Nigella sativa (*Habbatus sauda*): the perspectives for COVID-19 treatment

Firman Zulkifli Amin[1]*, Mila Kurnia Sari[2], Zulkifli Amin[1, 3]

Institutional address: [1]Faculty of Medicine, Universitas Indonesia, Jl. Salemba Raya No. 6, Jakarta Pusat 10430, DKI Jakarta, Indonesia. [2]Faculty of Medicine, Universitas Andalas, Komplek Kampus UNAND, Limau Manis, Pauh, Padang, Sumatera Barat, Indonesia. [3]Division of Pulmonology and Critical Care, Department of Internal Medicine, National Central Public Hospital of Dr. Cipto Mangunkusumo, Jl. Pangeran Diponegoro No. 71, Kenari, Senen, Jakarta Pusat 10430, DKI Jakarta, Indonesia.

*Corresponding author. E-mail address for Firman Zulkifli Amin: firman_za@hotmail.com. E-mail address for Mila Kurnia Sari: milakurniasari@outlook.co.id. E-mail address for Zulkifli Amin: zulkifliamin52@gmail.com.

Abstract

Background: *Nigella sativa* may have the potency to complement integrally in conditions of uncertain core basic needs of COVID-19 treatment. The understanding of immune responses occurring in the mechanism of COVID-19 caused by SARS-CoV-2 infection has brought attention to the more specific demand on the potential drug targeted for the treatment of patients with COVID-19.

Main text: The core basic needs in the treatment of COVID-19, based on the immune responses, that encompassing all the stage of diseases going through preventive until curative aspects consist of increased immunity using interferon; lung protective

function; anti-inflammatory by interferon-γ activation; and inhibition of hyaluronan-synthase-2 by 4-methylumbelliferone. *Nigella sativa* may give a role in all four core basic needs from the viewpoint of immune responses occurring in COVID-19 infection.

Conclusions: *Nigella sativa* may have the potency as a complementary therapy that may be applied in all stages of the core basic needs of COVID-19 treatment, which the scientific community may more consider its broad-range potential benefit of use in the COVID-19 treatment research.

Keywords: *Nigella sativa*, thymoquinone, SARS-CoV-2, COVID-19, treatment, therapy.

Introduction

Nigella sativa (also said as *Habbatus sauda* or black cumin) is a "wonder" herb from the Ranunculaceae family renowned as the remedy with a broad pharmacological spectrum of benefit [1]. *Nigella sativa* may have the potency to complement integrally in conditions of uncertain core basic needs of COVID-19 treatment. The integral role of *Nigella sativa* that may engage in the core basic needs of COVID-19 treatment, in our view, is comprehensible based on two-phase of immune responses [2] induced by COVID-19 infection. This understanding of immune responses occurring in the mechanism of COVID-19 caused by SARS-CoV-2 infection has brought attention to the more specific demand in research on the potential drug targeted for the treatment of patients with COVID-19.

Main text

The immunomodulatory ability of *Nigella sativa*, as a single-alternative therapy already provenly improving viral load in patients with Hepatitis C virus (HCV) that

were not eligible for therapy with interferon (IFN)/ribavirin [3], explained by significantly increasing macrophages and CD4+ T cells [4] along with significantly decreasing viral titer and increasing serum IFNγ levels [5], to our view, shows its potency to have a role in phase I of immune response encompassing asymptomatic and incubation period on the first stage of COVID-19 course and non-severe illness period of the second stage [6], which emphasizes the core basic need of immune protection by immune-boosting treatment, either utilizing IFN or antisera [2]. Of prominent, *Nigella sativa* is noted to be safe and side-effects are unremarkable. Therefore, *Nigella sativa* is considered usable for self-treatment, as an advantage consideration in the perspectives of preventive therapy in light to the quest of beneficial immunization in the field of SARS-CoV-2 vaccine research. In relation to this, the antiviral activity of *Nigella sativa* has also been demonstrated against cytomegalo virus infection; avian influenza (H9N2); Chistosoma Mansoni infection; Peste des petits ruminants (PPR) virus; Broad Bean Mosaic virus; human immunodeficiency virus (HIV); Zucchini Yellow Mosaic virus; Papaya Ring Spot virus [7] and the thymoquinone component of *Nigella sativa* is known to repress p16 protein and generate G1 phase cell cycle arrest in infected cells by human papillomavirus [8]. Furthermore, the *Nigella sativa* ability potency in exerting the required anti-inflammatory effects by activating IFNγ [5], in our notion, may also be advantageous for another core basic need of COVID-19 treatment because very severe patients may not have this activation ability due to T cells are not activated properly by infection of SARS-CoV-2 in phase II of the immune response [2], which is dominated by the cytokine release syndrome (CRS) that cause cytokine storms and, as a result, lung damage due to lung inflammation, defining severe conditions in the third stage of the disease course [6]. Rapid commencement of extensive inflammation

in the lungs and, consequently, leading to the fatality, showing white patches characteristics in CT scan images known as "ground glass" indicating clear liquid jelly resembled wet drowning-lungs. The presence of the fluid may be explained from acute respiratory distress syndrome (ARDS) occurring that relates to hyaluronan (HA) [9], which capable to absorb water until 1000 times greater its molecular weight [10]. The inflammatory cytokines' (tumour necrosing factor (TNF), interleukin (IL)-1) levels are notably high in the COVID-19 patients' lungs, which these cytokines are strong activators of HA-synthase-2 (HAS2) [10]. *Nigella sativa*, trough its thymoquinone component, known to generate the release of free 4-methylumbelliferone (4-MU) [8], an inhibitor of HAS2 as we notice, one core basic need mostly-overlook in COVID-19 treatment [2]. The efficacy of *Nigella sativa* in the prevention and treatment of inflammatory diseases has also been shown by the action of its thymoquinone component on inflammatory signalling pathways encompassing nuclear factor kappa B (NF-κB), mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription 3 (STAT3), peroxisome proliferator-activated receptor gamma (PPAR-γ), and protein kinase B (AKt), and apoptosis; pro-inflammatory mediators/cytokines; antioxidant enzymes and reactive oxygen species systems [11]. Of equally important, *Nigella sativa* has invaluable lung protector capacity [12], one of the core basic need in COVID-19 treatment [2], which in our view, applicable to prevent lung tissue further deteriorate and damage, which worthwhile to initiate even in asymptomatic persons and, substantial, in patients who yet not severely-infected.

Conclusions

Nigella sativa denotes indispensable potency to complement integrally that may be applied for all four core basic needs of COVID-19 treatment encompassing increased

immunity using IFN; lung protective function; anti-inflammatory by IFNγ activation and inhibition of HAS2 by 4-MU. The scientific community may more consider the broad-range potential benefit of the use of *Nigella sativa* in COVID-19 treatment research.

Abbreviations

Akt: Protein kinase B

ARDS: Acute respiratory distress syndrome

COVID-19: Coronavirus disease 2019

CRS: Cytokine release syndrome

CT-scan: Computed tomography scan

HA: hyaluronan

HAS-2: HA-synthase-2

HCV: Hepatitis C virus

HIV: Human immunodeficiency virus

IFN: Interferon

IFNγ: Interferon γ

IL-1: Interleukin 1

MAPK: Mitogen-activated protein kinase

NF-κB: Nuclear factor kappa B

PPAR-γ: Peroxisome proliferator-activated receptor gamma

PPR: Peste des petits ruminants

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

STAT3: Signal transducer and activator of transcription 3

TNF: Tumour necrosing factor

4-MU: 4-methylumbelliferone

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

This published article includes all data generated or analyzed during this study.

Competing interests

The authors declare to have no competing interests.

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Author's contributions

FZA and MKS contributed equally to this work. FZA conceptualized the study; analyzed and interpreted all data, and was a major contributor in writing the manuscript. MKS conceptualized the study; analyzed and interpreted all data, and was a major contributor in critically revised the manuscript. ZA inspired the study and critically revised the manuscript. All authors read and approved the final manuscript.

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