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Nigella sativa (Black Seed) as a Natural Remedy against Viruses

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Abstract

The currently available antiviral agents are associated with serious adverse effects, coupled with the increasing rate of viral resistance to the existing antiviral drugs. Hence, the search for alternative natural remedies is gaining momentum across the globe. *Nigella sativa Linnen,* also called black seed, is a medicinal plant that is gaining worldwide recognition and has been extensively investigated. The present work is aimed to review the existing literature on the antiviral efficacy of *Nigella sativa* extracts (oil and bioactive compounds). The findings reveal that numerous articles have been published on *Nigella sativa* and its beneficial effects against different kinds of diseases. However, the antiviral efficacy of *Nigella sativa* is yet to be given the proper research attention it deserves.

Keywords: *Nigella sativa,* Black seed, Antiviral activity, Viruses, Natural remedy

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INTRODUCTION

For a long time, viruses have been considered the most common pathogen to human; the last decades have witnessed outbreaks of various viral diseases, such as smallpox, an influenza pandemic (Spanish flu), the HIV/AIDS epidemic, and the ongoing Coronaviruses which have caused serious harm and public health threat globally (De Clercq, 2004; Wang, Wang, & Guan, 2012; Chen et al., 2020; Trilla, Trilla, & Daer, 2018; World Health organization, 2019; WHO, 2017b). For this reason, various antiviral agents have been recommended for clinical use, with the number of approved antiviral agents significantly increasing to around 37 (De Clercq, 2004). Regardless of these, the drug efficacy, toxicity, and cost of these drugs remain a challenge in the developing countries where viral infections are predominant (Abdel-Moneim et al, 2013; Kitazato, Wang, & Kobayashi, 2007; Vermani & Garg, 2002). Therefore, there is a shift towards finding more natural remedies to be considered as alternative medicinal choices to reduce and control the negative side effects of the conventional antiviral drugs; the natural remedies have been sought to serve as effective treatment options for viral infections at a lower cost (Agha, Ahmad, Islam, Gill, & Athar, 2010).

Natural products (herbs) have been used as traditional medicine for several decades. They have been extensively studied due to their vital role in managing human illness even though their safety and effectiveness are yet to be scientifically verified. According to the World Health Organization (WHO), up to 80% of the global population still relies on alternative therapy for their health (Farnsworth, Akerele, Bingel, Soejarto, & Guo, 1985). Different plant species, such as *Zingiber capitatum,* seaweed, green tea, and curcumin, have been evaluated for antiviral efficacy (Lin, Hsu, & Lin, 2014). *Nigella sativa* is one of these natural plants that have been previously documented to possess various medicinal activities, such as antibacterial, antidiabetic, anti-inflammatory, antioxidant, antifungal, anticancer, and antiviral activities (Ahmad et al., 2013; Yimer et al., 2019). Furthermore, some studies compared the effectiveness of *Nigella sativa* with other natural products. The antiviral and antioxidant activity of some herbal extracts including *Nigella sativa* had been evaluated by (Dorra, El-Berrawy, Sallam, & Mahmoud, 2019). In term of antiviral activity against influenza virus (H5N1), the study found that *Nigella sativa* (black seed) has a higher percentage of inhibition value at the maximum non-cytotoxic concentration when compared to *Zingiber officcinale* (Ginger), meanwhile in term of antioxidant activity all plant extracts exhibited a good antioxidant activity, however *Nigella sativa* extract exhibited a higher antioxidant activity than *Foeniculum vulgare* (Fennel). Moreover, crude and diluted extracts of *Nigella sativa* and *Zizyphus spina-christi* Mill plant have been compared for their inhibition effect against broad bean mottle virus (BBMV) on *Chenopodium amaranticolor* as a local lesion host for the virus. Crude extract of *Nigella sativa* proved to be more effective than the diluted extract in inhibiting the local lesions produced by (BBMV) when compared to the *Zizyphus* plant extracts (E. F. Mohamed, 2011). Ibrahim et al., 2017 examined water soluble extracts of black cumin (*Nigella sativa*) along with other natural spices products such as turmeric (*Curcuma longa*), black pepper (*Piper nigrum*), cardamom (*Elettaria cardamomum*) and aniseed (*Pimpinella anisum*) for their effect on the growth of pathogenic strains such as Aspergillus parasiticus strains and ability to produce aflatoxin contamination. The study found that black cumin has a moderate antifungal activity but it has a high potential to inhibit and control the production of aflatoxin contamination that is considered to be one of the most toxic substances that fungi produce after fungal infection. Sangi et al., 2018 compared the antihyperglycemic effect of some plants including black seed (*Nigella sativa*), mushroom (*Pleurotus ostreatus*), and ginger (*Zingiber officinale*) with metformin. The study has found that *Nigella sativa* and ginger have an effect in decreasing the serum glucose levels when compared to metformin and have the ability to regenerate pancreatic beta islets of Langerhans in the pancreas, while other plants such as mushroom can decrease the serum glucose levels but it does not have the ability to regenerate pancreatic beta cells.

However, despite the vast number of published articles on *Nigella sativa*, a review of its antiviral activity has yet to be conducted to date. Therefore, this paper aims to fill this gap by conducting a narrative review of the literature

on the antiviral efficacy of the extracts, oil and bioactive compounds of *Nigella sativa* against viruses. Although *Nigella sativa* as a natural remedy has been widely used as an alternative method for the treatment against viruses, it is still necessary to evaluate which therapeutic method and/or which compounds of *Nigella sativa* is effective in the treatment against viruses by reviewing the available literature which will provide data to determine the suitable combinations of therapeutic methods and compounds that might give great promise in finding a suitable remedy against viruses. In this way, the current study contributes to the *Nigella sativa* literature by identifying the aspects of its efficacy that needs to be experimentally evaluated.

***Nigella sativa* Overview**

One of the traditional herbal medicines that are currently gaining worldwide recognition and research attention is *Nigella sativa L.* This plant has been described as the Miracle Herb of the Century (Goreja, 2003), and known globally by different local names; for instance, the Arabian and Muslim community refer to this plant as Habbat Al-barakah, Al-habahat Alsawda, and Al-kamoun Alaswad while English speakers called it black cumin, black caraway or black seed (Zohary, Hopf, & Weiss, 2012)

Nigella sativa belongs to the family *Ranunculaceae*; it can grow up to 20-90 cm tall. It is a small flowering plant with finely divided leaves. It produces flowers (with 10 petals) of different shades, ranging from white and yellow to pink, blue and purple. Previous studies have reported the presence of various bioactive compounds from *Nigella sativa*, especially thymoquinone (TQ) which is the most essential bioactive compound in *Nigella sativa,* accounting for about 30-48% of the total bioactive compounds of *Nigella sativa*. Among the other reported bioactive compounds of *Nigella sativa oil* are carvacrol (6%-12%), thymohydroquinone (30%-40%), p-cymene (7%-15%), dithymoquinone, 4-terpineol (2%-7%), sesquiterpene longifolene (1%-8%), t-anethol (1%-4%), α-pinene, thymol, etc. (Ahmad et al., 2013; Asif et al., 2015; Houghton, Zarka, B., & Hoult, 1995). However, the most studied bioactive component of *Nigella sativa* oil is TQ owing to its numerous therapeutic properties (Woo, Kumar, Sethi, & Tan, 2012; Torequl Islam et al., 2016; Schneider-Stock, et al., 2014). Table 1 summarizes some important findings of TQ studies.

Both the essential oil and crude extract of *Nigella sativa* have proven and been reported to have several medicinal properties, such as antidiabetic (al-Awadi, Fatania, & Shamte, 1991), anticancer (M. A. Randhawa & Alghamdi, 2011), anti-inflammatory (Houghton et al., 1995), immunomodulatory (Mohamed Labib Salem, 2005) antioxidant (Meral, Yener, Kahraman, & Mert, 2001), antimicrobial (Randhawa, Alenazy, Alrowaili, & Basha, 2017), analgesic (Hajhashemi, Ghannadi, & Jafarabadi, 2004), cardiovascular disorders (Zaoui et al., 2002), antifungal (Elfadil, Fahal, Kloezen, Ahmed, & van de Sande, 2015), antiparasitic (Fattahi Bafghi, Vahidi, Anvari, Barzegar, & Ghafourzadeh, 2011), neurotoxicity (Khazdair, 2015), antinociceptive (Khazdair, 2015), antimalarial (Khazdair, 2015), and antiviral activities (Salem & Hossain, 2000).

Limitations of *Nigella sativa*

Despite all the pharmaco-therapeutics effects of *Nigella sativa*, some limitations of its usage and production raised during the clinical investigations that can limit its usage and clinical development. Some studies reported mild side effects of *Nigella sativa* when it was given as a treatment for certain diseases. Nausea, bloating, and burning sensation were observed when functional dyspeptic patients have been given 5 mL of *Nigella sativa* oil mixed with honey orally daily. These results were reported when this study evaluated the efficacy and safety of this mixture to have a gastro-protective and anti H. pylori activity. (Mohtashami et al., 2015). Other studies that examined *Nigella sativa* seeds on patients suffering from seasonal allergic rhinitis reported that use of *Nigella sativa* was effective in mild and moderate allergic rhinitis symptoms reduction, however adverse effects such as nasal dryness and diarrhea were observed in some patients, which are consider minor effects when compared with conventional drugs used for allergic rhinitis (Akhtar, 2016; A. Mohamed, Abdul, & Ahmed Alobaidi, 2012). In another study by Dogar et al., (2009) side effects such as pancreatitis, hyperbilirubinemia, diabetes mellitus, diarrhea and hypofibrinogenemia appeared when children with acute lymphoblastic leukemia were treated with L-asparaginase, while none of these serious

effects were observed in patients who received conventional treatment with *Nigella sativa* seeds in a powder form. However, the study concluded that low side effects associated with the consumptions *Nigella sativa* seeds were significantly less when compared to conventional therapy and the use of L-asparaginase, thus *Nigella sativa* has high beneficial properties as an anti-cancer agent if given in combination with other cytotoxic drugs. Some studies link these limitations of *Nigella sativa* and any herbal medicine to the short duration of treatment, loss to follow-up, small sample size and participants' preferences of herb use form (Akhondian et al., 2011; Griffin & Citkovitz, 2017; Rizka, Setiati, Lydia, & Dewiasty, 2017).

On the other hand, *Nigella sativa* has a number of limitations regarding its productions. TQ has been reported that it has limited bioavailability and exhibits light and heat sensitivity (Goyal et al., 2017). In addition, TQ is considered as a compound that has a rapid distribution and elimination from plasma when given via intravenous administration, while has relatively slower absorption after oral administration using a rabbit as an animal model (Alkharfy, Ahmad, Khan, & Al-Shagha, 2015). Another limitation reported by Mohammed et al., (2018) was poor water solubility. This limitation is closely linked to the different polarity of the oil and water that directly led to poor bioavailability due to decrease in the absorption rate in the gastrointestinal tract.

To prove safe usage and a good production of *Nigella sativa*, many efforts need to be undertaken to eliminate these limitations. Therefore, further clinical trials, experimental investigations, drug development and animal studies are required to address these limitations and enhance the therapeutics effects of *Nigella sativa*.

Antiviral Activity of *Nigella sativa*

***Nigella sativa* against Herpesviruses**

The antiviral efficacy of *Nigella sativa* and TQ against herpesviruses has been well documented. *Herpesviridae* is a big family of DNA viruses known to cause various diseases in humans and animals; herpesviruses are a common member of this family, with the α-herpesviruses being the most common subfamily. Herpesviruses are classified into herpes simplex viruses 1 and 2 (HSV-1, HSV-2), with HSV-1 being the cause of mouth ulcers while genital ulcers are caused by HSV-2, even though HSV-1 has been implicated in genital infections (Van Lint & Knipe, 2019). In 2012, the WHO estimated that about 3,709 million people globally had prevalent HSV-1 infection (67% global prevalence), while HSV-2 infection was estimated in 417 million people (11.3% global prevalence) (Looker et al., 2015). Numerous studies have observed that HSV can be treated with natural products like aloe vera (Rezazadeh, Moshaverinia, Motamedifar, & Alyaseri, 2016), seaweed species (H. Wang, Ooi, & Ang, 2008), and sandalwood oil (Benencia & Courreges, 1999). One study investigated the antiviral activity of *Nigella sativa* against HSV-1 and HSV-2 and found that *Nigella sativa* had a toxic effect on the host cell but showed a slight antiviral activity against HSV-1 (with an IC_{50} value of around 50 µg/mL against HSV-2) (Sokmen, 2001). Cytomegalovirus (CMV) is another highly prevalent member of the Herpesviridae. Murine cytomegalovirus (MCMV) is a β-herpesvirus that is associated with fatal and disseminated infections in immunocompromised animals; it is similar to the human cytomegalovirus that causes infections in immunodeficient persons. *Nigella sativa* oil has been reported to completely inhibit the viral load in the spleen and liver against MCMV infection (M L Salem & Hossain, 2000). Besides HSV and MCMV, Epstein–Barr virus (EBV), a human virus that belongs to the γ-herpesvirus family, also been studied (Zihlif et al., 2013). Avian Infectious Laryngotracheitis virus (ILTV) is caused by α-herpesviruses while the Gallid herpesvirus 1 species are responsible for respiratory disease in chickens and pheasants (Ou & Giambrone, 2012); both have been used to test for the antiviral activity of black seed extracts (Zaher, Ahmed, & Zerizer, 2008). The study showed that *Nigella sativa* inhibited the activity of ILTV at the concentration of 35 µM; this result was supported by the previous observations on the antiviral effect of *Nigella sativa* which linked the observed activity to TQ, the main bioactive compound of *Nigella sativa* with reported antimicrobial effect against various fungi, viruses, and bacteria (M. Randhawa et al., 2017).

***Nigella sativa* against human immunodeficiency virus**

Human immunodeficiency virus (HIV) infection is still considered the most global public

Table 1. Findings from selected studies showing the different activities of TQ compound

Activities of TQ	Study models	Effect observed	References
Antitumor and anti-angiogenic	Human osteosarcoma cell line (SaOS-2) Human umbilical vein endothelial cell	Apoptotic effect (decrease tumor angiogenesis and tumor growth through suppressing NF-κB)	(Peng et al., 2013)
Anti-inflammatory effects	Bone marrow aspirates collected from Osteoarthritis patients	(a) Up-regulation of the anti-inflammatory genes IL-4 and IL-10. (b) Up-regulation of pro-inflammatory genes namely IFN-g, TNF-a, COX-2, IL-6, IL-8, IL-16, and IL-12A. (c) The pro-apoptotic BAX gene was down-regulated while the SURVIVIN gene was up-regulated.	(Kalamegam et al., 2020)
Antibacterial activity	Human pathogenic bacteria	Exhibited a significant bactericidal activity against the majority of the tested bacteria and prevented cell adhesion to glass slides surface	(Chaieb, Kouidhi, Jrah, Mahdouani, & Bakhrouf, 2011)
Antiepileptic effects	Intractable epileptic children	Reduce the frequency of seizures	(Akhondian et al., 2011)
Antibacterial activity	Clinical bacterial strains	Exerted antibacterial activity against both gram-positive and gram-negative bacteria.	(Halawani, 2009)
Antinociceptive effects	Mice	(a) Increased animal reaction time to hot plate and in tail-pinch test. (b) Acetic acid-induced writhing was inhibited. (c) Pain response was inhibited in the first phase of formalin test.	(Amin & Hosseinzadeh, 2016)
Antitumor activity	Orthotopic model of pancreatic cancer *in vitro* and *in vivo*.	(a) A combination of gemcitabine and oxaliplatin more effective as an antitumor agent compared with either agent alone. (b) Killing of pancreatic cancer cells are induced by chemotherapeutic agents by down-regulation of nuclear factor-KB (NF-κB), Bcl-2 family, and NF-κB- dependent antiapoptotic genes.	(Banerjee et al., 2009)

health problem. The WHO report of November 2019 (WHO, 2019) showed that more than 32 million lives have been lost to HIV since it was first reported in 1981 (UNAIDS, 2006). Globally, approximately 37.9 million people were estimated to be living with HIV at the end of 2018 (World Health Organization, 2019). HIV is classified into the genus Lentivirus and belongs to the family of *Retroviridae*. Persons infected with HIV can gradually develop acquired immunodeficiency syndrome (AIDS) which is the terminal stage of HIV infection. HIV attacks the CD4 cells of the body, thereby weakening the immune system. This makes it hard to recover from simple infections that healthy people can easily fight off. After HIV infection, a person can live with the virus for about 2 to 15 years based on individual differences before progressing to the terminal phase that manifests as AIDS (WHO, 2019).

To date, there is no preventive vaccine or completely effective treatment against HIV. Recently, Onifade and his colleagues conducted several studies on the efficacy of a mixture of *Nigella sativa* and pure honey extracts to treat some HIV patients. They reported a wide range of activity against HIV via direct reduction of the viral load and/or increase of the CD4 count (Onifade et al., 2013; Onifade et al., 2011; Onifade & Jewell, 2012; Onifade A. A., Jewell A.P., Okesina, 2011, 2015; Onifade A.A., Jewell A.P., 2013; Onifade A.A., 2014).

***Nigella sativa* against Hepatitis C virus**

As per the WHO, approximately 71 million people were infected by the Hepatitis C virus (HCV) in 2015; hence, Hepatitis C is seen as a global public health issue that is mainly characterized by the high level of liver enzyme expression. These enzymes are the most obvious signs of hepatic injury because their cytoplasmic level normally increases following liver injury (Hajarizadeh, Grebely, & Dore, 2013. Egypt is one of the countries in the world with a high prevalence rate of HCV based on the morbidity and mortality rates; the highest prevalence percentage was reported in 2013 with around 10-15% out of the general population of Egypt as per reported by Abdel-Moneim et al. (2013) and Barakat, El Wakeel, & Hagag (2013). Both studies consistently proved that *Nigella sativa* seed oil significantly decreased the viral load and reduced the level of liver enzymes expression among the studied Egyptian HCV patients. Administration of *Nigella sativa* extract significantly increased the serum levels of total protein and albumin post-treatment, showing an improvement in clinical condition. The results of these two studies were in agreement with other studies that have shown similar effects in animals treated with *Nigella sativa* (al-Gaby, 1998; Shewita & Taha, 2011; Tollba, 2003). These results may be due to the hepatoprotective effects of the TQ content of *Nigella sativa* as having been reported by many studies (El-Dakhakhny, Mady, Lembert, & Ammon, 2002; Mansour, 2000). Although both studies used different extracts, such as seed oil extract and ethanolic extracts of *Nigella sativa*, they revealed that *Nigella sativa* is a safe extract that reduced the viral load and improved the clinical condition of the patients.

On the other hand, the outcome of a study (Oyero et al., 2016) showed that Alpha-zam (α- Zam) can be used as a selective inhibitor of HCV replication. α- Zam, as per previous studies, has a combined formula of a herbal remedy containing 60% *Nigella sativa* and 40% freshly harvested pure honey as the major constituents (Onifade et al., 2011; Onifade A.A., Jewell A.P., 2013; Onifade A.A., Jewell A.P., Okesina, 2011).

***Nigella sativa* against Newcastle disease**

Newcastle disease virus (NDV) infects different bird species globally, causing severe losses to farmers (Cattoli, Susta, Terregino, & Brown, 2011). Studies have reported positive effects of *Nigella sativa* oil, seeds, and other extracts on broilers in the form of improved growth performance when used as a dietary component (Durrani et al., 2007; Kumar & Patra, 2017; Shewita & Taha, 2011; Toghyani, Toghyani, Gheisari, Ghalamkari, & Mohammadrezaei, 2010). Other studies have also reported positive effects of *Nigella sativa* on the immune responses of poultry (Khan, Anjum, Parveen, Khawaja, & Ashraf, 2013; Yaseen, 2003). These findings were corroborated by A. U. Khan et al., (2018) who also observed a notable reduction in the mortality rate in embryonated chicken eggs, showing the ability of ethanolic extract of *Nigella sativa* to enhance immunity and decrease viral load against NDV.

***Nigella sativa* against Peste des petits Ruminants Virus**

Peste des petits Ruminants Virus (PPRV)

causes a serious viral infection of the respiratory system and gastrointestinal tract of animals, thereby producing high annual morbidity and mortality (Balamurugan, Hemadri, Gajendragad, Singh, & Rahman, 2014). Even though antiviral drugs and vaccination can control the spread of the virus, the use of herbal products against PPRV has been studied and proved to have similar effects as some antiviral drugs (T.C. & G., 2012; Wosu, 1989). *Nigella sativa* also has *in vivo* effect against PPRV in goats fed with *Nigella sativa* seeds and *in vitro* when infected cell lines were treated with *Nigella sativa* alcoholic extract (K. Aqil et al., 2017; Kiran Aqil et al., 2018). *Nigella sativa* showed significant antiviral activity against PPRV by decreasing the liver enzyme levels after treatment (Abdel-Moneim et al., 2013; Barakat, El Wakeel, & Hagag, 2013). This has been linked to the protective action of *Nigella sativa* due to the bioactivity of its components (Adam et al., 2016; Mohideen, Ilavarasan, Sasikala, & Thirumalai Kumaran, 2003). However, Kiran Aqil et al., (2018) described a suppressing activity of *Nigella sativa* against PPRV via increasing cell survival percentage and reducing the pathogenic effects of infected goats.

***Nigella sativa* against Coronaviruses**

Coronavirus was first described in 1931 by Dr. Oskar Seifried, a veterinarian, as a serious threat to animal health (Seifried, 1931). However, it was re-identified in the 1960s as a group of viruses that can cause both animal and human infections (Kahn & McIntosh, 2005). Coronavirus is a positive-sense enveloped single-stranded-RNA virus of the *Coronaviridae* family; it is classified into 4 recognized genera which are alpha, beta, gamma, and delta coronaviruses (Nakagawa, Lokugamage, & Makino, 2016). The members of the Coronavirus family are normally implicated in enteric and upper respiratory tract infections in humans and other animal species (Weiss & Navas-Martin, 2005). In most humans, it mainly causes mild infections of the upper respiratory tract. To date, there are seven identified human coronaviruses; these are 229E, NL63, OC43, HKU1, MERS-CoV, SARS-CoV, and SARS-CoV-2 (or COVID-19) (Geller, Varbanov, & Duval, 2012; Marty & Jones, 2020; Weiss & Navas-Martin, 2005). Coronaviruses have been the major cause of several global epidemics with high mortality; the first coronavirus-related epidemic, SARS, in 2002–2003, affected more than 8,000 persons with over 700 deaths (Anthony R. Fehr, & Stanley Perlman, 2015). In 2012, another novel human coronavirus infection called MERS-CoV or MERS was reported in the Middle East, causing respiratory tract infections mainly in the Middle East; MERS affected about 2,206 person while 787 deaths were recorded (Fehr et al., 2015). The ongoing COVID-19 is the latest coronavirus-related infection; it has affected more people than SARS or MERS within a shorter period (Marty & Jones, 2020). *Nigella sativa* is used for the treatment of respiratory diseases like chest congestion, shortness of breath, bronchospasm, and asthma in folk medicine (Goreja, 2003), while its bioactive compounds are used in pharmacological studies as effective ingredients to prepare drugs (Ahmad et al., 2013).

Nigella sativa extract has been evaluated for its efficacy in preventing the replication of coronavirus (CoV) during active coronavirus infection; the extracts successfully reduced the virus loads in the treated cases (Ulasli et al., 2014). Even though previous studies on the antiviral efficacy of *Nigella sativa* have shown significant results, the effect of the crude ethanol extract of *Nigella sativa* against the Avian infectious bronchitis virus (IBV) remains unclear. IBV is a gamma coronavirus that causes upper respiratory tract infection in birds, causing the laying of eggs with weakened and deformed shells. (C. Chen et al., 2014) found that *Nigella sativa* extract had no significant impact on the virus titres as it failed to inhibit IBV replication when compared to the control.

***Nigella sativa* against Influenza virus**

Influenza viruses belong to the *Orthomyxoviridae* family; this family can be sub-grouped into A, B, and C. They are implicated in most cases of respiratory tract infections that manifest in fever, headache, sneezing, muscle pains, sore throat, and joint pains; more severe conditions, such as pneumonia, are also associated with influenza virus infection (Blumel et al., 2009; Eccles, 2005). Influenza virus infection has been considered the most devastating epidemic that caused the highest mortality in humans. In 1918, the influenza A virus pandemic (Spanish flu) caused the death of approximately 40 to 50 million people (Trilla, Trilla, & Daer, 2008). Avian influenza A virus

(AIVs), called bird flu, is classified into subtypes based on different combinations of various viral surface proteins (such as hemagglutinin (HA) and neuraminidase (NA)). Several studies tested the effect of *Nigella sativa* on subtypes H9N2 and H5N2 against AIVs subtypes and found active inhibition of virus replication, enhanced immune response, and suppression of viral pathogenicity in poultry (Dorra et al., 2019; Mady, Arafa, Hussein, Aly, & Madbouly, 2013; S. Umar et al., 2016; Sajid Umar, Munir, et al., 2016; Sajid Umar et al., 2015; Sajid Umar, Rehman, et al., 2016). The study by (Sajid Umar et al., 2015) suggested that clinical signs in H9N2 infected birds showed improvement upon dietary supplementation with either *Nigella sativa seeds* and TQ, or their combination. The study also reported a decline in clinical symptoms upon supplementation with 3% *Nigella sativa* seed; the antibody titre was also increased against H9N2 AIV, thereby improving immune response and suppressed viral pathogenicity in the treated turkeys when compared to 1% dietary supplementation. Subsequent studies confirmed this dose-dependent effect as a higher antibody titre was observed with 6% *Nigella sativa* dietary supplementation compared to 1% and 3% dietary supplementation (Sajid Umar, Munir, et al., 2016). These findings suggested that turkeys fed with *Nigella sativa* exhibited higher levels of cytokine gene expression, leading to increased antiviral behaviour and suppressed pathogenesis of H9N2 viruses. Another study showed that the combination of TQ and other herbs as a single supplement significantly reduced the clinical signs in turkeys fed with this combination; this was attributed to the TQ content of *Nigella sativa* which improved the immune response and reduced the viral pathogenicity in the treated birds (S. Umar et al., 2016). These findings concurred with previous studies that revealed enhanced immune response upon treatment with *Nigella sativa* extracts (Ahmad et al., 2013; Dorucu, Ispir, Colak, Altinterim, & Celayir, 2009; Shewita & Taha, 2011). Also, the study reported that TQ, when fed to turkeys infected with H9N2, showed a lower viral load and increased expression of Interferon-gamma (IFNγ) levels. It may suggest that TQ can stimulate and induce proliferation of cytotoxic T-cells to allow increased viral clearance. Moreover, avian influenza virus subtype H5N1 has previously been reported to be treated with *Nigella sativa* extract. Ethanol extract of *Nigella sativa* showed moderate dose-dependent antiviral activity and prevented the replication of H5N1. Experimental works suggested that the inhibition may be mediated by increasing innate immunity (Dorra et al., 2019). However, another study found that *Nigella sativa* oil, when used as a vaccine adjuvant against H5N1, can exhibit a non-specific immunostimulant effect and induce cellular immune response that restricts the replication of H5N1 (Mady et al., 2013).

***Nigella sativa* against plant viruses**

A few studies have reported the antiviral efficacy of *Nigella sativa* extracts against plant viral infections; some of the reported studies are as follows:

***Nigella sativa* against Broad Bean Mosaic Virus**

Broad bean (*Vicia faba L*.) is one of the legumes affected by viruses globally (I. E. T. Mohamed &, El Bushra El Sheikh El Nur, 2010). Broad Bean Mosaic Virus (BBMV) is a member of the Bromoviruses and is considered a common virus in fava bean fields. The antiviral activity of *Nigella sativa* has been tested against BBMV on *Chenopodium amaranticolor* plant as a local lesion host both *in vitro* and *in vivo* (E. F. Mohamed, 2011). The study proved that the extracts reduced the virus-induced local lesions and increased the *in vitro* inhibition percentages. On the other hand, the *in vivo* experiments found that pre-inoculation treatment inhibition was more effective in reducing virus pathogenicity compared to post-inoculation treatment. However, the crude extract achieved higher inhibition percentages compared to the dilutions possibly due to its richness in bioactive compounds (Schneider-Stock et al., 2014; Torequl Islam et al., 2016).

***Nigella sativa against* Tobacco Mosaic Virus**

Tobacco Mosaic Virus (TMC) is another important plant virus that belongs to the genus Tobamovirus and is considered one of the top 10 plant viruses that cause significant economic losses in many crops (Scholthof et al., 2011). The antiviral activity of *Nigella sativa* extract has been evaluated on TMV in *Nicotiana glutinosa* and *Datura metel* as local lesion hosts of tobacco plants (El-Sayed, 2011). The results showed that

the extract achieved complete recovery from virus infection by complete inhibition of the replication of the virus.

***Nigella sativa against* Zucchini Yellow Mosaic Virus**

Besides BBMV and TMV, there are other pathogenic plant viruses, such as Zucchini Yellow Mosaic Virus (ZYMV); which is a member of the family *Potyviridae*. ZYMV causes a destructive worldwide epidemic in cucurbits. (Desbiez & Lecoq, 1997). The antiviral activity of *Nigella sativa* decoction and infusion seeds extract has been examined against ZYMV infection in watermelon seedlings. The outcome of the study showed that *Nigella sativa* inhibited the progression of ZYMV infection both *in vitro* and *in vivo*; it did not just inhibit the clinical signs of virus infection but increased the plant growth parameters. The disease severity, percentage of infection, and viral load were correlated with the observed disease symptoms as well (Elbeshehy, 2017). This result agreed with another study by Abdel-Shafi S (2013) who found that the treatment of squash plants with aqueous *Nigella sativa* extract improved plant recovery from ZYMV infection and improved the plant growth parameters because *Nigella sativa* extract was able to induce plant resistance against ZYMV infection. Based on these findings, *Nigella sativa* extracts can be considered safe and recommendable for use as biological control of plant viruses.

CONCLUSION

The use of natural extracts and derivatives in disease prevention and cure has been on the increase globally due to their high tolerance and low side effects. *Nigella sativa* is a well-known plant used in folk medicine for many decades now; it is considered a "miracle herb" due to its effectiveness in managing several disease conditions. The available scientific data on *Nigella sativa* has revealed that *Nigella sativa* oil, extracts, and components, particularly thymoquinone, can serve as natural remedies for many diseases. Moreover, the extracts of *Nigella sativa* are proven to exhibit different medicinal properties even though their antiviral activity has not been fully exploited. This review focused on reviewing most of the published studies on the antiviral effects of *Nigella sativa*, especially those that demonstrated the antiviral activity of *Nigella sativa* and its bioactive compounds against the different plant, animal, and human viruses. Based on the outcome of the review, further studies are recommended for the development of *Nigella sativa* as a natural antiviral drug against various viruses. It is hoped that this review would be helpful to the interested researchers in the future, and will motivate further experiments (both *in vitro*, *in vivo*, and clinical trials) on the antiviral efficacy of *Nigella sativa*. This review has some limitations. One of them was the difficulty in finding the full texts of some published papers as only the abstract was published. Moreover, only English-language articles and no other language studies were included in this review.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a contribution to the work, and approved the final manuscript for publication.

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