

# Clinical Trial of Black Seeds Against COVID – 19 in Kirkuk City/ Iraq

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## Abstract

In order to cope with Coronavirus Disease 2019 (COVID-19) pandemic, there is an urgent need for effective prevention and control measures. This study aims to explore the positive action of black seeds (BS) against COVID-19 in patients involved in the trail. It is a descriptive, comparative, and open-label study. In our study, (419) participants were divided into two groups. The studied participants included patients which received standard care treatment as a control group (CON) , while the (BS) group were patients received black seeds at a 40 mg/kg dose orally, once daily for 14 days plus standard protocol of treatment. The evidence of BS efficacy was obvious in the severity and outcome of infection with covid-19. A significantly higher severity of infection among control group 44 (17.0%) than the black seed group were noticed; the control group also showed 14 deaths (5.4%), while there were no deaths in black seeds group (0.0%). Thus, we can conclude that black seed is very effective in reducing the severity of covid-19 and preventing death in infected patients.

**Key words :** *Pandemic disease, COVID-19, Infection, medicinal plant, , Black seeds*

## Introduction

COVID19 storm shows its lethal face worldwide and it is still difficult to predict how long it will last, and how deadly it could be<sup>(1)</sup>. This disease mainly affected social life, particularly health care services in addition to daily treatment practices since the world health organization (WHO) declared SARS CoV-2 as a global pandemic in early 2020<sup>(2-5)</sup>. The COVID-19 infection primarily affects the respiratory system and is presented with cough, fever and sometimes pneumonia and shortness of breath and patients may deteriorate due to acute respiratory distress syndrome, as well as other clinical manifestations such as cardiac, gastrointestinal and central nervous system<sup>(6-10)</sup>. The WHO situational report recorded more than 20 million laboratory-confirmed

cases and 700 thousand global deaths since August 13, 2020<sup>(11)</sup>. The first identified case of COVID-19 in Iraq was in Najaf province in an Iranian student who came from Iran on 24 February 2020, followed by detection of the virus in 4 members of a family in Kirkuk province on 25 February who have previously visited Iran<sup>(12,13)</sup>. There is a globally very high challenge of COVID-19 because of the lack of proven treatment and its complicated transmission<sup>(14,15)</sup>. However, presence of several preventive health measures may be helpful in resolving primary complications among patients. Since April 2, 2020, there have been 291 active clinical specific trials to cope with COVID-19, including 109 pharmacological therapeutic trials to treat COVID-19 among adult patients<sup>(16)</sup>.

Till now, herbs are widely used to treat several diseases in many countries due to its excellent culturing compatibility with the human body and its safety<sup>(17)</sup>. This has led to a search for therapeutic alternatives, particularly among medicinal plants<sup>(18)</sup>. Nigella sativa belongs to the

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family Ranunculacea, and it is also known as black seed, black cumin seed, Habatul Baraka, Habatussawda and Kalonji<sup>(19)</sup>. *N. sativa* seeds are believed to have healing powers in traditional medicine and have long been used for treating a wide range of disorders including allergy, headaches, bronchial asthma, back pain, infections, obesity, hypertension and gastrointestinal problems<sup>(20-22)</sup>. The present study aims to evaluate the therapeutic value of black seeds in treatment of Covid19.

## Methodology

This study was conducted on patients diagnosed with covid-19. It was done during the period between 5<sup>th</sup> September and 15<sup>th</sup> November 2020 in Kirkuk city, Iraq. It is a randomized and open-label study, which was approved by the Institutional Ethics Committee. All the participants gave voluntary written and informed consent for this study. The diagnosis of infection with covid-19 was made on the basis of polymerase chain reaction (PCR) test on throat swab samples. Participants aged 13-90 years of both genders were enrolled in this trial. The included participants were randomized into two groups, participants of group CON (259) who received standard care treatment according to the standard protocol and considered as a control group, and (160) participants of BS group who received black seeds 40 mg/kg orally once daily for 14 days plus standard protocol. Standard care therapy was as recommended by the clinical management instructions for covid-19 established by the Iraqi Ministry of health. Black seed of 100% purity was used in the study which was commercially available and purchased from the local market in Kirkuk, Iraq. Patients having hypertension (HYP), ischemic heart disease (IHD), diabetes mellitus (DM), bronchial asthma (AS), morbid obesity (MO) or patients having more than one comorbidity (MIX) were included in the study too. While patients with severe illnesses requiring admission to intensive care unit, end stage renal disease requiring dialysis, severe chronic liver disease, pregnancy or breast feeding and allergy to any study medication were excluded from this trial. The severity of infection was grouped as: mild disease including patients with mild symptoms of covid-19 without evidence of pneumonia;

moderate infection when the patient had fever with pneumonia. Whilst severe class used for patients with: a- respiratory distress RR > than 30/m in adults, b- blood oxygen saturation less than 93% on ambient air, c- PaO<sub>2</sub> / FiO<sub>2</sub> less than 300, d- lung infiltrates >50% of the lung field within 24 hours. All the enrolled individuals were regularly followed up. Physical examination and investigations were done at 0, 14, 28, 42, 56 and 70 days of the study. A physical examination including assessment of vital signs was done at the start of the study and following the visits. Further laboratory tests, chest X-ray and CT scan were performed whenever necessary.

## Statistical Analysis

Data analysis were done using the IBM SPSS version 26. Proportions and 95% confidence intervals (95% CI) were calculated using descriptive statistics. P values were calculated by Chi-square test, using analytic statistics. Values were considered to be statistically significant when the obtained P-value was less than 0.05.

## Results

Baseline demographics of trial groups are shown in table (1). Groups included 419 patients, 212 (50.6%) of them were males and 207 (49.4%) females. The age groups ranged from (13-18) to (> 65) years. Table (2) showed the effectiveness of black seeds on covid-19 among the participants. Cross tabulation was performed to describe the association between black seeds group and severity as well as the final outcome of infection with covid19. Results of this study showed less infection severity in BS group, only 2 cases (1.3%) in comparison with 44 cases (17.0%) in the control group. In addition, there was 14 deaths (5.4%) as an outcome of infection, while no death was recorded in the BS group during the period of the study. On the other hand, the severity in the BS group was restricted to the age group (>65) years 1.3%. There was no statistically significant differences between the participants with respect to gender and comorbidities as shown in table (3).

**Table (1): Distribution of trial patients according to: age/ year , gender and comorbidity**

Baseline demographics		Control (N=259)	Black Seeds (N= 160)	Total ( N=419)	p value
Age	13-18	30 (7.2%)	11 (2.6%)	41 (9.8%)	0.142
	19-39	109 (26.0%)	58 (13.8%)	167 (39.9%)	
	40-65	106 (25.3%)	82 (19.6%)	188 (44.9%)	
	> 65	14 (3.3%)	9 (2.1%)	23 (5.5%)	
Gender	Male	132 (31.5%)	80 (19.1%)	212 (50.6%)	0.848
	Female	127 (30.3%)	80 (19.1%)	207 (49.4%)	
comorbidity	HYP	22 (5.3%)	15 (3.5%)	37 (8.8%)	0.263
	AS	5 (1.2%)	5 (1.2%)	10 (2.4%)	
	DM	9 (2.1%)	5 (1.2%)	14 (3.3%)	
	IHD	4 (1.0%)	3 (0.7%)	7 (1.7%)	
	MO	1 (0.2%)	5 (1.2%)	6 (1.4%)	
	MIX	22 (5.3%)	8 (1.9%)	30 (7.2%)	
	None	196 (46.8%)	119 (28.4%)	315 (75.2%)	

**Table (2): Effect of black seeds on severity and outcome of covid-19 infection among the participants**

Clinical presentation		Control	Black Seeds	Pvalue
Severity of infection	Mild	190 (73.4%)	151 (94.4%)	<0.001
	Moderate	25 (9.7%)	7 (4.4%)	
	Sever	44 (17.0%)	2 (1.3%)	
	Total	259 (100%)	160 (100%)	
Outcome of infection	Cure	245(94.6%)	160(100.0%)	0.003
	Death	14 (5.4%)	0 (0.0%)	
	Total	259 (100%)	160 (100%)	

**Table (3): Severity levels of infection with covid 19 among BS group according to age, gender and comorbidity**

Parameters		Severity levels			Total N=160	P value
		Mild N=151	Moderate N=7	Severe N=2		
Age	13-18	11 (6.9%)	0 (0.0%)	0 (0.0%)	11 (6.9%)	< 0.001
	19-39	56 (35.0%)	2 (1.3%)	0 (0.0%)	58 (36.3%)	
	40-65	77 (48.1%)	5 (3.1%)	0 (0.0%)	82 (51.2 %)	
	> 65	7 (4.4%)	0 (0.0%)	2 (1.3%)	9 (5.6 %)	
Gender	Male	74 (46.3%)	5(3.1%)	1(0.6%)	80 (50%)	0.510
	Female	77 (48.1%)	2(1.3%)	1(0.6%)	80 (50%)	
Comorbidity	HYP	15 (9.4%)	0 (0.0%)	0 (0.0%)	15 (9.4%)	0.036
	AS	4 (2.5%)	1 (0.6%)	0 (0.0%)	5 (3.1%)	
	DM	4 (2.5%)	1 (0.6%)	0 (0.0%)	5 (3.1%)	
	IHD	2 (1.3%)	1 (0.6%)	0 (0.0%)	3 (1.9%)	
	MO	5 (3.1%)	0 (0.0%)	0 (0.0%)	5 (3.1%)	
	MIX	7 (4.4%)	0 (0.0%)	1 (0.6%)	8 (5.0%)	
	None	114 (71.3%)	4 (2.5%)	1 (0.6%)	119 (74.4%)	

## Discussion

There is a direct association of the therapeutic effect of herbal medicine on its chemical compositions. *Nigella sativa* seed is a precious herbal medicine since it is traditionally used in treating many diseases. Owing to its wide range medical applications, this herb plant underwent extensive phytochemical studies, and numerous different compounds were isolated from it.

The black cumin seeds contain a yellowish fixed oil, amino acids, fats, proteins, reducing sugars, alkaloids, minerals, organic acids, tannins, crude fibers as well as vitamins<sup>(23,24)</sup>. It has anti-viral, anti-inflammatory, anti-oxidant, anti-histaminic, anti-microbial, analgesic and has immuno-modulation activity. These values make it a strong candidate for covid-19 treatment<sup>(25)</sup>.

*N. sativa* can kill or inhibit the virus via a multi prong strategy through targeting several viral sites or through host-virus interaction. Thus, it is distinguished from the other antiviral agents by targeting of the specific structure or pathway of SARS-CoV-2 infections (26). Previous studies portended that many flavonoids and phenolic compounds that exist in *N.sativa* seeds bound or docked to the SARS-CoV-2 spike protein–human angiotensin converting enzyme-2 receptor complexes (27,28).

In addition, it has been hypothesized that the antiviral effectiveness of *N.sativa* can be attributed to high serum levels of interferon-gamma, raised CD4 counts, augmented suppressor functions as well as enhanced macrophage numbers (29). An in-vitro study, linoleic acid also showed synergy with remdesivir, which is used as COVID-19 drug, leading to suppression of SARS-CoV-2 replications (30). On the other hand, the pathogenesis of SARS-CoV-2 infection is related to the overproductions of reactive oxygen species (ROS) and deprivations of the antioxidant systems (31). Thymoquinone which is the active ingredient in *N. sativa* seeds has demonstrated effects in reducing oxidative stress (32). Also it modulates or influences the immune-modulators such as IL-1, IL-6, IL-10, IL-18, TNF- $\alpha$  and the nuclear factor- $\kappa$ B, therefore, can significantly reduce the cytokine storm chances and consequent mortalities (33). Moreover, *N. sativa* seeds inhibited the inflammatory effects of the airways. On the other side, its immune-modulatory and anti-histaminic effects can prevent secondary infections. *N. sativa* seeds has anti-hypertensive, anti-diabetic, cardio-protective and bronchodilatory properties which make it more beneficial to control such diseases. While its anti-platelet and anti-coagulant effects may also safeguard patients with COVID from thromboembolic complication, which is the most important cause of complication and death (34-36).

This study has several limitations. The uncontrolled factors that potentially affect the results of this study included patient's diet such as taking some medical nutritional supplements. Besides, genetic factors, and psychological conditions received less attention in this study. For this reason, further clinical studies and double blind studies are necessary to confirm the role of

BS in the treatment of Covid19 which seems crucial to consider in the treatment protocols.

## Conclusions

It can be concluded that *N. sativa* seeds have been proven as a safe and potent adjunctive therapeutic agent against COVID-19. It reduces complications and prevents deaths. So, it is likely to lower the burden on health care systems in a significant manner.

**Ethical Clearance :** All experimental protocols were approved by the Institutional Ethics Committee. All the participants gave voluntary written and informed consent for this study.

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**Conflict of Interest:** The authors have declared no conflict of interest

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