

# Miracle Herb to Cure HIV-Black Seeds (*Nigella Sativa*): A Review

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## Abstract

The Acquired Immunodeficiency Syndrome (AIDS) damages the immune system and interferes with the body's ability to fight infections and it is caused by a retrovirus named Human Immunodeficiency Virus (HIV). The patients with HIV/AIDS are currently managed with Highly Active Antiretroviral Therapy (HAART) or a combination Antiretroviral Therapy (cART) which includes Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs), Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs), Integrase Strand Transfer Inhibitors (INSTIs), Fusion Inhibitors (FIs) and Chemokine Receptor antagonists (CCR5 antagonists). The World Health Organization (WHO) has suggested systematically testing ethnomedicines against HIV to find more options for the treatment of HIV/AIDS. This review focuses on the potentials of *N. sativa* in the management of HIV/AIDS. The antiviral potentials of *N. sativa* have been observed in many in-vivo and in-vitro studies while previous studies have confirmed the immunomodulatory effects of *N. sativa*. Above all, various pilot studies and case reports have demonstrated that the administration of *N. sativa* produced complete seroreversion of viral load in many HIV/AIDS patients, miraculously. Hence, *N. sativa* could be used alone or in combination with HAART therapy to cure the patients with HIV/AIDS.

**Keywords:** Acquired Immunodeficiency Syndrome, AIDS, Human Immunodeficiency Virus, HIV, Nigella Sativa, Black Cumin, Kalonji, Highly Active Antiretroviral Therapy, HAART

## Introduction

Acquired Immunodeficiency Syndrome (AIDS) is caused by the retrovirus Human Immunodeficiency Virus (HIV) which damages the immune system and interferes with the body's ability to fight infections. Modes of transmission of HIV principally include blood, sexual contact and mother-to-child.<sup>1</sup>

It has been reported by the Joint United Nations Programme on HIV/AIDS (UNAIDS) in 2017 that there were about 36.9 million people living with HIV across the globe <sup>2</sup> and in 2018 it has been estimated that there were 37.9 (32.7-44.0) million people living with HIV which increased from 24.9 (21.5-28.9) million in 2000 to 31.7 (27.3-36.8) million in 2010.<sup>3</sup>

The patients with HIV/AIDS are currently managed with Highly Active Antiretroviral Therapy (HAART) or a combination Antiretroviral Therapy (cART) which was introduced in 1996. Various stages of the viral life cycle of HIV is targeted by different classes of HAART agents including Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs) (abacavir, didanosine,

lamivudine, stavudine, tenofovir, and zidovudine), Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (delavirdine, efavirenz, nevirapine, rilpivirine), Protease Inhibitors (PIs) (atazanavir, darunavir, indinavir), Integrase Strand Transfer Inhibitors (INSTIs) (dolutegravir, elvitegravir, raltegravir), Fusion Inhibitors (FIs) (enfuvirtide) and Chemokine Receptor antagonists (CCR5 antagonists) (maraviroc).<sup>4</sup>

The WHO has suggested systematically testing ethnomedicines against HIV to find more options for the treatment of HIV/AIDS.<sup>5</sup> Hence, this review has focused on the potentials of *Nigella sativa* in the management of HIV/AIDS, as previous studies have confirmed that *N. sativa* has antiviral, immunomodulatory and anti-HIV properties.

*N. sativa* belongs to the Ranunculacea family and has been traditionally used to manage many conditions including common cold, warts, asthma, etc. for centuries. Moreover, *N. sativa* is used to treat infections and to manage common chronic conditions such as

obesity, diabetes, cardiovascular diseases, hypertension, and cancer. The chemical constituents such as terpenes, volatile oils, flavanoids, alkaloids, Saponins, fatty acids, tannins, and phytosterols have been identified in the phytochemical screening of *N. sativa*.<sup>6</sup> The prominent bioactive constituent of *N. sativa* is found to be thymoquinone (TQ) and it also contains other phytoconstituents such as dithymoquinone (DTQ), limonene, carvone, nigellidine,  $\alpha$ -hederin and many others.<sup>7</sup>

## Results and Discussion

The prevalence of use of herbal medicines is higher among the patients with HIV<sup>8</sup> and they may consider herbal medicines due to the reasons including HAART-associated anemia HIV-related symptoms like fever, joint pain, etc. Nevertheless, there is an enhanced

risk of adverse drug interactions between HAART and the herbal medicines.<sup>9</sup>

However, an animal study revealed that *N. sativa* extract did not exert any adverse drug interaction when combined with HAART therapy (Lamivudine, Zidovudine and Efavirenz). A significant increase in the White Blood Cells (WBC) count and no other changes in hematological parameters were noted by the administration of this combination.<sup>10</sup> In addition, *N. sativa* oil has attenuated the HAART-associated hyperinsulinemia, and insulin resistance by preventing reduction of size of pancreatic islets and dysregulation of insulin production, in Sprague-Dawley rats.<sup>11</sup> Various studies have confirmed that *N. sativa* has antiviral, immunomodulatory, and anti-HIV properties essential in the management of HIV/AIDS (Table 1).

**Table 1.** Studies Supporting the Use of *N. sativa* to Cure HIV/AIDS

S.No	Pharmacological Activity	Type of Study	Findings
1	Antiviral (Papaya Ring Spot Virus)	In-vitro study [11]	The volatile oil and acetone extract of <i>N. sativa</i> showed better antiviral activity against Papaya Ring Spot Virus.
2	Antiviral (Murine Cytomegalo virus)	Animal study [12]	<i>N. sativa</i> oil inhibit virus titers in spleen and liver in mice infected with MCMV virus.
3	Antiviral (Newcastle disease virus)	In-vitro study [13]	<i>N. sativa</i> extract has shown strong antiviral effect by increasing the number of lymphocytes and macrophages.
4	Antiviral (Hepatitis C virus)	In-vitro study [14]	Selective inhibition of HCV replication by Alpha-zam (herbal formulation of <i>Nigella sativa</i> seed).
5	Antiviral (Hepatitis C virus)	Clinical studies [15-17]	The antiviral efficacy of <i>N. sativa</i> has also been demonstrated against HCV by various clinical studies [15-17].
6	Immunomodulatory	Randomized, double-blinded placebo-controlled, 2 months, parallel-group clinical trial [20]	Modulation of T lymphocytes such as decreased CD8+ (suppressive lymphocyte), and increased percentage of CD4+CD25+ and the ratio of CD4+/CD8+
7	Immunomodulatory	Pilot study [21]	Significant increase in phagocytic and intracellular killing activities of polymorphonuclear (PMN) leukocyte and elevated CD8 counts.
8	Anit-HIV	Pilot study [22]	<ul style="list-style-type: none"> <li>The viral load (HIV-RNA) of stage I patients reduced from the average of 19000 copies/ml to undetectable level and of stage IV patients reduced from the average of 51000 copies/ml to &lt;1000 copies /ml.</li> <li>All the patients had increased CD4 counts too</li> </ul>
9	Anit-HIV		Undetectable viral load (HIV-RNA) and normal CD4 counts, which sustained even after 7 years of follow-up screening.
10	Anit-HIV		Undetectable viral load (HIV-RNA), normal CD4 counts and enhanced body weight.
11	Anit-HIV		Undetectable viral load (HIV-RNA) and increased CD4 counts, which sustained even after 4 years of follow-up screening.
12	Anit-HIV		Undetectable viral load (HIV-RNA) and enhanced CD4 counts.
13	Anit-HIV		Undetectable viral load (HIV-RNA) and enhanced CD4 counts, which sustained even after 10 years of follow-up screening.

## Antiviral

The antiviral efficacy of *N. sativa* has been confirmed against many viruses including Papaya Ring Spot Virus, Murine cytomegalovirus (MCMV), Newcastle disease virus (NDV), Hepatitis C Virus (HCV), and Peste des Petits Ruminants (PPR) Virus by in-vitro and in-vivo studies and HIV, and Hepatitis C Virus (HCV) by clinical studies.<sup>6</sup>

An in-vitro study, which evaluated the antiviral efficacy of volatile oil and acetone extract of *N. sativa*, revealed that both the volatile oil and acetone extract of *N. sativa* showed better antiviral activity against Papaya Ring Spot Virus.<sup>12</sup> An animal study also demonstrated that the intraperitoneal administration of *N. sativa* oil to mice infected with MCMV virus ensued in inhibition of virus titers in spleen and liver.<sup>13</sup>

Another in-vitro study on embryonated eggs inoculated with NDV virus found that *N. sativa* extract has shown strong antiviral effect by increasing the number of lymphocytes and macrophages.<sup>14</sup> Selective inhibition of HCV replication was observed in genotype 1b HCV replicon cells by the administration of Alpha-zam (herbal formulation of *Nigella sativa* seed).<sup>15</sup>

The antiviral efficacy of *N. sativa* has also been demonstrated against HCV by various clinical studies.<sup>16-18</sup> Proposed mechanisms of antiviral activity of *N. sativa* include increased levels of macrophages, interferon- $\gamma$  (IFN- $\gamma$ ) and CD4 counts.<sup>13</sup>

## Immunomodulatory

Cytokine producing T cells include CD4<sup>+</sup> T helper cells and CD8<sup>+</sup> T cytotoxic cells. Based on the profile of cytokine production, T helper cells are further sorted into type 1 T lymphocytes (Th1 cells) and type 2 T lymphocytes (Th2 cells). Th1 cells induce the production of cytokines including IFN- $\gamma$ , interleukin-2 (IL-2) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) against intracellular pathogens as a cell-mediated immune response while Th2 cells are essential for the development of humoral immunity against extracellular pathogens by inducing the production of cytokines (interleukins) such as IL-4, IL-5, IL-6, IL-10, and IL-13.<sup>19</sup>

Previous studies have demonstrated that *N. sativa* and its prominent active constituent thymoquinone have potential immunomodulatory activity by having profound stimulatory effects on cellular immunity and profound suppressive effects on humoral immunity.<sup>20</sup>

A randomized, double-blinded placebo-controlled,

two months, parallel-group clinical trial revealed that modulation of T lymphocytes such as decreased CD8<sup>+</sup> (suppressive lymphocyte), and increased percentage of CD4<sup>+</sup>CD25<sup>+</sup> and the ratio of CD4<sup>+</sup>/CD8<sup>+</sup> occurred by the administration of capsules of 500 mg *N. sativa* oil two times daily for two months in female patients with mild to moderate rheumatoid arthritis (RA).<sup>21</sup> In addition, a pilot study on 24 patients with allergic rhinitis sensitive to house dust mites demonstrated a significant increase in phagocytic and intracellular killing activities of polymorphonuclear (PMN) leukocyte and elevated CD8 counts, by the oral supplementation of 2 g/day of *N. sativa* seed for 30 days.<sup>22</sup>

## Anti-HIV

*N. sativa* might be a potential herb to treat patients with HIV/AIDS as it is having potent antiviral and immunostimulant activities. Several clinical studies demonstrated that *N. sativa* induced complete sero-reversion and recovery in many patients with HIV/AIDS.

A pilot study on 51 HIV-positive patients in the WHO staging I, II, III, and IV demonstrated that the administration of 10 ml of  $\alpha$ -Zam (herbal concoction containing 60:40 of *N. sativa* and honey) three times daily, ensued in relief of signs and symptoms of HIV infection within four weeks of commencement of  $\alpha$ -Zam therapy. At the end of the study period of 16 months, it was observed that the viral load (HIV-RNA) of stage I patients reduced from the average of 19000 copies/ml to an undetectable level and stage IV patients reduced from the average of 51000 copies/ml to <1000 copies/ml. In addition, it has also been observed that all the patients had increased CD4 counts by an average of 262, 310, 457 and 510 cells/ $\mu$ L in respective to their WHO staging I, II, III, and IV, at the end of the study period.<sup>23</sup> Furthermore, a case report on a 25-year-old man with HIV infection (WHO staging III) who took herbal concoction therapy (herbal concoction containing 60:40 of *N. sativa* and honey) three times a day regularly for five months, revealed that HIV screening became negative and the CD4 count was 420 cells/mm<sup>3</sup>, at the end of four months. Moreover, repeated follow up screening for seven years confirmed that the patient had undetectable viral load (HIV-RNA) and normal CD4 counts.<sup>24</sup>

Another pilot study on six patients with confirmed HIV-infection showed that the oral administration of

10 ml of  $\alpha$ -Zam (herbal concoction containing 60:40 of *N. sativa* and honey) three times daily resulted in disappearance of signs and symptoms of HIV infection within 20 days of commencement of  $\alpha$ -Zam therapy. Furthermore, the viral load of participants decreased from  $42,300 \pm 1500$  copies/ml to an undetectable level along with an elevation of CD4 count from the average of  $227 \pm 9$  to  $680 \pm 12$  mm<sup>3</sup>/ $\mu$ L and an enhancement of body weight from an average of  $53 \pm 2$  kg to  $63 \pm 2$  kg, at the end of the study period of four months.<sup>25</sup>

Another case report on a 46-year-old man with HIV viral (HIV-RNA) load of 27,000 copies/ml and CD4 count of 250 cells/mm<sup>3</sup> observed that the oral administration of 10ml two times daily of *Nigella sativa* concoction (60:40 of *N. sativa* and honey) resulted in disappearance of symptoms such as fever, malaise and diarrhea within seven days and multiple papular pruritic lesions within 20 days. Moreover, the viral (HIV-RNA) load of the patient has been diminished to an undetectable level ( $\leq 50$  copies/ml) and the CD4 count increased to 650 cells/mm<sup>3</sup>, at the end of the study period of six months. Repeated screenings of viral load and CD4 showed a sustained seronegativity and normal CD4 count for four years without *N. sativa* therapy.<sup>26</sup>

A pilot study on three patients with confirmed HIV-infection (WHO staging III), higher viral load (43000, 38000 and 41000 copies/ml) and decreased CD4 count (250, 260 and 230 mm<sup>3</sup>/ $\mu$ L) demonstrated that the oral administration of 10ml three times daily of *Nigella sativa* concoction (60:40 of *N. sativa* and honey) ensued in disappearance of symptoms such as fever on the 5<sup>th</sup> day, diarrhea on the 7<sup>th</sup> day and oral thrush on the 16<sup>th</sup> day of commencement of herbal therapy. At the end of the study period of six months, it was observed that the viral load (HIV-RNA) was in an undetectable level ( $\leq 50$  copies/ml) and CD4 count were enhanced to the levels of 510, 530 and 540 mm<sup>3</sup>/ $\mu$ L.<sup>27</sup> Furthermore, a case report on a 27-year-old pregnant woman with HIV infection revealed that a herbalist treated her with 10ml three times daily of *Nigella sativa* concoction (60:40 of *N. sativa* and honey) as she was not eligible for antiretroviral therapy due to her higher CD4 count (350 cells/ $\mu$ L). At the end of the study period (one year), the patient faced undetectable viral (HIV-RNA) load ( $\leq 50$  copies/ml) and enhanced CD4 count (750 cells/ $\mu$ L) and repeated serology screenings which determined

that the patient has shown undetectable viral load and elevated CD4 count not less than 750 cells/ $\mu$ L, for 10 years.<sup>28</sup>

### Concomitant Use of HAART Medicines and *N. sativa*

The modification of the effects of one drug by the administration of other drug(s), herbs, supplements, food or alcohol is defined as drug interaction.<sup>29,30</sup> The drug interaction that increases the toxicity or decreases the therapeutic potential is known as adverse drug interaction, which is considered as preventable medication error.<sup>31</sup>

About 85% of commonly used Antiretroviral (ARV) drugs are metabolised by Cytochrome P-450 (CYP) 3A4/5 enzyme while other ARVs are metabolised by CYP2B6, CYP2C9, CYP2C19, CYP2D6 enzymes and uridine 5'-diphospho-glucosyltransferase (UGT) enzymes.<sup>32</sup> The potential of drug interactions is higher among HIV/AIDS patients as they need to undergo life-long HAART or cART therapy for at least three antiretroviral drugs which may result in polypharmacy and adverse drug interactions by the addition of newer drugs to treat any comorbidity.<sup>33</sup> Polypharmacy is defined as an inappropriate use of multiple medications and the risk of adverse drug interactions increases as the number of concomitant medications goes higher.<sup>34</sup>

A pilot study by Onifade AA et al. observed no adverse drug interaction in HIV patients who used *N. sativa* and HAART therapy concomitantly.<sup>23</sup> In addition, a cross-sectional study by Endale Gurmu A et al. suggested that *N. sativa* could be used additionally in the management of patients with HIV/AIDS along with HAART therapy.<sup>35</sup>

Furthermore, a study by Chandra S et al. demonstrated that the administration of *N. sativa* oil in HAART (nelfinavir [200 mg/kg], zidovudine [50 mg/kg] and efavirenz [20 mg/kg])-treated rats resulted in attenuation of hyperinsulinemia induced by chronic HAART therapy through the dysregulation of insulin secretion from pancreatic  $\beta$ -cells and peripheral action of insulin.<sup>36</sup> Another study by Chandra S et al. determined that thymoquinone (prominent active constituent of *N. sativa*) induced a suppression of protease inhibitors (nelfinavir (5-10  $\mu$ M), saquinavir (5-10  $\mu$ M), and atazanavir (8-20  $\mu$ M)-associated augmented generation of reactive oxygen species (ROS), enhanced superoxide dismutase (SOD) levels and insulin resistance syndrome

(IRS) ensuing in increased glucose-mediated insulin secretion, in pancreatic  $\beta$ -cells of rats.<sup>37</sup>

An animal study by Onifade AA et al. revealed that there was no significant adverse drug interaction due to the concomitant use of  $\alpha$ -zam (herbal concoction of *N. sativa* and honey) and HAART therapy (lamivudine, zidovudine and nevirapine) in wistar rats.<sup>38</sup>

Furthermore, Mudie K demonstrated that the combined use of aqueous extract of *N. sativa* and HAART medications (lamivudine, zidovudine and efavirenz) increased the WBC count significantly in rats without any hematotoxic effect.<sup>39</sup>

## Conclusion

The WHO has suggested testing ethnomedicines systematically against HIV to find more options for the treatment of HIV/AIDS. The antiviral potentials of *N. sativa* have been observed in many in-vivo and in-vitro studies while previous studies have confirmed the immunomodulatory effects of *N. sativa*. Above all, various pilot studies and case reports demonstrated that the administration of *N. sativa* produced complete seroreversion of viral load in many HIV/AIDS patients, miraculously. Furthermore, no adverse drug interaction was observed in HIV/AIDS patients who used *N. sativa* and HAART therapy concomitantly. Actually, the combination has shown some beneficial effects including the suppression of HAART-associated hyperinsulinemia. Hence, *N. sativa* could be used alone or in combination with HAART therapy to cure patients with HIV/AIDS.

## Conflict of Interest

The authors declare that they have no conflicts of interest.

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None.

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