MEDICINAL EFFECTS OF NIGELLA SATIVA IN GYNECOLOGICAL DISORDERS: A SYSTEMATIC REVIEW

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MEDICINAL EFFECTS OF *NIGELLA SATIVA* IN GYNECOLOGICAL DISORDERS: A SYSTEMATIC REVIEW

S. H. K. Deepthika [1], K. P. K. R. Karunagoda [2] and P. K. Perera [* 2]

Faculty of Indigenous Medicine [1], Gampaha Wickramarachchi University of Indigenous Medicine, Yakkala, Sri Lanka.
Institute of Indigenous Medicine [2], University of Colombo, Colombo, Sri Lanka.

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Correspondence to Author:
P. K. Perera

Senior Lecturer,
Department of DravyagunaVignana,
Institute of Indigenous Medicine,
University of Colombo, Colombo,
Sri Lanka.

E-mail: drkamalperera@yahoo.com

ABSTRACT: Comprehensive search of previously published research was conducted in PubMed, Science Direct, Scopus, and google scholar databases for studies published between 2012 and August 2021. The keywords used in combination to search for articles included *Nigella sativa* and "Gynecology". In the first stage, the total articles obtained from searching the above databases using the above keywords were pooled together, and duplicate articles were removed. The remaining articles were primarily screened by reading the title and abstracts and selecting the most relevant articles. In the last stage, articles were reviewed again by reading the entire article, and those that did not meet the inclusion requirements were eliminated. A manual search was conducted using the reference list of the included research publications to collect additional data. In the various databases, the literature search found the following number of research articles: PubMed (n=11), Science Direct (n=35), Scopus (n=07), and Google Scholar (n=1070). After removing duplicates, there were 1062 articles. Those articles were further screened first by reading topics and abstracts and secondly, reading full text that did not match the inclusions was removed. After removing those articles, there were 40 articles, and after adding 05 manual search articles, finally, 45 articles were included in the systematic review. *Nigella sativa* has medicinal benefits for gynecological disorders such as PCOS, menopause-related issues, Hyperprolactinemia, Candidiasis, Trichomoniasis, Cervical cancer, Breast cancer, ovarian cancer, Premenstrual syndrome and Pre-eclampsia. *Nigella sativa* also improves endometrium, oocyte maturity and quality and reduces ovarian tissue damage without any adverse effects.

INTRODUCTION: Herbal drugs are used by nearly 80% of the world's population for health care, particularly in developing countries, according to the World Health Organization [1]. *Nigella sativa*, a species of the Ranunculaceae family, is a widely used plant in Ayurveda medical system. It is also known in English as "Black cumin" and "Black seed," in Sinhala as "Kaluduru" and in Sanskrit as "Krishna-jira." Almost seeds of the *Nigella sativa* have medicinal use [2]. This plant is cultivated in Panjab and Bihar in India [3]. The seeds are considered bitter and pungent in taste.

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Ayurveda mentions its properties as a stimulant, analgesic, appetizer, digestive, deodorant, aromatic, anthelmintic, emmenagogue, galactagogue, diuretic, thermogenic, febrifuge, carminative and it is widely used for a variety of diseases in the respiratory, digestive, reproductive, urinary and central nervous systems [4, 5]. *In-vitro* and *in-vivo* research had demonstrated and proven medicinal effects of *Nigella sativa* such as, antidiabetic activity, cardiovascular activity, gastroprotective

activity, pulmonary activity, central nervous system activity, nephroprotective activity, hepatoprotective activity immuno-modulation activity, antioxidant activity, antimicrobial activity and reproductive activity, *etc*. This systematic review was aimed to analyze the most recent scientific research and provide a complete overview of the medical effects of *Nigella sativa* in gynecological problems that have been scientifically validated.

MATERIAL AND METHODS: A systematic review of published full research papers reporting the medicinal effects of *Nigella sativa* in gynecological disorders was designed based on the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement guidelines [6]. Eligibility criteria are based on the PICO (Population, Intervention, Comparison, Outcomes) approach, study design, Language, and date.

1. Types of Studies: The therapeutic effects of *Nigella sativa* on gynecological illnesses were explored in this systematic study.

1.1. Inclusion Criteria: All the published full research papers within the period of 2012 to August 2021, written in English, studied the effect of *Nigella sativa* on gynecological problems were included.

1.2. Exclusion Criteria: Other than English, research articles were written in a variety of other languages, Research papers published before the year 2012, abstract-only papers, journals with no full text available, case reports, case series, and systematic review studies were all eliminated.

1.3. Types of Outcomes: The primary outcome was the medicinal effect and secondary outcome was safety or adverse effects of *Nigella sativa*.

1.4. Search Strategy: A comprehensive search of previously published research articles was conducted in PubMed, Science Direct, Scopus, and google scholar databases for studies published between January 2012 and August 2021. The keywords used in combination to search for articles included "*Nigella sativa*" and "Gynecology." Other filters were selected as the limit to medicine, dentistry and complementary medicine. All relevant articles were gathered from databases in the first stage. The total articles found by searching the above databases with the above keywords were pooled together in the second stage, and duplicate articles were excluded. The remaining papers were often screened by reading the titles and abstracts, with the most relevant articles chosen. In the last stage, included articles were reviewed again by reading the entire article and those that did not meet the inclusion criteria were eliminated. A manual search was conducted via the reference list of the included research publications to collect additional data.

1.5. Evaluation of Article Quality: Two authors independently assessed the quality and acceptance of the articles.

1.6. Data Extraction: Information related to the study was collected, including the year of publication, authors' name, Type of study, Population, Sample size, intervention, outcomes, and Reference.

RESULTS AND DISCUSSION:

2. Literature Search: Using the above-mentioned search parameters, the following number of research articles were found in the various databases; PubMed (n=11), Science Direct (n=35), Scopus (n=07) and Google scholar (n=1070). After removing duplicates, there were 1062 articles. Those articles were further screened first by reading topics and abstracts, and secondly, reading full text that did not match the inclusions was removed. After removing those articles, there were 40 articles, and after adding 05 additional articles, finally, 45 articles were included in the systematic review. **Fig. 1** summarizes the search approach. Finally, 13 clinical trials, 19 *in-vivo* studies, and 17 *in-vitro* research were analyzed in **Tables 1, 2,** and **3.**

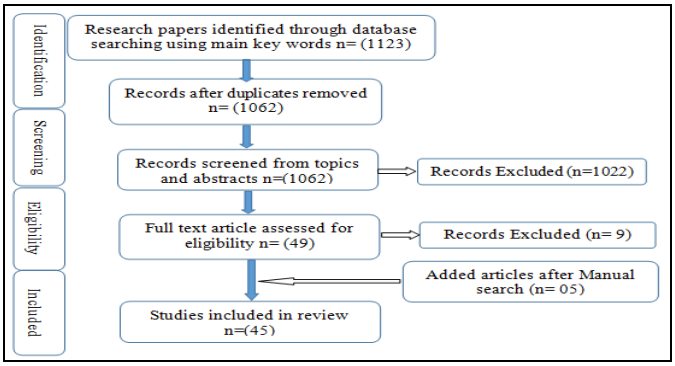

FIG. 1: SUMMARIZED SEARCH STRATEGY

***2.1 In-vivo* Evidence to Relive Primary Dysmenorrhea and Premenstrual Syndrome:** Using isolated uterine horns, Aqel and Shaheen investigated the effects of the volatile oil of *Nigella sativa* seeds on the uterine smooth muscle of rats and guinea pigs *in-vitro*. The volatile oil from Nigella seeds suppressed both spontaneous and oxytocin-induced contractions in the uterine smooth muscle of rats and guinea pigs [7]. *N. sativa*'s analgesic effect has also been clinically demonstrated [8, 9]. Except for depression and stomach bloating, *Nigella sativa* oil was found to diminish the intensity of all Premenstrual syndrome symptoms [10] and Huseini *et al*. verified the analgesic effects of *Nigella sativa* on patients with cyclic mastalgia [11].

2.2 *In-vivo* Evidence to Improve Oocyte Maturity and Quality: *In-vivo* animal studies have also shown that supplementing mice with *N. sativa* improves oocyte quality and preimplantation embryo development, resulting in improved reproductive performance [12, 13]. To improve reproductive performance, a nutritional supply of *N. sativa* seeds could be utilized instead of hormonal therapies. Protein, fat, carbs, vitamins, minerals, and beta-carotene are all abundant in *N. sativa* seeds [14, 15].

***2.2 In-vivo* Evidence to Improve Endometrium:** Raith A. S. Al-Saffar and Mohammad K. M. Al-Wiswasy conducted an *in-vivo* study on the pharmacological effects of *Nigella sativa* on the reproductive system in experimental rats.

As a result, vaginal smears of rats treated with a crude aqueous extract of *Nigella sativa* seeds showed a shorter vaginal cycle with a prolongation of both the estrus and metestrus phases; the diestrus phase was undetectable and showed an increase in the uterine wet weight of all experimental subgroups, with a profound and persistent diffuse endometrial hypertrophy, and enhanced glandulogenesis.

This adds to the evidence that the administrated crude aqueous extract of *N. sativa* seeds has a postovulatory, progesterone-like effect, as seen in the vaginal smears of treated rats. As a result, this suggests that *N. sativa* may have elicited its effects by boosting the endogenous release of estrogen and/or progesterone [16].

***2.3 In-vivo* Evidence to Relieve PCOS Symptoms:** In a double-blind placebo-controlled clinical trial, researchers used two soft gel capsules of *Nigella sativa* oil (500 mg each capsule) or placebo at night for sixteen weeks to prove the effect of *Nigella sativa* oil on oligomenorrhea, amenorrhea, and laboratory characteristics in patients with the polycystic ovarian syndrome. Menstruation was assessed using the cycle length, the duration, the occurrence of menstruation, and the severity of bleeding. The intervention group's menstrual interval was considerably shorter than the control group's following the trial. The intervention group had a considerably higher menstrual cycle frequency than the placebo group. As a result, it had proven *N. sativa* is a potential alternative treatment for PCOS-related menstrual abnormalities [17].

The average duration of menstruation and the monthly cycle ratio increased significantly, according to a pilot study conducted by Seyedeh Atieh Naeimi *et al*. additionally, the significant reduction in metabolic variables such as triglycerides, cholesterol, AST, and especially FBS and fasting insulin improved insulin resistance. As a result, it had suggested that *N. Sativa* could treat PCOS patients with oligo-amenorrhea [18].

Another randomized clinical research had done to see if supplementing metformin with thymoquinone (bioactive component derived from *Nigella sativa*) could help with symptoms of the polycystic ovarian syndrome. Patients who received a combination of black cumin oil capsules and metformin had a significant reduction in the number of patients suffering from amenorrhea or oligomenorrhea, significant weight loss (reduced BMI), body fat redistribution (reduced W/H ratio), regaining oxidative balance with a significant increase in antioxidant enzymes such as superoxide dismutase activity and regaining oxidative balance. The large drop in body weight in patients treated with a combination of thymoquinone and metformin may have increased sex hormone binding globulin (SHBG), and a subsequent fall in free testosterone levels may have contributed to the return of regular menstrual periods [19]. Phyto estrogenic effect of *Nigella sativa* is another reason for the reduced menstrual intervals [20].

Thymoquinone's anti-inflammatory and anti-oxidant properties have also been linked to the return of menstrual cyclicity [21]. Recent research has linked oxidative stress to the etiology of PCOS and shown that taking antioxidants improved symptoms significantly [22]. In an *in-vivo* study to determine the anti-androgenic and insulin-sensitizing effects of *Nigella sativa* oil on polycystic ovary and related dyslipidemia and redox abnormalities, it was discovered that *Nigella sativa* oil dramatically decreased the number of cystic follicles. The effects of *N. sativa* oil on serum levels of E2 (Estradiol) and LH were significantly decreased and lowered serum T (Testosterone), and FSH levels [23].

***2.4 In-vivo* Evidence to Relieve Menopause-related Problems:** Treatment with *N. sativa* has a therapeutic and protective effect on weight gain, lipid profile, blood glucose, and hormone levels in the perimenopausal period and is thought to play an important role in the development of metabolic syndrome following menopause [24]. Menopause is linked to an increase in oxidative stress as well as a drop in several antioxidant markers. The use of garlic extracts and *Nigella sativa* seeds may assist the better balance between blood oxidants and antioxidants in healthy postmenopausal women, according to a study conducted by Randa M Mostafa *et al*. Low amounts of plasma malondialdehyde were found, along with enhanced erythrocyte glutathione peroxidase and superoxide dismutase activity, in this investigation [25].

Parhizkar *et al*. studied the effect of methanol and hexane extract of *N. sativa* on vaginal epithelial cells in menopausal mice in an animal study. The findings revealed that *N. sativa*, particularly its methanol extract, had estrogenic properties that are lower than conjugated estrogens. This characteristic can be utilized to treat hormone replacement therapy in women who have reached menopause[26]. Maryam Molaie *et al*. tested the efficacy of a phytotherapeutic intervention with *N. Sativa* and *Vitex agnus-castus*. According to their randomized, double-blind, placebo-controlled pilot trial, using a combination of *N. sativa* and *Vitex agnus-castus*to improves the outcome of citalopram in managing hot flashes is an effective supplementary therapy [27]. *Nigella sativa*, on the other hand, has been shown to be ineffectual in terms of vasomotor symptoms and sleep quality in menopausal women [28]. In ovariectomized rats, *Nigella sativa* extract did not improve memory performance. Despite this, Sahak's research shows that *N. Sativa* can increase spatial working memory in Sprague Dawley normal mice [29]. This could be attributed to several factors. The first determinant is the exposure time of *N. sativa*. The injection of *N. sativa* to hypo estrogen mice was done for three weeks (21 days) in this study, whereas the prior study had *N. Sativa* exposure for 20 weeks. Another aspect that may influence the effect of *N. sativa* in this study is the neuron's state at the moment *N. sativa* is administered. If the neurons that regulate the memory system have just diminished cell function and have not suffered structural damage because of the degeneration process, memory enhancements will be more obvious [30].

***2.5 In-vivo* Evidence to Decrease Prolactin:** After the third week of administration with a liquid solution of *Nigella sativa*, *in-vivo* studies showed a significant drop in prolactin hormone levels in newly parturition rabbits [31]. Hence, *Nigella sativa* seeds can thus be used to treat infertility and menstrual cycle irregularities caused by excessive prolactin hormone production during and after lactation.

2.6 *In-vivo* Evidence to Relieve Candidiasis: Farzaneh Adiban Fard *et al.* tested the therapeutic effects of *Nigella sativa Linn* seed powder on *Candida albicans* Vaginitis in a randomized, triple-blind, placebo-controlled clinical experiment. They gave the study group Nigella sativa Linn capsules and clotrimazole vaginal cream for seven days and the control group placebo capsules and clotrimazole vaginal cream. After treatment, there was a statistically significant difference in vaginal itching, discharge, irritation, vulvovaginal redness, and inflammation between the two groups. The study group's culture and wet mount findings improved dramatically after therapy. In most frequent symptoms and indicators of vaginitis, a combination of *Nigella sativa L*. capsules and clotrimazole vaginal cream was more beneficial than clotrimazole vaginal cream alone[32]. *In-vivo* investigations have also shown that *N. sativa*'s therapeutic impact is achieved by reducing the number of fungal colonies while boosting IgM levels [33, 34].

Thymoquinone (TQ) is a major constitute of *Nigella sativa* oil and in some studies, directly used the TQ-containing cream and proved that the anti-candidiasis activity was increased according to the concentration of TQ and had no significant effects on the growth of normal cell lines [35].

2.7 *In-vitro* Evidence to Relieve Trichomoniasis: Several *in-vitro* studies have investigated the impact of *Nigella sativa* on *Trichomonas vaginalis*. The parasite is highly toxic to *Nigella sativa* oil, which causes severe cell damage, including cytoplasmic and nuclear damage [36]. After 96 hours of additional, the inhibitory effect of *N. sativa* alcoholic extract on the number and activity of Trichomonas vaginalis parasites were shown, and doses of 650 and 750 mg/ml showed the strongest inhibitory action for parasite growth [37]. Also, the crude extract of *N. sativa* is an anti-trichomonas agent, particularly when combined with metronidazole, which has a high synergic effect [38]. *Nigella sativa* oil could be a viable, less expensive, and safer alternative to metronidazole in the treatment of trichomoniasis [39].

2.8 *In-vitro* Evidence to Relieve Cervical Cancer: The volatile oil derived from the seeds of *N. sativa* has anticancer characteristics like cisplatin and could be used as adjuvant therapy. It lowers adhesion protein in cervical cancer cells and diminishes it in a dose-dependent way. Morphological research revealed shrinkage and apoptotic alterations in grown cells, confirming the anticancer activity [40]. Ethanol extract of *N. sativa*also significantly inhibited proliferation and colony formation and induced apoptosis in cervical cancer cells [41]. Further, thymoquinone (a key bioactive component derived from *Nigella sativa*) has been studied in vitro and found to be a potential chemotherapeutic agent for cervical cancer. It decreases cell viability in a dose- and time-dependent way [42, 43].

2.9 *In-vitro* and *In-vivo* Evidence to Relive Ovarian Cancer: As mentioned above, thymoquinone (TQ) is a powerful anti-ovarian cancer treatment that works by modifying apoptotic activity. Several *in-vitro* and *in-vivo* investigations have been conducted to demonstrate its anticancer properties in the ovary. TQ inhibited ovarian cancer cell multiplication while increasing apoptosis and autophagy. However, the ethnicity of cells had a significant impact on the chemotherapy's effectiveness. TQ primarily affects the autophagy mechanism to suppress tumor proliferation in ovarian cancer of the Chinese population [44, 45]. Thymoquinone and cisplatin (a chemotherapy medication used in allopathic medicine) both demonstrated comparable anticancer effects. Cisplatin lowered tumor cell growth while increasing apoptosis, resulting in a lower total tumor burden. Combining TQ with cisplatin reduced these markers further, demonstrating that the medications work together [46, 47].

2.10 *In-vitro* and *In-vivo* Evidence to Relieve Breast Cancer: Overexpression of the chemokine receptor type 4 (CXCR4) has been linked to enhanced cell proliferation and metastasis, as well as serving as a predictor of poor prognosis in breast cancer patients. The effect of thymoquinone generated from *Nigella sativa* seeds on the expression and regulation of CXCR4 in breast cancer cells and the influence of bone metastases in a breast cancer mice model have been investigated. Thymoquinone has suppressed tumor growth and significantly reduced tumor vascular volume in a dose-dependent manner. TQ at dosages of 2 or 4 mg/kg b.w. administered intraperitoneally for four weeks can inhibit the growth and spread of breast cancer tumors [48]. Another two *in-vitro* studies were conducted to examine TQ's anti-angiogenic properties and the cytotoxic effects of thymoquinone-loaded nanostructured lipid carrier (TQ-NLC) on breast and cervical cancer cells lines. Thymoquinone was shown to have a dose-dependent effect on the viability of human breast MDA-MB-231 cells. TQ-NLC exhibited antiproliferative action in all cell lines in a dose-dependent manner, which was most cytotoxic towards breast cancer (MDA-MB-231) cells [49, 50].

***2.11 In-vivo* Evidence to Reduce Tissue Damage of the Ovary:** Two animal experiments had done to highlight *Nigella sativa*'s ovarian tissue-protective properties. The effects of *Nigella sativa* in experimental ischemia and ischemia/reperfusion (I/R) injury in rat ovaries were evaluated biochemically and histopathologically, and it was proven that *Nigella sativa* administration is effective in reversing tissue damage caused by ischemia and/or ischemia/reperfusion in ovaries [51].

Another study had used a rat model of ovarian torsion to assess the effects of *Nigella sativa* oil on ovarian oxidative damage following ischemia-reperfusion injury and found that *Nigella sativa* oil is ineffective in reducing oxidative stress-related biochemical damage in ovarian ischemia-reperfusion injury. However, antioxidant effects were observed [52].

***2.12 In-vivo* Evidence to Relive and Prevent Post-partum Infections:** To determine infection prevention management during post-partum with administering *Nigella sativa*, an *in-vivo* study was done and found that provision of *Nigella sativa* did not affect the average number of leukocytes, lymphocytes, and monocytes in adult female mice after childbirth [53].

***2.13 In-vivo* Evidence of Favorable Effects for Pre-eclampsia:** Pre-eclampsia is characterized by high blood pressure and proteinuria at 20 weeks or more of pregnancy [54]. An ischemic placenta fills the bloodstream with soluble chemicals and cell debris, causing systemic inflammation and maternal oxidative stress. This causes endothelial dysfunction and the severe symptoms that lead to pre-eclampsia [55]. To keep the circulatory system running smoothly, healthy endothelial cells produce a balanced amount of endothelium-derived relaxing factors (EDRFs) and endothelium-derived contracting factors. Nitric oxide (NO) is an EDRF that induces smooth muscle relaxation in blood vessels. Even in arterioles, smooth muscle relaxation causes blood vessel dilatation, lowering vascular resistance and enhancing tissue perfusion [56]. *In-vitro* studies of the effect of *Nigella sativa* ethanol extract on nitric oxide (NO) levels and renal arteriole diameter in a pre-eclampsia mouse model revealed that treatment with *N. sativa* ethanol extract increases NO (nitric oxide) levels and enlarges renal arteriole diameter in a dose-dependent manner [57]. Another study looked at the effects of a black cumin seed ethanol extract on angiotensin II type 1-receptor autoantibody (AT1-AA- A is a factor known to be involved in pre-eclampsia.) serum levels and endothelin-1 (ET-1, which causes changes in renal function, increased Total Peripheral Resistance (TPR), and eventually hypertension) expression in the placenta in a pre-eclampsia patient. In a pre-eclampsia mouse model, ethanol extract of black cumin seeds decreases AT1-AA serum levels and represses ET-1 expression in the placenta [58].

TABLE 1: CLINICAL STUDIES OF *NIGELLA SATIVA*

S. no.	Population	Sample size	Form of *Nigella sativa*	Dosage	Duration	Studied Disease/condition
1	Women with cyclic mastalgia	159	*N. sativa* oil	2 g of *N. sativa* seed oil	2 months (2 cycles)	Cyclic mastalgia
2	PCOS patients and complaining of amenorrhea or oligomenorrhea with or without hirsutism.	207	Black cumin oil	500 mg capsules tds	6 months	PCOS
3	Females with PCOS	10	*N. Sativa* seed powder	2 g capsules/day	16 weeks	PCOS
4	PCOS patients with oligo-amenorrhea	84	*N. sativa* oil	500 mg two soft gel capsules	16 weeks	PCOS
5	Perimenopausal women	69	Pure powdered *N. sativa*	1600mg/day	12 weeks	Reproductive health and metabolic profile among perimenopausal women
6	female students	124	*Nigella sativa* oil	Rubbed 1-2 drops nocte	7 days	Premenstrual syndrome
7	female students	124	*Nigella sativa* oil	Rubbed 1-2 drops nocte	8 days (repeated for three menstrual cycles.)	Primary Dysmenorrhea
8	female students	70	*Nigella sativa* powder	1gr /8h	first 3 days of menstruation	Primary Dysmenorrhea

					for two cycles	
9	Menopausal women	46	Nigella Sativa seed powder	500mg Capsule /day (morning)	8weeks	Menopausal syndrome
10	Menopausal women	60	*Nigella sativa* seed powder	600 mg /day	8 weeks	Sleep Disorder and Vasomotor Symptoms in Menopausal Women
11	Menopausal women	48	*Nigella Sativa* seed powder	(1000 mg) capsules (Melissa officinalis, fennel extract, and Nigella sativa powder) /day	8 weeks	Sexual dysfunction in menopausal women
12	Menopausal women	30	*Nigella Sativa* seed powder	two garlic soft gels per day (equivalent to 2000 mg of fresh garlic bulb) and crude black seed grounded to powder in a dose of 3 g/ day	8 weeks	Antioxidant effect in healthy postmenopausal women
13	Women with candidiasis	100	*Nigella Sativa* seed powder	(500 mg) capsules bd	14 days	Candidiasis

TABLE 2: *IN-VIVO* ANIMAL STUDIES OF *NIGELLA SATIVA*

S. no.	Population	Sample size	Form of *Nigella sativa*	Dosage	Duration	Studied Disease/Condition
1	albino female mice	75	*N. sativa* oil	(1.0% vs. 2.0%)	30 days	Oocyst maturity and quality
2	female albino mice	50	*N. sativa* seeds	5.0%	4 weeks	Oocyst maturity and quality
3	fertile Norway albino female rats	50	crude aqueous extract of the seeds of *Nigella sativa*	0.2g / 100g body weight	10 days	Improve endometrium
4	Female Sprague-Dawley rats	40	*N. sativa* oil	5 or 10 ml/kg/day)	56 days	PCOS
5	female albino Sprague-Dawley rats	120	*N. sativa* extract in the first experiment, methanol, hexane and SFE extracts of *N. sativa* in the second experiment and thymoquinone in the third experiment	300, 600 and 1200 mg/kg in the first experiment, 300mg/kg in the second experiment and 15mg/kg in the third experiment	21 days	Menopausal syndrome
6	*Bilateral ovariectomy* not pregnant adult Wistar rats	20	*Nigella sativa* extract	1,25; 2,5; 5; 10 and 20 mg/kgBB	4 weeks	Spatial Memory Performance in menopausal syndrome
7	Ovariectomized Sprague Dawley rats	40	methanol extract and hexane extract of *N. sativa*	300 mg/kg/day	21 days	Menopausal syndrome
8	Ovariectomized rats	40	*Nigella sativa* extract chaw palate	300 mg/kg, 600 mg/kg and 1200 mg/kg	21 days	Postmenopausal Syndrome
9	female Wistar albino rats	36	*N. sativa* seeds	500- mg/kg	3 hrs	Ovarian tissue damage
10	female albino	48	*Nigella sativa* oil	2 ml/kg	1hr	Ovarian tissue

	Wistar rats					damage
11	Wild-type C57BL/6 mice	6	Thymoquinone	20 mg/kg thrice weekly	10 to 30 days	Ovarian cancer
12	Wild-type C57BL/6 mice	6	Thymoquinone	20 mg/kg thrice weekly	30 days	Ovarian cancer
13	Seven-week-old NCr-Foxn1nu, female mice	7	thymoquinone (TQ), derived from the seeds of *Nigella sativa*	2 or 4 mg/kg b.w five times a week	4 weeks	Breast cancer
14	Female albino mice	50	Thymoquinone containing cream	different concentrations (1%,2%, 4%, 6%, 8% and 10%) once daily	6 days	Candidiasis
15	female Wistar rats	28	*Nigella sativa* extract	5mg/mL of N. sativa extract	48 h	Candidiasis
16	female Wistar strain rats	28	*Nigella sativa* extract	6.6 mL/kg of body weight	3 days	Candidiasis
17	adult female mice after giving birth	25	*Nigella sativa* ethanol extract	2.6mg, 3.9mg, 5.2mg, 6.5mg /day	7 days	post-partum infection
18	pregnant mice	30	*Nigella sativa* ethanol extract	500, 1000, 1500, and 2000 mg/kg body weight/day	4 days	Preeclampsia
19	BALB/c mice	30	*Nigella sativa* ethanol extract	1500 mg/BW/day	5days	Preeclampsia

TABLE 3: *IN-VITRO* RESEARCH STUDIES OF *NIGELLA SATIVA*

S. no.	Cell line / Tested Organism	Form of *Nigella sativa*	Dosage	Studied Disease/condition
1	Isolated uterine horns of rats and guinea pigs	Volatile oil of *Nigella sativa* seeds	Different concentrations of the oil (0.04-0.20 mg/ml)	Ant oxytocic potential of the uterine smooth muscle of rats and guinea pigs.
2	Cervical cancer cell (HeLa, HEp-2 and HF-5 cells	*N. sativa* ethanol and aqueous extracts	25, 50, 75 and 100 µg/ml	Cervical cancer
3	HeLa cell lines	*Nigella sativa* volatile oil	different concentrations (10, 100, 1000)	Cervical cancer
4	Human cervical cell lines, Siha and C33A	Thymoquinone	10-60 µM	Cervical cancer
5	Cervical cancer cell lines SiHa and CaSki	Thymoquinone	1, 5, 10, 20 and 40 µM	Cervical cancer
6	Cervical cancer cell lines (HeLa and SiHa)	Thymoquinone	3.0–200 µM	Cervical cancer
7	Mouse ovarian cancer cells (ID8-NGL cells)	Thymoquinone	20 mg/kg	Ovarian cancer
8	SK-OV-3 (human ovarian cancer cell line)	Thymoquinone	10umol/L, 15umol/L, 20umol/L, and 25umol/L	Ovarian cancer
9	ID8-NGL mouse ovarian cancer cells	Thymoquinone	25 µM	Ovarian cancer
10	Ovarian cancer cells (HO-8910 and SKOV3 cells)	Thymoquinone	40µM, 80µM	Ovarian cancer
11	Human breast MDA-MB-231 cell line	Thymoquinone	0.781, 1.562, 3.125. 6.25,12.5, 25, 50, 100, 200 and 400 µM	Breast cancer
12	Breast cancer (MDA-MB-231 and MCF-7) cells	Thymoquinone	3.125 and 6.25 μM	Breast cancer
13	Human breast cancer (MCF7, MDA-MB-231, and BT-549) cell line	thymoquinone (TQ), derived from the seeds of *Nigella sativa*	25, 50, or 100 µM	Breast cancer
14	*Trichomonas Vaginalis*	*Nigella sativa*	NsO :500 µg/ml, NsCr	Trichomonas Vaginitis

		Alcoholic (NsCr) extract and oil (NsO)	extract :1 mg/ml	
15	*Trichomonas Vaginalis*	*N. sativa* oil	500, 750, 1000µg/ml	Trichomonas Vaginitis
16	*Trichomonas Vaginalis*	*N. sativa* oil	450, 550, 650 and 750) mg/ml	Trichomonas Vaginitis
17	*Trichomonas Vaginalis*	*Nigella sativa* crude extracts	9 mg/mL,	Trichomonas Vaginitis

Nigella sativa was proven its medicinal benefits for gynecological problems such as PCOS, menopause-related issues, Hyperprolactinemia, candidiasis, Trichomoniasis, Cervical cancer, Breast cancer, ovarian cancer, Premenstrual syndrome and Pre-eclampsia, according to available *in-vitro* and *in-vivo* evidence. These effects were given to several forms of *Nigella sativa* seeds, including crude powder, ethanol extract, methanol extract, hexane extract, aqueous extracts, and oil. *N. sativa*'s estrogen and progesterone-boosting properties could help with follicular maturity, follicular quality, endometrial enhancement, and menopause-related symptoms. Its anti-inflammatory and antioxidant effects also have a favorable impact on ovarian function.

Further, its anti-inflammatory and anti-oxytocic potential effects relieve primary dysmenorrhea and premenstrual syndrome. The action of thymoquinone (TQ), a key bioactive component derived from *Nigella sativa*, was used in most research. Ten research papers used thymoquinone directly, while others used *Nigella sativa* as a source of thymoquinone. It reduces tumor growth by regulating apoptotic activity while not affecting normal cell lines' proliferation. Thymoquinone also prevents organ damage by free radicals by preventing the formation of Reactive Oxygen Species. As a result, *Nigella sativa* can help with various cancer treatments and has favorable effects on pre-eclampsia. *Nigella sativa* was found to be extremely poisonous to the parasite. It produces severe cell damage, including cytoplasmic and nuclear death, and can be utilized in antifungal and trichomonas vaginalis treatments safely and efficiently. The review's limitation was that most of the research papers were identified on Google Scholar, with only a few publications found in other well-known databases.

CONCLUSION: *Nigella sativa* has medicinal benefits for gynecological disorders such as PCOS, menopause-related issues, Hyperprolactinemia, Candidiasis, Trichomoniasis, Cervical cancer, Breast cancer, Ovarian cancer, Premenstrual syndrome and Pre-eclampsia, according to the available *in-vitro* and *in-vivo* evidence. *Nigella sativa* also increases endometrium, oocyte maturity, and quality and reduces ovarian tissue damage without any adverse effects; to further evaluate whether these impacts have public health implications, randomized controlled clinical trials will be required.

Declarations:

Availability of Data and Materials: All data generated or analyzed during this study are included in this published article.

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