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Black Seeds (*Nigella sativa*) for the Management of COVID-19 in Pregnant and Breastfeeding Women: An Insight

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Authors' contributions

This work was carried out in collaboration among all authors. Author NMPM wrote the paper. Authors TBH, FAA and SMAK designed the study, graphical explanations, supporting tables, references, analyses and helped to write the paper and edited the manuscript. Author MM validation the results. All authors read and approved the final manuscript.

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ABSTRACT

Aims: About 10% of pregnant women were suspected or confirmed with SARS-CoV-2 infection, while the risk of admission to the intensive care unit (ICU) and the use of invasive mechanical ventilation reach up to ~ 5%. This review aimed to discuss the potential of black seeds (*Nigella sativa*) in the management of COVID-10 in pregnant and breastfeeding women. *Nigella sativa* is a medicinal cum nutraceutical herb that is used in many traditional medicine systems to manage several ailments including asthma, back pain, headache, and many others.
Methodology: Online databases such as LitCOVID, Web of Science, Google Scholar, bioRxiv, medRxiv, Science Direct, EBSCO, Scopus, and EMBASE were searched to identify all scientific data relevant to the use of *N. sativa* in the treatment of COVID-19 pregnant patients. The safety and efficacy of *N. sativa* and thymoquinone were reported in different experimental studies on pregnant as well as lactating animals. Moreover, several clinical studies and in silico molecular docking studies demonstrated the potential of *N. sativa* in the management of COVID-19.
Results: The data indicate that *N. sativa* seeds in powdered or oil form can be employed as a potential adjunct therapy to manage COVID-19 in pregnant and lactating women to prevent disease severity and hospitalizations.
Conclusion: Based on these results, pregnant women with COVID-19 may use powdered *N. sativa* seeds or oil as adjunctive therapy along with standard care, to prevent severe illnesses and hospitalizations.

Keywords: COVID-19; pregnant women; lactating women; Nigella sativa; thymoquinone.

1. INTRODUCTION

"COVID-19 is an extremely contagious transmissible respiratory disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)" [1-4]. "As per the World Health Organization (WHO) novel Coronavirus (COVID-19) Situation Board, as of 16th Mar 2022, there are ~460 million confirmed cases and ~6 million deaths" [5]. A systematic review and meta-analysis of 192 studies estimated that ~10% of pregnant women were suspected or confirmed for SARS-CoV-2 infection, with ~5% at risk of admission to the ICU and use of invasive mechanical ventilation [6].

1.1 COVID-19 in Pregnant Women

The risk of susceptibility to viral pathogens and severity of respiratory infections is increased in pregnant women due to the anatomical, physiological, and immunological changes occur during the pregnancy. Several anatomical changes including relaxation of the ligaments in the ribs, elevation of diaphragm, decreased (5%) total lung capacity (TLC), increased (30-40%) tidal volume (TV), decreased (20%) expiratory reserve volume, increased transverse diameter of thoracic cavity, and decreased the compliance of chest wall, which eventually can result in 20-30% reduction in the functional residual capacity (FRC), and hypoxia [7]. Similarly, the physiological changes during the pregnancy such as increased metabolic rate (15%), enhanced oxygen consumption (20%), decreased FRC, and mismatch between ventilation and perfusion can increase the severity of respiratory infections. Pregnancy can also induce immunological changes such as pro-inflammatory state in the first trimester, anti-inflammatory state in the second trimester, and pro-inflammatory state again in the third trimester, which may increase the COVID-19 complications [8-10].

WHO stated that the risk of severity of SARS-CoV-2 [11-13] infection is increased in pregnant women. Besides, the risk of serious COVID-19 outcomes among pregnant women is higher with advanced age, higher body mass index (BMI), and comorbid conditions such as hypertension, and diabetes [14]. The centers for disease control and prevention (CDC) identified other additional risk factors that can increase the severity of COVID-19, which include the living or working in a community with high numbers of COVID-19 cases, living or working in a community with low levels of COVID-19 vaccination, working in places where the social distancing is difficult to maintain and being part of some racial and ethnic minority groups (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/pregnant-people.html).

"The most frequent symptoms of COVID-19 among pregnant women include fever, cough,

and dyspnea, while the most common laboratory findings include elevated levels of C reactive protein (CRP), white blood cells and procalcitonin and lymphopenia. Additionally, ground glass appearance was revealed frequently on the chest X-rays or computed tomography (CT) scans of pregnant women with COVID-19. The most common maternal outcomes of COVID-19 include cesarean delivery (C-section), preterm delivery, preeclampsia, and other outcomes, whereas the most frequent neonatal outcomes of COVID-19 include low birth weight, small gestational age, fetal distress and preterm birth" [15].

"The risk of vertical transmission (mother to fetus or neonate) of SARS-CoV-2 infection is considered generally low probably due to the low expression of angiotensin converting enzyme 2 (ACE2) in the placenta. The pregnant women recovering from mild or moderate COVID-19 should be encouraged to attend scheduled antenatal appointments after the period of self-isolation, as per the recommendations of the Royal College of Obstetricians and Gynecologists (RCOG). Besides, the American College of Obstetricians and Gynecologists (ACOG) recommends that the pregnant women should not be withheld from SARS-CoV-2 vaccination. Moreover, the International Federation of Gynecology and Obstetrics (FIGO) recommends COVID-19 vaccination for pregnant and breastfeeding women" [16].

1.2 Management of COVID-19 During Pregnancy

SARS CoV-2 virus is responsible for many lethal outcomes and hence preventing the viral entry or halting the viral replication at the earlier stage of infection would help to save many lives. Many repurposed drugs including the drugs inhibiting the viral entry and/ or the viral fusion such as umifenovir, Baricitinib, camostat mesylate, and Nafamostat mesylate, in addition to those can block the replication of the virus, such as favipiravir, remdesivir, Lopinavir/ ritonavir, Ribavirin, Sofosbuvir, chloroquine, and hydroxychloroquine were employed to manage the patients contracting SARS-CoV-2 infection [17]. Although, remdesivir has been approved by Food and Drug Administration (FDA) for emergency use, the data on its use in pregnant and lactating women is very limited [18]. On the other hand, several countries including China, India, Korea, and others promote the use of herbal or traditional medicines alone or as adjuvants to the standard allopathic treatment of COVID-19 [19]. Moreover, WHO encourages the use of scientifically-proven herbal or traditional medicines [20-25] for the management of COVID-19. Hence, our review aims to assess the potential use of black seeds (*N. sativa*) in the management of COVID-19 in pregnant and lactating women. "*N. sativa* is a commonly used spice and flavoring agent in food preparations. Traditionally, *N. sativa* is used to treat many ailments, including respiratory illnesses, infection, inflammation, common cold, headache, nasal congestion, rheumatic diseases, digestive tract illnesses, warts and many others. *N. sativa* has been successfully used in various clinical as well as experimental studies, which demonstrated the antiviral, anti-inflammatory, antioxidant, anticoagulant and other pharmacological and medicinal properties that are related to the signs and symptoms of COVID-19. Moreover, *N. sativa* has antihypertensive, antidiabetic, anticancer, anti-obesity and other pharmacological and medicinal properties that would help to manage COVID-19 patients with comorbidities such as hypertension, obesity, diabetes, cancer, and others" [26,27].

2. METHODS

Literature search was conducted through major electronic bio-medical databases such as LitCOVID, Web of science, Google Scholar, Science Direct, EBSCO, Scopus, and EMBASE to identify the published scientific articles relevant to the use of black seeds (*N. sativa*) for the management of COVID-19 in pregnant and lactating women. Terms like SARS CoV-2, COVID-19, Pregnant women, Lactating women, Herbal medicine, Black seeds, *Nigella sativa*, Traditional medicine, and Thymoquinone were used. This current review includes all the literature irrespective of the study design.

3. RESULTS AND DISCUSSION

3.1 Potential Use of *N. sativa* in Pregnant and Lactating Women

The important concern of using herbal drugs during the pregnancy is the probability of embryotoxicity and fetotoxicity. Some commonly used herbs during the pregnancy found beneficial, whereas others are associated with detrimental effects [28-31]. However, the safety and efficacy of *N. sativa* and its major constituent, thymoquinone, have been demonstrated by various pregnant animal studies.

3.2 Clinical Use of *N. sativa* in Pregnant Women

N. sativa is commonly used by pregnant women in African region to manage common cold symptoms, nausea, vomiting and other conditions. Administration of 10 ml of a concoction from *N. sativa* and honey (60:40) 3 times daily for 1 year in a HIV-positive pregnant woman ensued an undetectable viral load (sustained seronegative for HIV-RNA) and enhanced CD4 counts [32].

3.3 Safety and Efficacy of *N. sativa* in Pregnant Animals

Several experimental studies (Table 1) have determined the safety and efficacy of *N. sativa* and TQ in pregnant animals. The embryotoxicity and fetotoxicity of *N. sativa was evaluated in pregnant rats, administered with 50, and 300 mg/kg of* hydro-alcoholic extract of *N. sativa from day 1 to day 10 of pregnancy, while no significant adverse effects were observed on the duration of pregnancy, the percent of stillbirth, the number of newborns, and the weight of neonates* [33]. Moreover, the safety of long-term consumption of *N. sativa* during the pregnancy was evaluated in an experimental animal study, in which female rats were orally fed with 0.8 ml of *N. sativa* oil daily from 1 day before mating until the off spring of the second pregnancy. The administration of *N. sativa* led to a significant raise in number of total off spring and male offspring, better blood chemical parameters and behavioral activities among off spring [34].

An experimental study of 24 pregnant albino rats revealed that the oral administration of 100 mg/kg of *N. sativa oil from the 7th day of gestation to the first day after delivery, showed no differences in the serum levels of hepatic* enzymes (aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and malondialdehyde (MDA) levels in both the mother and offspring animals compared to control group. Moreover, concomitant administration of *N. sativa* oil with gibberellic acid ensued a significant reversal effect on gibberellic acid-associated elevation of serum levels of AST, ALT, MDA and gibberellic acid-associated attenuation of serum levels of antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). In addition, administration of *N. sativa* oil led to a marked improvement in the histopathological changes of liver induced by gibberellic acid in mother groups and their pups [35].

Administration of 500, 1000, 1500, and 2000 mg/kg ethanolic extract of *N. sativa for 5 days to pregnant mice with* preeclampsia resulted in decreased expression of renal endothelin-1 (ET-1) and enhanced renal endothelial nitric oxide synthase (eNOS) expression in a dose-dependent manner [36]. *Similar study on pregnant mice with preeclampsia ensued a significant reduction of the serum levels of soluble fms-like Tyrosine kinase-1 (sFlt-1 or sVEGFR-1) and elevation of the serum levels of vascular endothelial growth factor (VEGF) in a dose-dependent manner* [37]. Another study showed an increase in the nitric oxide (NO) levels and enlarged renal arteriole diameter of pregnant mice with preeclampsia administered with *N. sativa* ethanol extract in a dose-dependent manner [38]. Similarly, the administration of 500, 1000, 1500, and 2000 mg/kg of ethanolic extract of *N. sativa* in pregnant mice with preeclampsia led to attenuation in the serum levels of angiotensin II type 1-receptor autoantibody (AT1-AA) and the expression of endothelin-1 (ET-1) in the placenta [39]. Decreased levels of tumor necrosis factor-α (TNF-α) and interleukin-8 (IL-8) were observed in pregnant mice with preeclampsia when treated with 1500 mg/kg of ethanolic extract of *N. sativa* of 15-19 days of gestation [40]. A significant reduction in the serum levels of interleukin-6 (IL-6) and expression of p65 placenta nuclear factor-kB (NF-kB) were observed with the administration of 1500 mg/kg of ethanolic extract of *N. sativa* in pregnant mice with preeclampsia from 15-20 days of gestation [41]. The administration of 1500, and 2000 mg/kg of ethanolic extract of *N. sativa* in pregnant mice with preeclampsia also resulted in decreased expression of inducible nitric oxide synthase (iNOS) in the kidney [42].

Phytovagex is a pessary formulation of *N. sativa* administered for pregnant rats with vaginal fungal infection. Administration of Phytovagex during the first half of pregnancy (1-10 days of gestation) was not associated with any detrimental effects including the duration of pregnancy, delivery, early pup growth, number of newborns, weight of neonates, percent of stillbirth, and the viability of ovary cells [43]. Additionally, the supplementation of 1 mg/kg of *N. sativa extract* in pregnant rats with streptozotocin-induced gestational diabetes led to a protective effect against diabetic

embryopathy and fetal loss presumably through its antioxidant property [44].

Ameliorative potential of *N. sativa oil against the fetotoxic effect of* Bispyribac sodium, a commonly used herbicide was demonstrated in an experimental animal study of female pregnant rats was demonstrated *at* 1 ml/kg/day *N. sativa oil from 6-15 days of pregnancy* [45]. Moreover, the protective effect of *N. sativa oil was demonstrated against the toxic effects of* valproic acid on mice offspring. The administration of 0.2 ml of *N. sativa oil daily led to a* significant improvement in valproic acid-associated neurodevelopmental disorders including maladaptive behaviors, speech and learning impairments, muscular weakness, anxiety, and autism-like disorders, in mice offspring [46].

3.4 Safety and Efficacy of Thymoquinone in Pregnant Animals

The embryotoxic and teratogenic potential of thymoquinone (TQ), the main constituent of N. sativa, was investigated in an experimental study involving pregnant rats, which were intraperitoneally administered with TQ at 3.12, 6.25, 12.5, and 25 mg/kg from 7^{th} to 16^{th} day of gestation. The results showed no significant changes in the fetal sex ratio, resorptions, and litter size were noticed [47]. Similarly, a single intraperitoneal administration of 15 mg/kg of TQ to pregnant rats on day 11 or 14 of gestation did not cause any maternal or embryonic toxicities, whereas higher doses (35 and 50 mg/kg) of TQ induced maternal and embryonic toxicities including reduction in maternal body weight and fetal resorption, in dose- and time-dependent manners [48]. The oral lethal dose (LD50) of TQ is 250-794 mg/kg in rats and 300-2400 mg/kg in mouse, whereas, the intraperitoneal LD50 TQ is 57 mg/kg in rats and 90.3-104 mg/kg in mice [49].

"Supplementation of TQ in pregnant rats with streptozotocin-induced gestational diabetes during pregnancy and lactation periods resulted in significant effect on the number and mean body weight, improved diabetic complications, and T-cell immune responses in their offspring" [50]. Similarly, "the supplementation of 20 mg/kg/day of TQ in pregnant mice with streptozotocin-induced gestational diabetes during pregnancy and lactation periods ensued a significant effect on the number and mean body weight along with significant improvements in the levels of blood glucose, insulin, lipids, plasma pro-inflammatory cytokines and free radicals in their offspring" [51].

An experimental animal study demonstrated that the administration of TQ at 40 and 80mg/kg for 7 days in female Wistar rats before conception ensued a significant suppression of seizure stages and duration of tonic-clonic seizures in their pentylenetetrazole (PTZ)-induced epileptic offspring [52]. Similarly, another experimental animal study observed that the administration of TQ at 10 and 40mg/kg in pregnant rats led to anticonvulsant effects against pentylenetetrazol (PTZ)-induced seizure in offspring via significant reduction of seizure duration and decreased seizure stages. Moreover, the administration of TQ at higher doses (80mg/kg) particularly at the 2^{nd} week of gestation caused discharge [53]. Moreover, alleviation of histological and immunohistochemical changes in lung tissue via reduced inflammatory cell and eosinophils infiltration, around the bronchi and bronchiole walls of female pregnant asthmatic rats was observed by 10 mg/kg/day of TQ administration during the last 5 days of pregnancy compared to dexamethasone treatment [54].

3.5 Clinical use of *N. sativa* in Lactating Women

N. sativa has been used for decades in breastfeeding mothers to increase the volume of breast milk [55]. The galactagogue potential of *N. sativa* was demonstrated in a clinical study of 38 postpartum mothers who consumed *N. sativa* cookies for 10 days. The consumption of *N. sativa* cookies increased the volume of breast milk with the highest volume on the 7^{th} day of postpartum [56].

3.6 Safety and Efficacy of *N. sativa* in Lactating Animals

An experimental study of lactating rats demonstrated a significant increase in the milk production by the administration of 0.5 g/kg *N. sativa* aqueous extract and 1 g/kg *N. sativa* ethanol extract. Enhanced growth and weight gain also observed among pups administered by both extracts [57]. Similarly, administration of *N. sativa* to lactating albino mice for 15 days led to a significant increase in the litter weight and serum levels of prolactin [58]. The galactagogue action of *N. sativa* may occur presumably through the stimulation of prolactin, which is the hormone responsible for breast milk production and breast tissue growth and through increased numbers of

rumen bacteria that increase the production of volatile fatty acids that is followed by an increase in the milk production [59].

4. ANTIVIRAL POTENTIAL OF *N. sativa* AGAINST COVID-19

The antiviral efficacy of *N. sativa* against the human immune deficiency virus (HIV) [60] and the hepatitis C virus (HCV) were demonstrated in various clinical studies through significant reduction of viral load [61]. "Moreover, the antiviral efficacy of *N. sativa* against many viruses including Hepatitis C Virus (HCV), Murine cytomegalovirus (MCMV), Papaya Ring Spot Virus, Avian influenza (H9N2), Newcastle disease virus (NDV) and Peste des Petits Ruminants (PPR) Virus has been demonstrated *in vitro* and *in vivo"* [62].

"COVID-19 patients have been observed with hyper inflammatory status, higher oxidative stress, hypercoagulability, and other conditions. Hence, they are managed with various adjunctive therapies including corticosteroids, interferons, monoclonal antibodies, interleukin-1 (IL-1) inhibitors, TNF-α inhibitors, colchicine, etoposide, ruxolitinib, anticoagulants, convalescent plasma, immunoglobulins, mesenchymal stem cells, natural killer (NK) cells, and inhaled nitric oxide (iNO) along with repurposed antiviral drugs [63]. Corticosteroids like dexamethasone or methylprednisolone could be used to manage hospitalized pregnant women because of SARS-CoV-2 infection" [64]. "The anti-inflammatory activity of *N. sativa seeds or oil has been determined by different* randomized, placebo-controlled clinical trials via *significant reduction of serum levels of high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α) and other inflammatory markers"* [65-68]. *The higher oxidative stress and intensification of the levels of free radicals associated with COVID-19 can lead to several pathological conditions. In response, N. sativa seeds or oil, which possesses antioxidant activity demonstrated by various* randomized, placebo-controlled clinical trials, could be used [69-71]. Furthermore, COVID-19-associated coagulopathy, which could be pulmonary intravascular coagulopathy (PIC) locally at lungs and progresses to Sepsis-induced coagulopathy (SIC) or disseminated intravascular coagulation (DIC) systemically [72] can be managed by prophylactic anticoagulants, according to the International Society on Thrombosis and Hemostasis, American Society of Hematology and other expert organizations [73]. Various international guidelines including International Society of Infectious Disease in Obstetrics and Gynecology (ISIDOG), International Society of Ultrasounds in Obstetrics and Gynecology (ISUOG), RCOG and others recommend the use of low molecular weight heparin (LMWH) at a prophylactic dose (Enoxaparin 40 mg once daily through out hospital stay) in pregnant women with COVID-19 to avoid thromboembolism [74]. *N. sativa seeds or oil could be employed in this case since it* has a *potential anticoagulant activity, which is demonstrated in clinical study* [75] and other *in vitro* studies [76,77]. We also observed *in vitro* different molecules of *N. sativa* against SARS-CoV-2 and identified the most active ones thymoquinone and dithymoquinone [78-80].

Several clinical studies have demonstrated "the potential use of *N. sativa* in the management of patients with COVID-19. In addition, various molecular docking studies evaluated the potential of bioactive phytoconstituents of *N. sativa* such as thymoquinone, dithymoquinone, thymohydroquinone, thymol, nigellidine, nigellone, and α-hederin against the entry and replication of SARS-CoV-2" [26,27].

Table 1. Experimental studies of the safety and efficacy of *N. sativa* and TQ in pregnant and lactating animals

Sl. No.	Type of animals	Treatment	Outcome
1	Pregnant rats	50, and 300 mg/kg of hydro-alcoholic extract of *N. sativa* from day 1 to day 10 of pregnancy	No significant adverse effects were observed on duration of pregnancy, percent of stillbirth, number of newborns, and weight of neonates [33]
2	Female rats	0.8 ml of *N. sativa* oil daily from 1 day before mating until the offspring of second pregnancy completed the weaning age	Significant raise in number of total offspring and particularly male offspring, better blood chemical parameters and behavioral activities among offspring [34]

Sl. No.	Type of animals	Treatment	Outcome
3	Pregnant albino rats	100 mg/kg of *N. sativa* oil from the 7th day of gestation till 1 day after delivery	No differences in the serum levels of hepatic enzymes (Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT)), and malondialdehyde (MDA) levels in both the mother and offspring animals [35]
4	Pregnant mice with Preeclampsia	500, 1000, 1500, and 2000 mg/kg of ethanolic extract of *N. sativa* for 5 days	Decreased expression of renal endothelin-1 (ET-1) and enhanced renal endothelial nitric oxide synthase (eNOS) expression in dose dependent manner [36]
5	Pregnant mice with Preeclampsia	500, 1000, 1500, and 2000 mg/kg of ethanolic extract of *N. sativa* for 5 days	Reduction of serum levels of soluble fms-like Tyrosine kinase-1 (sFlt-1 or sVEGFR-1) and elevation of serum levels of vascular endothelial growth factor (VEGF) in dose dependent manner [37]
6	Pregnant mice with Preeclampsia	500, 1000, 1500, and 2000 mg/kg of ethanolic extract of *N. sativa* for 5 days	Increased nitric oxide (NO) levels and enlarged renal arteriole diameter in a dose-dependent manner [38]
7	Pregnant mice with Preeclampsia	500, 1000, 1500, and 2000 mg/kg of ethanolic extract of *N. sativa* for 5 days	Attenuation of serum levels of angiotensin II type 1-receptor autoantibody (AT1-AA) and the expression of the endothelin-1 (ET-1) in the placenta [39]
8	Pregnant mice with Preeclampsia	1500 mg/kg of ethanolic extract of *N. sativa* from 15-19 days of gestation	Decreased levels of tumor necrosis factor-α (TNF-α) and interleukin-8 (IL-8) [40]
9	Pregnant mice with Preeclampsia	1500 mg/kg of ethanolic extract of *N. sativa* from 15-20 days of gestation	Significant reduction of serum levels of interleukin-6 (IL-6) and expression of p65 placenta nuclear factor-kB (NF-kB) [41]
10	Pregnant mice with Preeclampsia	1500, and 2000 mg/kg of ethanolic extract of *N. sativa* for 5 days	Decreased expression of inducible nitric oxide synthase (iNOS) in the kidney [42]
11	Pregnant rats	Phytovagex (Pessary formulation of N. sativa) from 1 to 10 days of gestation	No significant effect on the duration of pregnancy, delivery, early pup growth, number of newborns, weight of neonates, percent of stillbirth, and on the viability of ovary cells [43]
12	Pregnant rats with streptozotocin-induced gestational diabetes	1 mg/kg of *N. sativa* extract from 1-17 days of gestation	Protective effect against diabetic embryopathy and fetal loss presumably through its antioxidant property [44]
13	Female pregnant rats exposed to Bispyribac sodium	1 ml/kg/day of *N. sativa* oil from 6-15 days of pregnancy	Fetotoxicity associated with Bispyribac sodium ameliorated [45]
14	Pregnant mice exposed to Valproic acid	0.2 ml of *N. sativa* oil daily	Significant improvement in Valproic acid-associated neurodevelopmental disorders (maladaptive behaviours, speech and learning impairments), muscular weakness, anxiety and autism like disorders, in the offspring [46]
15	Pregnant rats	TQ (3.12, 6.25, 12.5, and 25 mg/kg) from 7th to 16th day of gestation	No significant changes in fetal sex ratio, resorptions, and litter size [47]

Sl. No.	Type of animals	Treatment	Outcome
16	Pregnant rats	single intraperitoneal administration of 15, 35, and 50 mg/kg of TQ on day 11 or 14 of gestation	15 mg/kg of TQ did not produce any maternal or embryonic toxicities 35, and 50 mg/kg of TQ induced maternal and embryonic toxicities including reduction of maternal body weight and fetal resorption, in a dose and time dependent manner [48].
17	Pregnant rats with streptozotocin-induced gestational diabetes	20 mg/kg/day of TQ	Significant effect on the number and mean body weight, improved diabetic complications, and T cell immune responses in their offspring [49].
18	Pregnant mice with streptozotocin-induced gestational diabetes	20 mg/kg/day of TQ	Significant effect on the number and mean body weight along with significant improvements in the levels of blood glucose, insulin, lipids, plasma pro-inflammatory cytokines and free radicals in their offspring [50].
19	Female Wistar rats	TQ (40 and 80mg/kg/day) for 7 days	Significant suppression of progress of seizure stages and duration of tonic-clonic seizures in their pentylenetetrazole (PTZ)-induced epileptic offspring [52].
20	Pregnant rats	TQ (10 and 40mg/kg/day)	Significant reduction of seizure duration and decreased seizure stages in offspring [53].
21	Female pregnant asthmatic rats	TQ (10mg/kg/day) for last 5 days of pregnancy	Alleviation of histological and immunohistochemical changes in lung tissue [54].
22	Lactating rats	0.5 g/kg/day of aqueous extract of *N. sativa* and 1 g/kg/day of ethanolic extract of *N. sativa*	Significant increase in milk production [57].
24	Lactating albino mice	*N. sativa* diet for 15 days	Significant increase in litter weight and serum levels of prolactin in lactating mice [58].

5. CONCLUSION

The safety of *N. sativa* and its prime constituent thymoquinone (TQ) on pregnancy has been established by acute and subacute toxicity studies performed on animals and their use in therapeutic doses were not associated with any embryotoxicity and fetotoxicity. Besides, several experimental animal (pregnant) studies demonstrated the safety and efficacy of *N. sativa* and TQ against preeclampsia, gestational diabetes, epilepsy and other conditions. In addition, the galactagogue potential of *N. sativa* was determined in a clinical study and in few other animal studies. Moreover, various clinical studies have proven the antiviral, antioxidant, anti-inflammatory and other pharmacological effects of *N. sativa.* For these reasons, we tested *in vitro* different molecules of *N. sativa* against SARS-CoV-2 and identified the most active ones (Thymoquinone and Dithymoquinone) with potential antiviral activity. Above all, several clinical studies and in silico molecular docking studies demonstrated the potential of *N. sativa* in the management of COVID-19. The safety and efficacy of *N. sativa* would further be established in pregnant women with COVID-19 by performing randomized controlled clinical trials in future.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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