ancient Indian Ayurvedic therapy, *N. sativa* has been used to treat gastrointestinal problems and skin diseases to respiratory disorders (Salem, 2005). *N. sativa* is a traditional Chinese botanical that strengthens the immune system, regulates digestion, and promotes effective respiration. It is said to have those properties which control oxidative species. The historical use of *N. sativa* as a potent method of treatment underlies the religious and cultural significance it gained. Its effective application in the practice of traditional medicine throughout many cultures has provided solid evidence to validate its health benefits (Ahmad et al., 2021).

PLANT ELUCIDATION

Leaves of the *N. sativa* plant are longitudinal, green, and finely divided. Light blue and white in color, the flower has petals that can range anywhere from 5 to 10. The fruits are contained within inflated capsules as shown in Fig. 1. In groups of 37 linked follicles, the capsules are then divided. Each follicle has a large number of black oval seeds with a diameter of roughly 1mm (Randhawa, 2005; Gholamnezhad et al., 2016). It is a member of the plant genus *Ranunculaceae*. The Crowfoot family is another name for this group. The roughly two thousand species of flowering plants that make up this group are divided into forty-three genera and can be found all over the globe. The largest of all is Ranunculus genus and *N. sativa* is one of the total six-hundred species.

The plant's seeds are known in the English language as "Black cumin", while they are known as "Haba Al-Barrakah" in Arab nations. The common name of *N. sativa* in Urdu is "Kalwannji." In Persian, it is referred to as "Siyah Danch"(Sultan et al., 2012). *N. sativa* is grown in Syria, Sri Lanka, Turkey, and in South East Asia. The best circumstances for cultivating this plant are found in Egypt, which is known for generating high-quality seeds (Naz, 2011).

CHEMICAL CONSTITUENTS AND COMPOSITION

It contains oils, proteins, carbohydrates, and fibers. The chemical makeup of *N. sativa* has an ingredient called quinone, which is also called thymoquinone (TQ), and is primarily responsible for the plant's medical usefulness (Sahak et al., 2016). Thymoquinone is the primary component of volatile oil and exhibits numerous pharmacological qualities, including hepatoprotective (Hassanein et al., 2016; Laskar et al., 2016; Saheb et al., 2016), anti-inflammatory (Abd-Elbaset et al., 2017), antibacterial (Goel & Mishra 2018), antioxidant (Erol et al., 2017), fungicidal (Almshawit & Macreadie 2017), nephroprotective (Kotb et al., 2018) and anticancer (Majdalawieh et al., 2017). There is also literature showing evidence for the molecular mechanism of this molecule. Other components found in the *N. sativa* include p-cymene, carvacrol, thymohydroquinone (THQ), dihydro thymoquinone (DHTQ),

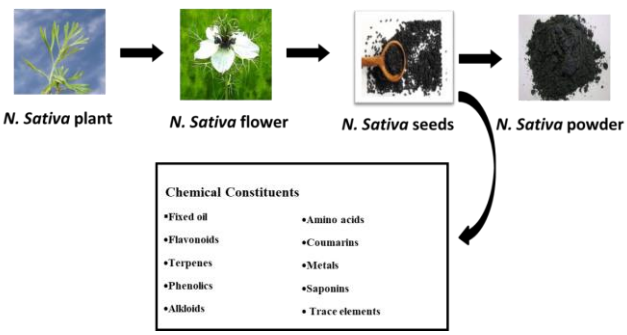

Fig 1. Morphological representation and chemical constituents of *N. sativa*.

α-thujene, thymol, t-anethole, β-pinene, α-pinene, and γ-terpinene. The main chemical constituents have been described in Fig 1. (Ahmad et al., 2021).

BIOLOGICAL EFFECTS OF *NIGELLA SATIVA*

Anti-Inflammatory

Significant anti-inflammatory and anti-nociceptive effects are produced by *N. sativa*. thymoquinone and *N. sativa* oil both have anti-nociceptive effects through activating supraspinal opioids. It has been suggested that it prevents leukocytes and lipid peroxidation from producing eicosanoids. They prevent the metabolism of arachidonic acid by inhibiting the 5-lipoxygenase and cyclooxygenase pathways (Pise & Padwal 2017). Eicosanoids and reactive oxygen species are examples of inflammatory factors that are important in the development of inflammatory disorders. According to (Majdalawieh & Fayyad 2015) ulcerative colitis and allergic encephalomyelitis are two of the most common inflammatory diseases. Thymoquinone's anti-inflammatory and antioxidant capabilities considerably ameliorate ulcerative colitis and allergic encephalomyelitis (Choudhary et al., 2001). Because of its anti-inflammatory properties, the oil obtained from the seeds of *N. sativa* is widely used in the Mediterranean region (Bordoni et al., 2019). With its anti-inflammatory and tissue growth-stimulating properties

N. sativa has been shown to have a therapeutic effect on the healing of wounds (Sallehuddin et al., 2020). Pro-inflammatory mediators including IL-2, IL-4, IL-6, and IL-12 were decreased by *N. sativa* (Khazdair et al., 2021). TQ present in *N. sativa* modifies anti-inflammatory signaling pathways (Ojueromi et al., 2022). *N. sativa* is a potential alternative medicine to reduce inflammation in conditions like gingivitis and enhance general health outcomes (Rahman et al., 2023).

Antioxidant

Strong antioxidant activity in *N. sativa* extracts and essential oils has been documented (Sultan et al., 2012). Thymoquinone has been shown to have an antioxidant impact on several illnesses, including encephalomyelitis, asthma, diabetes, and a variety of cancers. Thymoquinone also functions as a free radical and superoxide scavenger while maintaining the activity of enzymes, namely glutathione peroxidase, glutathione-S transferase, and catalase. Thymoquinone has been shown to have nephroprotective effects and to reduce the expression of the genes for SSAT and CYP3A1 through antioxidant processes (Mansour et al., 2002). It produces glutathione-dihydrothymoquinone when it combines with glutathione (GSH), NADH, and NADPH, providing proof of its effectiveness as a free radical scavenger. Because of its antioxidant activity and inhibition of DNA synthesis, thymoquinone has been demonstrated to have a significant chemopreventive effect against MC-induced fibrosarcoma tumors (Mansour et al., 2002). People like herbal medicines due to their safety profile. According to studies (Ahmad, 2018) a combination of *N. sativa* demonstrates protection against methyl nitrosourea-induced oxidative stress antioxidant characteristics protect from diabetes by enhancing the antioxidant enzyme glutathione peroxidase and lowering blood glucose and lipid levels. Even at low doses, its oil inhibits the production of lipid peroxide and lactate dehydrogenase and increases the availability of glutathione and superoxide dismutase, concurrently reducing lipid peroxidation and free radical formation (Houghton et al., 1995). Tocopherols and other bioactive chemicals in *N. sativa* enhance the body's overall antioxidant capacity (Soleimanifar et al., 2019). The highest antioxidant activity was found in methanolic extract of *N. sativa* seeds which reduced intracellular ROS release (Pop et al., 2020). The ability of *N. sativa* seeds to reduce ferric levels and serve as an antiradical scavenger promises effective antioxidant activity (Dalli et al., 2021). Its seeds efficiently produced AuNPs which showed high antioxidant activity (Veeramani et al., 2022). Its oil and thymoquinone are strong scavengers of superoxide radicals (Sakib et al., 2023).

Antifungal

Resistance is a big issue since antifungal medications are used excessively. Researchers have shown interest in plant-based medications as viable alternatives to conventional therapies for fungi infections (Doudi et al., 2014). The main cause of the antifungal action is N. sativa's thymoquinone. Dermatophytes, molds, and yeasts were resistant to the antifungal effects of thymoquinone, thymohydroquinone, and thymol. Moreover, its extracts showed antifungal activity against *Candida albicans* (Randhawa, 2005; Moghim et al., 2015). Thymoquinone suppresses *in vitro Aspergillus niger* and Fusarium solani activity in a manner comparable to that of the antifungal medication amphotericin-B. They discovered that three major types of dermatophytes—*Trichophyton*, *Epidermophyton*, and *Microsporum*—were moderately sensitive to this plant. While ether extracts of *N. sativa* also show antifungal activity, they act more favorably at higher concentrations. The majority of dermatophytes are inhibited 80–100% by extracts in the range of 40 mg/ml, whereas thymoquinone's minimum inhibitory concentrations against various dermatophytes ranged from 0.125 to 0.25 mg/ml (Aljabre et al., 2005). The phytochemical profile of N. sativa confirms antifungal properties due to the presence of octadeconic acid, linoleic acid, pentadecanoic acid, and 1,2,3,4 butaneteterol (Aftab et al., 2019). *N. sativa* is effective against a number of fungal pathogens including *Aspergillus niger*, *Aspergillus flavis*, and *Microsporum canis* (Zishan & Manzoor 2020). Nigellothionis found in *N. sativa* that show strong antimycotic activity (Barashkova et al., 2021). Oil obtained from *N. sativa* has strong antifungal properties (Zouirech et al., 2022). Simple co-precipitations of FeCl3 and FeSO4 in a substrate disperse combination of N. sativa offers cost-effective biomedical and antifungal applications (Malik et al., 2023).

Antibacterial

The volatile oil of *N. sativa* contains thymohydroquinone, which is highly effective against gram-positive bacteria like *Staphylococcus aureus*. The concentration-dependent inhibitory activity of *N. sativa's* diethyl-ether extract on *S. aureus*, a gram-positive bacteria, and *Pseudomonas aeruginosa* and *Escherichia coli*, a gram-negative bacteria, was examined (Aljabre et al., 2015). With several medications like doxycycline, chloramphenicol, erythromycin, nalidixic acid, and lincomycin, *N. sativa* has shown an additive effect. *N. sativa* extract produced outcomes that were nearly identical to those of the topical antibiotic mupirocin in the treatment of infants with *staphylococcal* pustular skin infections (Rafati et al., 2014). Many multi-drug resistant gram-positive and gram-negative

bacteria, including resistant *S. aureus* and *P. aeruginosa*, responded well to *N. sativa* in the treatment of *P. aeruginosa* infection, honey, and *N. sativa* have synergistic antibacterial properties (Salman et al., 2008). A mouthwash with chlorhexidine gluconate is used to treat bacterial infections because it is germicidal. It has been demonstrated that *N. sativa* oil extract outperforms chlorhexidine gluconate in the treatment of *S. mutan*s infection and other common dental infections (AlAttas et al., 2016). PVA-Nigella nanofibrous mat (PNNM) is a viable wound dressing material with string antibiotic properties (Ali et al., 2021). The seed extracts are a natural source of nutraceuticals since they contain chemical components associated with their antibacterial capability (Zouirech et al., 2022). Moreover, seed extracts showed promising antibacterial properties (Kumar et al., 2023).

Antiviral

According to research, *N. sativa* boosts natural killer (NK) cell activity, T helper cells (T4), suppressor T cells (T8), and T cells in healthy volunteers (Aljabre et al., 2015). In addition to the immunity enhancement the *N. sativa* has inhibitory effects on HIV (Khan, 1999). Patients with the hepatitis C virus were given 450 mg capsules of *N. sativa* oil three times per day for three months in a trial. Significant improvements in oxidative stress, viral load, albumin, total protein, platelet, and RBC levels, as well as reductions in these levels, were seen. The increase in RBC count assists in lowering membrane lipid peroxide levels and decreasing the risk of hemolysis (Tavakkoli et al., 2017). The main components of *N. sativa* have been shown to possess potential as natural antiviral agents against new coronaviruses (Ahmad et al., 2021). *In vitro* screening of two compounds DTQ and HTQ showed promising antiviral activity against coronaviruses (Esharkawy et al., 2022). The major chemical components of *N. sativa* showed the basis for formulating the drug for chikungunya (Kumar et al., 2023).

Anticancer

Over the world, public health concerns about cancer are on the rise. According to Khan et al. (2011), thymoquinone from *N. sativa* has promised anti-carcinogenic, anti-neoplastic, anti-mutagenic, and anti-proliferative effects on a variety of tumor cells. It serves as a chemoprotective agent and is used with therapeutic medicines to reduce harmful side effects (Khader et al., 2007). One of *N. sativa's* active ingredients, alpha-hederin (HN) has emerged as a potential anticancer agent (Adamska et al., 2019). Ns-AgNps may be considered a potential option in anticancer therapy (Almatroudi et al., 2020). The oil obtained from *N. sativa* extracts contains anti-tumor properties (Albakry et al., 2023).

Anti-Infertility

In a randomized clinical trial, 5ml of *N. sativa* oil improved sperm count, semen volume, and pH (Kolahdooz et al., 2014). The weight of the reproductive organs, the number of mature Leydig cells, and the total quantity of spermatocytes were all observed to rise when 300 mg/kg body weight of *N. sativa* seeds were administered for 60 days (Mohammad et al., 2009). In addition, *N. sativa* oil revealed the capacity to counteract the toxic effects of sodium valproate on testicular degeneration, lipid peroxidation, and aberrant sperms. Thymoquinone has demonstrated various protective roles in response to oxidative stress, including superoxide anion scavengers direct cytoprotective effects, and androgen activities (Hala & Wahb 2011).

EFFECTS ON MALE INFERTILITY

The plant *N. sativa* contains a variety of chemical substances, such as alkaloids, thymoquinone, and alpha-hedrein. The most prevalent and thoroughly researched active ingredient in *N. sativa*, thymoquinone, has been shown to have antioxidant, anti-inflammatory, and anticancer properties. Another active substance with demonstrated anticancer and immunomodulatory properties is alpha-hederin (Ahmad et al., 2013). It has proven applications in treating infertility (Al-Tawalbeh et al., 2023).

The possible impact of *N. sativa* on male fertility has been examined in many kinds of research. According to one rat study, treatment with *N. sativa* seed extract increased sperm viability, motility, and count. In a different investigation, thymoquinone therapy enhanced the quantity, mobility, and shape of rat's sperm. Moreover, it has been demonstrated that *N. sativa* lowers oxidative stress and inflammation in the testes, which can enhance general reproductive health as summarized in Fig 2. (Ahmad et al., 2013).

Fig 2. The effects of *Nigella sativa* on male fertility.

Effect on testis

The primary active ingredient of *N. sativa*, thymoquinone, has antioxidant properties. This effect was investigated in

comparison to morphine's harmful effects on male mice. According to the study, morphine has a deleterious impact on testicular size. This seems to be caused by the generation of free radicals and ROS, which have a harmful effect on the testis' sensitive cells (Tavakkoli et al., 2017). Thymoquinone, an antioxidant, has shown protective effects against free radical damage. It also increased LH and FSH levels, which improved testis shape and weight. By acting as an antioxidant and cytoprotector, reduces the damage that MSG causes to the testis (Abd-Elkareem et al., 2021). The TQ in *N. sativa* protects the endocrine tissues from reactive oxygen species (Wani et al., 2022). By improving malondialdehyde activity *N. sativa* significantly improved sperm quality (Almujaydil et al., 2023). Under the effect of *N. sativa* oil, the testicular parameters were significantly improved in rabbits (Umar et al., 2017).

Effect on epididymis and testosterone level

When *N. sativa* (Ranunculaceae) seeds were used as an aqueous extract on male albino rats for 60 days, the weight of the reproductive organs and the cauda epididymis sperm count significantly increased (Tavakkoli et al., 2017). When *N. sativa's* alcoholic extract was administered to male rats for 53 days, it showed a notable increase in testosterone and FSH. According to a different study, *N. sativa* extract can boost testosterone production by raising both LH secretion and the activity of the hypothalamic-pituitary-testicular axis (Mohammad et al., 2009). *N. sativa* improves serum testosterone levels in males (Leisegang et al., 2021). Its oil showed protective effects against bisphenol-A-induced testicular toxicity in rats (Hatipoglu et al., 2023). It also improves spermatogenesis (Umar et al., 2015).

Sperm and prostate parameters

Male albino rats were given *N. sativa* seeds aqueous extract, which led to a noticeably increased sperm count and motility in the cauda epididymides and testicular ducts (Parandin et al., 2012). Another study, however, found that while there was no discernible difference in sperm motility and viability, it did have a significant positive impact on various other sperm characteristics (Jalili et al., 2016). Moreover, spermatogenesis, sperm motility, and viability were all improved by the antioxidant *N. sativa* thymoquinone, which also showed protective properties against the harmful effects of morphine treatment on male mice.

EFFECT ON FEMALE FERTILITY

Effect on ovarian function

N. sativa has been shown to enhance ovarian function Fig 3. Studies on female rats reveal that seeds from *N. sativa* increase the number of ovarian follicles. As a result, oocyte production

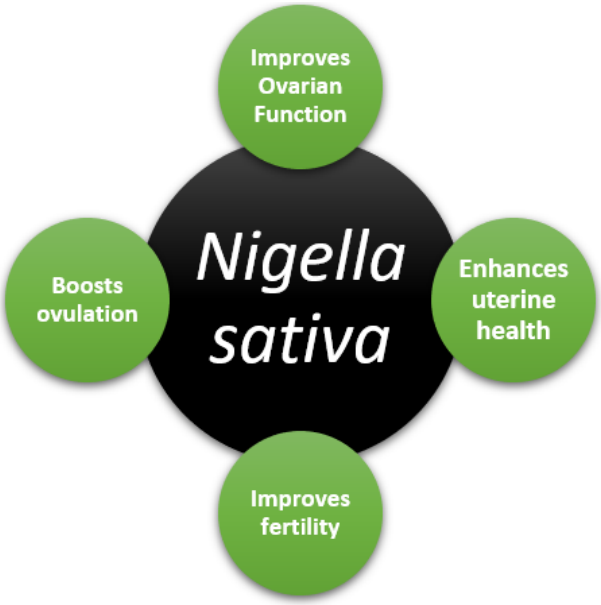

Fig 3. The effects of *Nigella sativa* on female fertility.

increased during each cycle of release (Mohammed & Al-Suwaiegh 2023). A study in rats found that seeds from *N. sativa* stimulate high concentrations of luteinizing hormone (LH) and follicle-stimulating hormones (FSH). Ovulation of ovarian bulbs requires both of these hormones. These results suggest that *N. sativa* may excite ovarian function and perhaps even ovulation. (Kooti et al., 2016).). It also protects the ovary from a wide variety of deleterious effects (Sukatendel et al., 2021). Thanks to its anti-oxidative properties, TQ can enhance ovarian function. Alaee et al. (2023) have noted improvement in cases of polycystic ovaries when treated with *N. sativa* extracts (Alaee et al., 2023).

Effect on uterine health

It impacts positively uterine health. In addition, seeds of *N. sativa* are needed to thicken the uterine lining, which is essential for implantation and conception (Goyal et al., 2017). In another study on menopausal rats, it was found that *N. sativa* oil increased the levels of estrogen and progesterone which are important to keep a healthy uterus. This indicates that *N. sativa* may help protect uterine health, and even promote a normal pregnancy (Fard et al., 2021). *N. sativa* was seen to have positive effects on infertility and other female reproductive diseases (Fard et al., 2021). A placebo-controlled, randomized double-blind clinical experiment on infertile women found that *N. sativa* markedly increased the number of pregnancies. These

results suggest that *N. sativa* may, in fact, increase female fertility and the chances of pregnancy (Modaresi, 2012). Female infertility is an excellent target for *N. sativa*.

Effects on overall reproductive health

N. sativa has been said in various ways to be good for female reproductive health. Studies have indicated that *N. sativa* functions as a potent antioxidant and anti-inflammatory agent, playing an important role in protecting the uterus from oxidative stress or inflammation. It also serves as an estrogen and can lead to the development of a normal uterus for pregnancy (Kooti et al., 2016). The benefits of *N. sativa* may be anti-oxidative, anti-inflammatory, or estrogenic (Mohammed & Al-Suwaiegh 2023)

CONCLUSION

Nigella sativa has been found to strengthen both male and female fertility, as well as enhance reproductive health. After taking this, the testosterone level of males as well as sperm motility, count, and morphology have all been shown to improve. Females are no exception as it can also enhance ovarian function, regulate menstruation, and lead to better pregnancy outcomes. One of the active compounds in *N. sativa*, thymoquinone has been shown to possess antioxidant and anti-inflammatory properties as well as immunomodulatory effects. Perhaps this is what lies behind its beneficial effect on reproductive health. These characteristics make *N. sativa* a natural remedy for infertility and other problems related to reproduction. However, research is still lacking concerning the action mechanisms and appropriate dosages of *N. sativa* to enhance fertility and reproductive health. What's more, it should be pointed out that *N. sativa* is not an alternative to standard treatments for fertility or other reproductive illnesses. Or it may simply act as an adjunctive therapy. In summary, the data indicates that *N. sativa* is a safe and effective herbal remedy that can be used to enhance male or female fertility as well as reproductive functions. This could prove a cheaper, more accessible option for people who favor organic and holistic healthcare.

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