Original

Nigella sativa oil (NSO) as an adjuvant in the management of mild COVID-19 infection in Kaduna state

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Abstract

Background: To assess the efficacy of Nigella sativa oil (NSO) in the management of mild COVID-19 infection in Kaduna state.

Method: Quasi-experimental study among 51 mild COVID-19 cases enrolled in Hamdala isolation center from 27th October, 2020 to 20th May, 2021. Outcome variables were viral clearance, resolution of symptoms and duration of hospital stay after commencement of the different treatment regimen at level of significance $P < 0.05$ and effect size (Cohen's D 0.2= small, 0.5=medium and ≥0.8 = large).

Result: Out of the 51 people enrolled in the study, 26 (51%) were placed on NSO plus usual care while 25 (49%) were on usual care alone with Mean age (SD) of 30.77±14.56 and 32.60±17.50 respectively. There were 16 (61.5%) females and 10 (38.5%) males in the NSO group and 19 (76%) females with 6 (24%) males in the usual care group. More patients on NSO have symptoms 12 (46.2%); ranging from fever, malaise, anosmia and loss of taste compared to 8 (32.0%) of the usual care group. Mean recovery time was significantly shorter 4.50±1.51 days in the NSO group, compared to 7.38±2.20 in the usual care with medium effect size (t-value = -3.483, Cohen's D = 0.7, P = 0.003). Repeat PCR test was significantly different 48hours after commencement of treatment between groups, with large effect size (t=2.706, Cohen's D=0.8, p=0.009).

Conclusion: NSO as add-on therapeutic agent was associated with faster recovery, viral clearance and shorter duration of care than usual care alone in patients with mild COVID-19 infection.

Keywords: *Nigella Sativa* oil, COVID 19, quasi-experimental, mild, illness duration, RT-PCR, usual care

Introduction

The coronavirus disease was first identified due to an outbreak of the respiratory disease in Wuhan City,

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China.[1,2] The disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) previously called 2019-nCoV.[3,4] The WHO first declared COVID-19 as an epidemic in 2019, and subsequently global pandemic in 2020 due to the peculiarity with which the disease spread across the globe.[5] Over 500 million cases with more than 6 million deaths globally have been documented.[1] In Nigeria, more than 250,000 confirmed cases and 300 confirmed deaths were reported.[2,3] In Kaduna, more than 11,000 index laboratory-confirmed positive cases, and 82 deaths were documented.[6] The COVID-19 is characterized by asymptomatic/mild symptoms, severe illness, and death. Symptoms may develop from two to fourteen days following exposure to the virus and may include: fever, cough, and shortness of breath, chest tightness, muscles or body aches, headache, loss of taste or smell, and sore throat.[5,6]

Several treatment modalities have been employed but most strategies used are supportive and preventive, aimed at reducing morbidity and transmission and with the vaccines currently advocated for prevention of severe disease especially in vulnerable individuals like the elderly.[7] Finding cure for this pandemic has moved up the priority list for scientific medical research in order to curb the menace caused by the pandemic. There are now just a few pharmaco-therapeutic medications that are effective against COVID-19.[8] In order to cure coronavirus infection, supplementary herbal medications are being examined due to their abundance of biologically active components.[9] *Nigella sativa* (N. sativa, black seeds) belongs to the *Ranunculacea* family and it is also known as black cumin seed, black seed, Habbatul Barakah, Habbatus sawda, kalonji, and it is a native to Southwest Asia.[10]

The active constituents of *N. sativa* such as nigellidine and α-hederin have been identified as potential inhibitors of SARS CoV-2.[11] The biological activities and therapeutic potential of N. sativa have been thoroughly investigated, and it has been found to have a wide range of biological and therapeutic effects, including diuretic, antihypertensive, antidiabetic, anticancer, immunomodulatory, analgesic, antimicrobial, anthelmintic, analgesic and anti-inflammatory, spasmolytic, bronchodilator, gastroprotective, hepato-protective, renal protective, and *N. sativa* seeds are frequently used to treat a wide range of illnesses, including bronchitis, asthma, diarrhea, rheumatism, and skin conditions.[12,13]

The current global Pandemic came with serious therapeutic challenges; antiviral agents neither provide a cure for COVID-19 nor prevent its relapse. These agents are often accompanied by debilitating adverse reactions including influenza-like symptoms, lactic acidosis, hematologic abnormalities, and neuropsychiatric symptoms.[14,15] The development of new, affordable and accessible pharmacological agents to overcome these barriers has become a major goal in mitigating this ravaging pandemic. Therefore, this study is intended to evaluate the potential efficacy for using N. sativa in patients with COVID-19.

Method

The study was conducted at the Hamdala alternate Isolation, the largest isolation center in the Kaduna state Infectious Disease Control Center (IDCC), Kaduna state Nigeria with a total bed capacity of 96. There were other isolation centers were located in Kakuri, Zaria and Kafanchan. The state had managed more than 10,000 COVID-19 cases.

Study design

This study was a quasi-experimental study conducted among mild COVID-19 cases under the care of the case management pillar of the State rapid response team. The cases were managed with either usual care alone (Zinc 20mg bid, Multivitamin I once daily and Vitamin C 200mg three times a day) on one side and Nigella sativa Oil (5ml twice daily) as an add-on therapy on the other side. Ethical Clearance was obtained for the Kaduna state Health Research Ethics Committee (HREC).

Study population

They consisted of patients aged between 18 and 65 years with reverse transcriptase–polymerase chain reaction (RT-PCR) test–confirmed COVID-19 who presented with mild illness (WHO clinical progression scale 2-4)[16] defined as SPO2 > 93%, respiratory rate ≤ 24 cycles/minute and at least one of the following: contactless infrared forehead thermometer temperature of ≥37.8, cough, sputum production, nasal discharge, myalgia, headache or fatigue on admission. Patients who satisfied the criteria, signed written informed consent and agreed to comply with the study protocols and who were admitted into the isolation Center were included. Patients with known hypersensitivity to NSO (as reported by the patient) were excluded.

Sample size and sampling methodology

Confirmed COVID-19 patients who presented to Hamdala Isolation center were evaluated and categorized as either mild, moderate or severe cases as defined by World Health Organization (WHO) as follows;

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Mild cases: Symptomatic patients without evidence of viral pneumonia or hypoxia (SpO2 >93% on room air) are classified as a mild disease
Moderate cases: patients with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SpO2≥ 90% on room air.
Severe cases: patient with grunting respiration, respiratory rate >30 breaths per minute, spO2 < 90% for adults or <92% in children, requiring oxygenation.

Patients with mild disease were consecutively enrolled between October 27th, 2020, and May 20th 2021, and were assigned to receive a 6-day course of NSO in addition to usual care. The people were recruited consecutively until the end of the study period. The NS group received *Nigella sativa* Oil 5mls orally daily for up-to 6 days in addition to usual care (Zinc sulphate 20mg daily, Vit. C 200mg three times a day and a Multi vitamin one capsule), while the control group received usual care alone. The study participants were assessed for clinical symptoms daily. During the study, all patient underwent a second SARS-CoV-2 RT-PCR test within the next 48 hours. If the patient tested negative, they were deemed to have cleared the infection and their treatment stopped. In case of a positive test, a third PCR test was performed on day 5 with no further follow-up. The primary outcomes were viral clearance (negative RT-PCR for the SARS-CoV-2 RNA), alleviation of clinical symptoms. Secondary outcomes included reduction in duration of hospital stay.

Statistical analysis
Data analysis was done using IBM SPSS version 26 and Stata 12. Data was summarized using frequencies and percentages for categorical variables. Association between categorical variables were tested using chi square at a level of significance p< 0.05. Means and standard deviations of the normally distributed data were compared using an independent *t*-test at level of significance at (Cohen's D 0.2 = small effect, 0.5 = medium effect and ≥0.8 larger effect). Non-normally distributed data were described as medians ± interquartile range.

Results

Out of the 51 people enrolled in the study, 26 (51%) were placed on NSO plus usual care while 25 (49%) were on usual care alone with Mean age (SD) of 30.77±14.56 and 32.60±17.50 respectively which was not statistically significant (t= -0.407, P= 0.686). There were 16 (61.5%) females and 10 (38.5%) males in the NSO group and 19 (76.0%) females with 6 (24.0%) males in the usual care group and it was not statistically significant (X^2 = 1.22, p= 0.266). There was statistical significant difference between the participants religion (X^2 = 5.684, 0.01), but no statistical significant difference between tribe, employment status, level of education and marital status and the type of treatment regimen. **Table 1.**

More patients on NSO have symptoms 12 (46.2%) and was not statistically significant (X^2 = 1.07, P= 0.301). More patient with fever, body weakness, anosmia and loss of taste were managed on NSO. The mean duration of illness was found to be less in NSO group 4.50±1.51compared to 7.38±2.20 in the usual care group and was statistically significant (t-test = -3.482, P = 0.003). 13 (50%) of the NSO group tested negative at 48hrs compared to 4 (16%) and was statistically significant (X^2 = 6.63, P = 0.010).**Table 2**

The mean recovery time was found to be shorter 4.50±1.51 days in the NSO group, compared to 7.38±2.20 in the usual care and was statistically significant with medium effect size (t-value = -3.483, Cohen's D = 0.7, P = 0.003). Also, repeat PCR test was found to be statistically significant 48hours after commencement of treatment between the intervention and controlled group, with large effect size (t= 2.706, Cohen's D = 0.8, p=0.009).**Table 3**

Patients on NSO reported side effects ranging from unpleasant odor, throat and gastric irritations which resolved spontaneously from the 2nd day of treatment. **Figure 1**

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Table 1: Socio-demographic characteristics of the respondents

Socio-demographic Variables	NSO (%)	Usual care (%)	Chi square	P-value
Mean age ± SD	30.77±14.56	32.60±17.50	-0.407*	0.686
Gender				
Male	10 (62.5)	6 (37.5)	1.238	0.266
Female	16 (45.7)	19 (54.3)		
Tribe				
Hausa	13 (65.0)	7 (35.0)	2.588	0.108
Non-Hausa	13 (41.9)	18 (58.1)		
Religion				
Islam	17 (68.0)	8 (32.0)	5.684	0.01**
Christianity	9 (34.6)	17 (65.4)		
Occupation				
Employed	10 (50.0)	10 (50.0)	0.0127	0.910
Unemployed	16 (51.6)	15 (48.4)		
Level of Education				
Below tertiary	9 (69.2)	4 (30.8)	2.352	0.125
Tertiary	17 (60.7)	11 (39.3)		
Marital status				
Currently married	13 (56.5)	10 (43.5)	0.514	0.473
Not currently married	13 (46.4)	15 (53.6)		

* T-test
** Significant at p<0.05

Table 2: Clinical characteristic of the respondents

Clinical characteristics	NSO (%)	Usual care (%)	Test statistic Chi square	w	P-value
Symptoms					
Present	12 (60.0)	8 (40.0)	1.07	0.20	0.301
Absent	14 (45.2)	17 (54.8)			
Fever					
Yes	10 (58.8)	7 (41.2)	0.0654	0.10	0.798
No	2 (66.7)	1 (33.3)			
Body weakness					
Yes	10 (58.8)	7 (41.2)	0.065	0.10	0.798
No	2 (66.7)	1 (33.3)			
Anosmia					
Yes	10 (76.9)	3 (23.1)	4.432	0.20	0.035*
No	2 (28.6)	5 (71.4)			
Loss of taste					
Yes	9 (64.3)	5 (35.7)	0.357	0.10	0.550
No	3 (50.0)	3 (50.0)			
PCR at 48 hours					
Positive	13 (38.2)	21 (61.8)	6.63	0.20	0.010*

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Negative	13 (76.5)	4 (23.5)			
PCR at day 5					
Positive	3 (33.3)	6 (66.7)	0.125	0.10	0.724
Negative	10 (40.0)	15 (60.0)			

*significant at p<0.05
w = effect size index (0.10= small, 0.30=medium, 0.50= large)

Table 3: Duration of illness and viral clearance

Characteristics	NSO mean (SD)	Usual care Mean (SD)	t-test (df)	Cohens D	P-value
Mean duration of illness	4.50±1.51	7.38±2.20	-3.483 (18)	0.70**	0.003*
Negative PCR at 48hrs	1.50 (0.51)	1.16 (0.37)	2.706 (49)	0.80***	0.009*
Negative PCR at day 5	1.77 (0.44)	1.71 (0.46)	0.343 (32)	0.14	0.734

* Significant at p<0.05
** Medium effect size
*** Large effect size

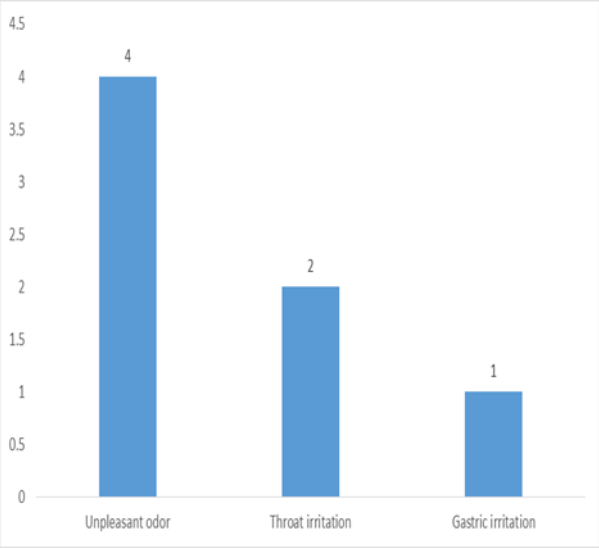

Figure 1: Side effects of NSO as reported by the respondents

Discussion

The study found that Nigella sativa oil (NSO) as an add-on therapeutic agent was associated with faster recovery of symptoms, viral clearance and shorter duration of care than usual care alone for patients with mild COVID-19 infection. However present with some side effects not noticed in the control group.

The survey revealed that most of the patients admitted were asymptomatic to mild presentation. This corroborate findings of Oyefabi et al., and Idris et al., in the same population and other global studies that COVID-19 patients were mostly asymptomatic to mild presentations.[2,3]

The symptoms found in this survey were mainly fever, malaise, loss of taste and smell. These findings corroborated the findings of Osibogun et al.[16] and Sampaio et al.[17]

The study revealed that most patients in the NSO group recovered earlier than the control group, mean recovery time was found to be shorter in patients treated with NSO compared to those treated with usual care alone. The results in our study are consistent with findings from a recent clinical trial of NSO in adults hospitalized with mild COVID-19 conducted by Koshak *et al* in Saudi Arabia, which recruited 173 hospitalized adult patients with mild COVID-19 and concluded the percentage of recovered patients in NSO group was significantly higher than that in the control group and also the mean duration to recovery was also shorter for patients receiving NSO compared with the control group.[18] In addition, another randomized placebo clinical research study of Honey and *Nigella Sativa* (HNS) conducted by Ashraf *et al* [19] in Pakistan showed that among 210 patients with moderate COVID 19, HNS resulted in ~50% reduction in time taken to alleviate symptoms as compared to placebo (Moderate (4 versus 7 days). The survey also showed that patients in the NSO group have viral clearance faster than the control group and tends to go back to their functioning earlier. This also corroborate findings of Koshak et al., in Saudi Arabia,[18] Ashraf et al.[19] and Imran et al.[20] that HNS cleared the virus 4 days earlier than placebo group in moderate (6 versus 10 days) and also significantly improved symptoms, viral clearance and mortality in COVID-19 patients.

Some notable side effects have been experienced by some patients in the intervention group, which is attributed to oral ingestion of NSO. The most common adverse effects were throat and gastric irritations and unpleasant odor. This finding is consistent with the findings of several

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studies carried out around the globe regarding the side effects of NSO.[21,22] However these effects spontaneously resolved within 2nd day of commencement of therapy without any residual effect.

Strengths and Limitations of the study

The study will affect clinical practice and direct future research in the field of emerging infectious diseases. The researchers are confident that the outcome of the study will be useful for decision making on the use of NSO for the management of COVID-19 mild cases in Kaduna state. This study could provide meaningful suggestions for proper application of NSO in the treatment of COVID-19.

The limitations of the study include but not limited to; First, the lack of random assignment is a limitation of this study. Second, we recognize that our sample size was small. Third, the study did not enroll severely or critically ill patients, or patients at increased risk of poor outcome with many comorbidities and was conducted in only one center and finally there was no treatment with NSO alone, therefore it is add-on therapy.

Significance of the findings of the study

Considering the economic crisis related to the COVID-19 pandemic, the use of *Nigella sativa* will particularly be beneficial for impoverished populations in resource limited settings.

The inexpensive over the counter treatment regimen would be a valuable source to lower the burden on healthcare system while significantly dampening impact of the disease. Addition of the nutraceuticals will add great value to lower the morbidity/mortality against COVID-19. The study will affect clinical practice and direct future research in the field of emerging infectious diseases. Nevertheless, these findings should be tested and replicated in further multi-national, larger clinical trials. A multinational study with a larger sample size is required to investigate potential variations in responses to the treatment in COVID-19 patients from different racial and ethnic origins.

Conclusion

NSO as an add-on therapeutic agent was associated with faster recovery of symptoms, viral clearance and shorter duration of care than usual care alone for patients with mild COVID-19 infection. These findings should be tested and replicated in further multi-national, larger clinical trials. A multinational study with a larger sample size is required to investigate potential variations in responses to the treatment in COVID-19 patients from different racial and ethnic origins.

Declarations

Ethical consideration: Ethical Clearance was obtained for the Kaduna state Health Research Ethics Committee (HREC). Written and informed consent was obtained from each participant.

Authors' contribution:

Conceptualization: Idris U, Abdulmajid M, Umar IM, Abdu-Aguye I.
Data collection: Idris U, Musa AN, Ogunsina AM,
Data analysis: Oyefabi AM, Idris U. Manuscript draft: Abdulmajid M, Olasinde TA, Idris U.
Final manuscript review: Abdu-Aguye I, Olasinde TA, Oyefabi AM, Ogunsina AM.

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