

# Tomato flu or tomato fever (hand, foot, and mouth disease) - potential of black seeds (*Nigella sativa*) as adjuvant therapy

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## ABSTRACT:

As there is no specific antiviral drug approved, the patients with tomato flu or tomato fever (hand, foot, and mouth disease (HFMD)) are managed mainly with symptomatic treatment and supportive care.

This review article focuses on the beneficial effects of adjuvant therapy of black seeds (*Nigella Sativa*) in the management of tomato fever (HFMD).

The literature was searched in online databases including Medline/PubMed/PMC, Google Scholar, Science Direct, Ebsco, Scopus, Web of Science, Embase, and reference lists, to identify relevant publications that determined potential effects of black seeds (*N. sativa*) related to signs and symptoms of tomato fever (HFMD).

Several clinical and preclinical studies demonstrated antiviral, anti-inflammatory, antioxidant, and immunomodulatory properties of black seeds (*N. sativa*) which would help patients with tomato fever (HFMD).

Adjuvant use of *N. sativa*, along with symptomatic treatment and supportive care, would be beneficial for patients with HFMD to enhance the recovery rate, as numerous clinical as well as preclinical studies determined antiviral, anti-inflammatory, antioxidant, and immunomodulatory properties of *N. sativa*. The safety and efficacy of *N. sativa* in patients with HFMD would further be established by future randomized controlled clinical trials.

— **Keywords:** Hand, foot, and mouth disease, Tomato flu, Tomato fever, Enteroviruses, Coxsackie virus, *Nigella sativa*, Black seeds, Kalonji, Thymoquinone.

## INTRODUCTION

Hand, foot, and mouth disease (HFMD) is otherwise colloquially and misleadingly termed as tomato fever or tomato flu due to the appearance of red, painful blisters that could be enlarged to the size of a tomato, on a patient's body. HFMD is caused by enteroviruses (EV) including Coxsackie A16 (CA16) virus, Coxsackie A6 (CA6) virus, enterovirus A71 (EV A71) virus, Coxsackie B viruses and Echo viruses, and it affects mainly children under 10 years old<sup>1</sup>. Enteroviruses (EV) belong to *Picornaviridae* family, and they are single-stranded, positive-sense RNA viruses<sup>2</sup>.

A recent outbreak of HFMD occurred in children younger than 5 years, in Kerala, India. As of July 26, 2022, the local government hospitals of Kerala have reported<sup>3</sup> more than 82 cases since the first case, reported<sup>3</sup> on May 6, 2022. Moreover, 26 cases (1-9 years old) of HFMD were reported from the Indian state Odisha as well<sup>3</sup>.

The risk factors of HFMD may include younger age (under 5 years), male sex, poor hygiene, preschool attendance, and close contact with neighborhood children<sup>4</sup>. Common clinical features of tomato flu (HFMD) include high fever, rashes, intense joint pain, body aches, nausea, vomiting, diarrhea, dehydration, fatigue, and flu-like symptoms<sup>3</sup>.



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HFMD is confirmed<sup>1</sup> by Enterovirus reverse transcription-polymerase chain reaction (RT-PCR) of viral swabs of lesions. The phylogenetic analysis<sup>1</sup> of “Kerala Tomato Flu” revealed that the disease is caused by CA16 virus, which is common in India.

Molecular and serological tests are performed to distinguish HFMD as most of the symptoms are similar to dengue, chikungunya, zika virus, varicella-zoster, and herpes viral infections<sup>3</sup>.

HFMD is highly contagious, and it can spread easily through nasal and throat secretions and stool. Preventive measures include regular hand hygiene, staying away from infected children, isolation of infected individuals, and sanitization of surroundings and belongings of sick people<sup>5</sup>.

There is no specific approved antiviral drug for the treatment of HFMD and the patients with HFMD can be managed by symptomatic treatment and supportive care. The patients should be isolated and receive adequate rest, plenty of fluids to avoid dehydration, and hot water sponge to relieve irritation and rashes<sup>3</sup>.

Higher recovery rate was achieved in mild HFMD cases, by the use of antiviral traditional Chinese herbs (Lan-Qin)<sup>6</sup>. Similarly, we propose the adjuvant use of black seeds (*Nigella sativa* or *N. sativa*) in the management of children with tomato flu (HFMD) along with the symptomatic treatment and supportive care, as many clinical and preclinical studies<sup>7,8</sup> have demonstrated the antiviral, anti-inflammatory, antioxidant, and immunomodulatory properties of *N. sativa*.

## RESEARCH METHODS

The literature was searched in online databases including Medline/Pubmed/PMC, Google Scholar, Science Direct, Ebsco, Scopus, Web of Science, Embase, and reference lists, to identify published studies, which established beneficial effects of black seeds (*N. sativa*) related to signs and symptoms of LayV infection, using keywords like: Hand, foot, and mouth disease, Tomato flu, Tomato fever, Enteroviruses, Cocksackie virus, Black seeds, *Nigella sativa*, Kalonji, and Thymoquinone.

## USE OF *N. SATIVA*

*N. sativa* is a food, as well as medicinal plant, that belongs to the *Ranunculaceae* family. *N. sativa* has been approved by United States Food and Drug Administration (FDA)<sup>9</sup> as food and is regarded “Generally Recognized as Safe (GRAS) by the Flavor and Extract Manufacturers Association (FEMA)<sup>9</sup>. *N. sativa* has been traditionally used for several decades to manage patients with a wide variety of diseases. Various traditional medicine systems including Unani, Ayurveda, Siddha, and others, have always used *N. sativa* to manage patients with several diseases. The phytochemical analysis<sup>10</sup> of *N. sativa* revealed the presence of various bioactive phytoconstituents including thymoquinone (TQ), thymohydroquinone, thymol,  $\alpha$ -pinene, nigellidine, nigellimine, nigellidine, fatty acids, vitamins, minerals, fiber and many others.

Tomato fever (HFMD) is predominantly caused by enteroviruses (CA16 and EV71) and the severe cases of HFMD may experience neurological and cardiopulmonary complications due to higher levels of inflammatory mediators (cytokines and chemokines). Patients with severe HFMD are seen with higher levels of inflammatory mediators, such as interferon- $\gamma$  (IFN- $\gamma$ ), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1)<sup>11</sup>. Several clinical and preclinical studies<sup>7,8</sup> have demonstrated the antiviral, anti-inflammatory, antioxidant, and immunomodulatory properties of *N. sativa*. Hence, we propose the use of black seeds (*Nigella sativa* or *N. sativa*) as adjuvant therapy along with the symptomatic treatment and supportive care in the management of children with tomato flu (HFMD).

Adjuvant use of *N. sativa* may enhance recovery rate in HFMD cases as several clinical, animal, *in vivo*, and *in vitro* studies demonstrated<sup>7,8</sup> antiviral, anti-inflammatory, antioxidant, and immunomodulatory properties of *N. sativa*.

## ANTIVIRAL EFFICACY OF *N. SATIVA*

*N. sativa* supplementation was found to be effective against Severe Acute Respiratory syndrome-coronavirus-2 (SARS-CoV-2) in several clinical as well as *in silico*, and *in vitro* studies<sup>7,8</sup>. Inhibition of SARS-CoV-2 viral entry/fusion and/or viral replication were observed by different phytoconstituents of *N. sativa* such as thymoquinone, dithymoquinone, thymohydroquinone, thymol, nigellidine, nigellone, and  $\alpha$ -hederin<sup>7,8</sup>. Moreover, a complete seroreversion of Human Immunodeficiency Virus (HIV), and elevated CD4 and CD8 counts were noted in different pilot studies and case reports, by the supplementation of *N. sativa*<sup>12</sup>. Additionally, *N. sativa* has established antiviral efficacy against several other viruses including Hepatitis C virus (HCV), avian influenza (H9N2), Newcastle Disease Virus (NDV), Murine cytomegalovirus (MCMV), herpesviruses, Epstein-Barr virus (EBV), Peste des Petits Ruminants (PPR) Virus, Broad bean mosaic virus (BBMV), Zucchini yellow mosaic virus (ZYMV), and Papaya ring spot virus<sup>13,14</sup>.

## ANTI-INFLAMMATORY POTENTIALS OF *N. SATIVA*

The severe cases of HFMD may experience neurological and cardiopulmonary complications due to higher levels of inflammatory mediators (cytokines and chemokines). Several randomized controlled clinical trials<sup>15-17</sup> have demonstrated the anti-inflammatory potential of *N. sativa* via significant reduction of TNF- $\alpha$ <sup>15,16</sup>, and high-sensitivity C-reactive protein (hs-CRP)<sup>17</sup>.

## ANTIOXIDANT PROPERTIES OF *N. SATIVA*

The antioxidant efficacy of *N. sativa* may protect against virus-associated oxidative damages. Several randomized controlled clinical trials<sup>15-19</sup> have established the antioxidant effects of *N. sativa* through significant eleva-

tion of total antioxidant capacity (TAC), and superoxide dismutase (SOD) levels<sup>15,16,18</sup>, and significant reduction of malondialdehyde (MDA) concentrations<sup>19</sup>. Overall, the supplementation of *N. sativa* ensued in significant reduction in inflammatory mediators and oxidative stress markers that were established by many randomized controlled clinical trials<sup>15-19</sup>.

## IMMUNOMODULATORY ACTIVITY OF *N. SATIVA*

*N. sativa* supplementation may assist to control HFMD via enhanced cellular immune responses (T lymphocyte proliferation, CD4+ T cell activation), and modulation of T helper cell 1 (Th1) response (secretion of IL-2, IL-12, IFN- $\gamma$ , TNF- $\alpha$ ), as well as T helper cell 2 (Th2) response (secretion of IL-4, IL-5, IL-10, and IL-13)<sup>20</sup>.

No adverse effects have been observed in clinical trials<sup>21,22</sup> with pediatric participants and *N. sativa* supplementation has been observed<sup>21</sup> to be devoid of hepatotoxicity and renotoxicity in a clinical study<sup>21</sup>, which included participants from the age of 8 to 40 years. In addition, adjuvant therapy of *N. sativa* protected children from drug-associated toxicities such as doxorubicin-induced cardiotoxicity<sup>22</sup>, and iron overload-induced oxidative stress<sup>23</sup>.

## CONCLUSIONS

Adjuvant use of *N. sativa*, along with symptomatic treatment and supportive care, would be beneficial for the patients with HFMD to enhance the recovery rate, as numerous clinical<sup>7,8</sup>, and preclinical studies<sup>13,14</sup>, determined antiviral, as well as anti-inflammatory, antioxidant, and immunomodulatory properties of *N. sativa*. The safety and efficacy of *N. sativa* in patients with HFMD would further be established by future randomized controlled clinical trials with pediatric participants.

### CONFLICT OF INTEREST:

The authors declare that there are no conflicts of interest.

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None declared.

### AUTHORS' CONTRIBUTIONS:

The manuscript was conceptualized, and drafted by NMPM. IRB and AHJ critically revised the manuscript. All authors read and approved the final manuscript.

### ETHICAL APPROVAL AND INFORMED CONSENT:

Not applicable.

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