ORIGINAL ARTICLE

Preventive Value of Black Seed in People at Risk of Infection with COVID – 19

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ABSTRACT

In early 2020, the world health organization (WHO) declared Covid-19 as a global pandemic. Little is known about the potential protective factors against this viral disease. This study aimed to evaluate the preventive role of black seed (BS) in reducing infection rates with Covid-19 in people involved in the study. It is a descriptive, non-randomized and open-label study in which (376) participants were divided into two equal groups. The control group (CON) included participants who didn't take the black seeds, while the (BS) group included participants who took black seeds once daily at a 40 mg/kg orally. Knowing that the prophylactic efficacy of the black seed was seen through a smaller percentage of infected people at risk. A significantly lower infection rate was observed among black seed group 68 (36.2%) in comparison with the control group 180 (95.7%). Also, the (BS) group showed reduced incidence of infection at intermediate 12 (17.6 %) and low 0 (0.0 %) levels of exposure to risk factors. Therefore, we can conclude that black seed has the ability to reduce infection rates of covid-19 in people at risk.
Key words: Covid-19, Prevention, Black seed

INTRODUCTION

Coronavirus disease 2019 (COVID-19) causes respiratory tract illness which may lead to severe progressive pneumonia, multi-organ failure and death in critically ill patients. The first patient was recorded in Wuhan, China, in December, 2019, and the continuous outbreak has been characterized as a pandemic by the World Health Organization (WHO)[1,2]. In China, SARS-CoV-2 was recorded to be a cause of (84,180) confirmed infections, and more than (4000) deaths in April, 2020, and the virus spread to more than 200 countries in the world[3,4]. According to the WHO report (March 6, 2020), the crude mortality ratio is 3–4%, whereas these rates vary by country, patient age and presence of co-morbidities. The critical challenges to manage the current COVID-19 pandemic are due to a lack of an effective drug against the SARS-CoV-2[5-9]. Researchers and clinicians around the world are competing to find a treatment that works for COVID-19. Till now, herbs are used mainly in the treatment in several developing country for primary health care due to their excellent culturing compatibility and acceptance in the human body as well as their lesser side effects[10,11]. *Nigella sativa* "black seed", is a flowering plant that grows in countries bordering the Mediterranean Sea, and in Pakistan, India, and Iran[12]. In the past 2 decades, various pharmacological or medicinal aspects of black seed (BS) including its antibacterial, antioxidant, anticancer, anti-inflammatory, immuno-modulatory, analgesic, diuretic, antihypertensive, neuroprotective, antidiabetic and hepatoprotective properties, have been reported[13-15]. Also, it has been used in clinical research for neurological disorders, hyperlipidemia, obesity, lung disease, hypertension, thyroid dysfunction, hepatitis, rheumatoid arthritis and male infertility[16-20]. Furthermore, it has shown to decrease the replication of SARS-CoV *in vitro* in cell cultures[21.] Molecular docking studies have shown that some of its' components such as nigelledine, α-hederin and thymoquinone have high affinity with several SARS-CoV-2 enzymes and proteins[22] . Until today, the therapeutic strategies to deal with this infection are only supportive. This study will highlight the value of using black seed in persons at risk of covid-19 infection. It is hypothesized that black seed may play a protective role for SARS-Cov2 infections.

METHODS

Study Design: In the current non-randomized clinical controlled study, (376) participants were recruited from August 2020 to January 2021 and were followed up weekly by telemedicine. The ethics committee of Kirkuk Health Directorate in Iraq approved this study and granted a waiver of informed consent from study participants. Inclusion criteria included male or female participants, 19 years of age or older who are considered to be a risk individuals. At risk individuals, in the opinion of the investigator, are classified into 3 levels (categories): The high risk group which included Healthcare delivery, healthcare support, medical transport and people who have an infected member in the family. The intermediate risk group, which included those who were in contact with the general public (e.g. schools, high-population-density work environments, some high-volume retail settings), including individuals returning from locations with widespread Covid-19 transmission. The low risk group, which included people who had minimal occupational contact with the public and other coworkers. Exclusion criteria included any previous positive test for covid-19 by polymerase chain reaction (PCR) test, symptomatic for covid-19, people suffering from severe infection and requiring admission to intensive care unit, pregnant or breast feeding women, and allergy to any study medication. The participants were divided into two equal groups (ranging from 19-39 to > 65 years): The control group (CON): 188 participants including 95 males and 93 females who didn't consume black seeds. The

black seed group (BS): 188 participants including 93 males and 95 females, who were consuming black seed at 40 mg / kg orally once daily before breakfast meal during the course of the study.

Main Outcomes and measures: The occurrence of infection with covid-19 disease was observed through the appearance of clinical symptoms on the participants in this study, which included fever, dry or productive cough, wheezing, headache, chest tightness, difficulty with exertion, shortness of breath, sore throat, malaise and diarrhea. The individual components of all definitions of clinical symptoms were recorded separately and checked by 2 physicians authors (Kadhm Ali and Tunjai Namiq).

Statistical analysis: Descriptive analyses of the variables were expressed. Differences in distributions of participant characteristics were reported using differences with 95% CIs. Categorical data were compared using the χ2 test. The test was 2-sided, and a P value less than 05 was considered statistically significant. All analyses were performed with SPSS, version 26.0

RESULTS

Demographics and characteristics: A total of (376) participants with equal male and female numbers 188 (50%) for each were included in this study (Table 1). Their age groups ranged from (19-39) to (> 65) years. The most common age group was (40-65), with a percentage of 199 (52.9 %). A total of 239 (63.6%) participants had a high level of exposure to risk, while 13 (3.5%) of them had a low level of exposure to risk.

The results showed that out of (376) participants, 248 (66%) were infected with covid-19, and 128 (34%) participants were not infected. Most uninfected participants with covid-19 (120 of 128) were shown to be within the black seed group, compared with those who did not take the black seed, (difference, 95% CI) as shown in figure (1).This indicates the value of black seed in reducing infection rates among the participants. Cross tabulation was performed to describe the association between black seed group and levels of exposure to risk of catching covid-19. The results showed that the lowest incidence of infection was seen at the intermediate 12(17.6 %) and the low 0% levels compared to those at the high level 56 (82.4%) group, and there was statistically significant differences between the BS participants with respect to exposure to risk as shown in figure (2).

Infection	Control	Black Seeds (n=188)	Total
Infected	180(95.7%)	68(36.2%)	248(66%)
Uninfected	8(4.3%)	120(63.8%)	128(34%)

P value <0.001

Levels of exposure to risk	Infection with Covid 19		Total
	Infected (N=68)	Un infected (N=120)	
High	56(82.4%)	56(46.7%)	112(59.6%)
Intermediate	12(17.6%)	57(47.5%)	69(36.7%)
Low	0(0.0%)	(5.8%)	7(3.7%)

P value <0.001

Table 1: Distribution of study participants according to age, gender and levels of exposure to risk

Baseline demographics		Control (N=188)	Black seed (N=188)	Total (N=376)	P value
Age	19-39	69 (37.8%)	71 (36.7%)	140 (37.2%)	0.970
	40-65	100 (53.2%)	99 (52.7%)	199 (52.9 %)	
	> 65	19 (10.1%)	18 (9.6%)	37 (9.8 %)	
Gender	Male	95 (50.5%)	93(49.5%)	188 (50%)	0.837
	Female	93 (49.5%)	95(50.5%)	188 (50%)	
Levels of exposure to risk	High	127 (67.6%)	112 (59.6%)	239 (63.6%)	0.273
	Intermediate	55 (29.3%)	69 (36.7%)	124 (33.0%)	
	Low	6 (3.2%)	7 (3.7%)	13 (3.5%)	

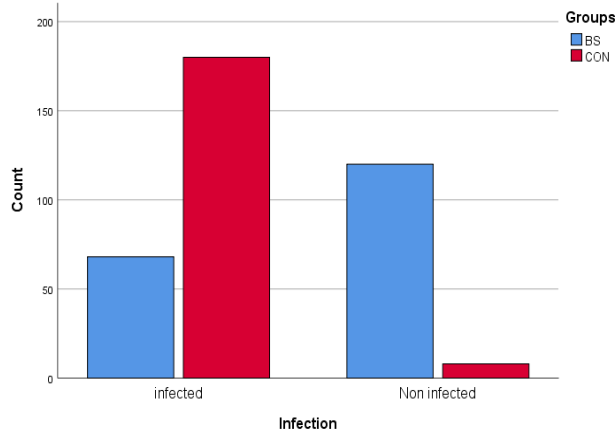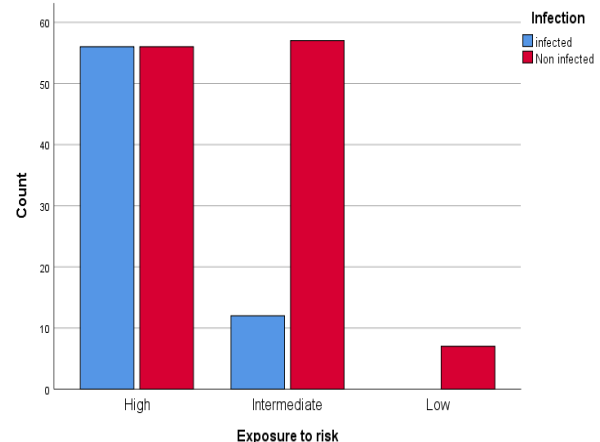Fig. 1: The effect of black seeds on the incidence of infection with Covid 19

Fig. 2: Relationship between the incidence of covid-19 and levels of exposure to risk among the black seed group

DISCUSSION

Pulmonary inflammation is a major pathophysiological feature of Covid-19 patients where oxidative and immune processes are included. Thus, finding a multi-potential and protective treatment to prevent such respiratory distress is the major purpose for effective treatments against Covid-19 infection[23,24]. Previous studies that assessed *N. sativa* (black seed) safety generally introduced this plant as a safe medicinal herb[25]. Several published studies confirmed pharmacological abilities of such compounds to regulate the inflammatory cytokine during obstructive respiratory diseases. In another aspect, regarding respiratory distress cases, several researchers investigated the effect of black seeds on the patients' immune systems[26,27]. Thymoquinone (TQ) (2-Isopropyl-5-Methyl-1,4-Benzoquinone) is the major bioactive constituent of *Nigella sativa*. This compound was shown to exhibit many activities as an anti-oxidant, anti-histaminic, anti-tumor, analgesic, anti-alzheimer, hepato-protective, neuro-protective, reno-protective, histone protein modulators, insecticidal and anti-ischemic [28]. It acts on antagonizing the side effect resulting from indirect ROS level elevation, and the anti-oxidant activity of TQ may be correlated to the quinnone structures redox properties and unlimited effectiveness of TQ for crossing the substantial barrier to the cellular alcoves[29,30].

The virus that causes Covid-19 infection has 3 important proteins called papaine-like proteases (PLPro), 3C-like protease (3PLPro), and spike proteins (SPs) as seen in SARS virus, and these are the inducing goals for drugs development. These proteins might be target of black seeds' compound to recognize favorable molecules in the treatment of covid-19. The molecular docking studies revealed that "Nigellidine" & "α- hederin" of *Nigella sativa* caused inhibition of covid -19 & SARS viruses and reported same or better results than those drugs applied in the intensive care unit for treating patients. Also gave evidences that *N. sativa* decelerates COVID-19 and might give similar or better outcomes than FDA approved treatments[31,32].

CONCLUSIONS

It can be concluded from our study that black seed has a preventive effect in people at risk of contracting Covid-19 .

REFERENCES

1- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020 Feb 15;395(10223):497-506.

2- Davoodi L, Abedi SM, Salehifar E, Alizadeh- Navaei R, Rouhanizadeh H, Khorasani G, Hosseinimehr SJ. Febuxostat therapy in outpatients with suspected COVID- 19: A clinical trial. International journal of clinical practice. 2020 Nov;74(11):e13600.

3- Zhang G, Zhang J, Wang B, Zhu X, Wang Q, Qiu S. Analysis of clinical characteristics and laboratory findings of 95 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a retrospective analysis. Respiratory research. 2020 Dec;21(1):1-0.

4- Shang J, Wang Q, Zhang H, Wang X, Wan J, Yan Y, Gao Y, Cheng J, Li Z, Lin J. The relationship between diabetes mellitus and COVID-19 prognosis: a retrospective cohort study in Wuhan, China. The American journal of medicine. 2021 Jan 1;134(1):e6-14.

5- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020 Feb 15;395(10223):497-506.

6- Tabata S, Imai K, Kawano S, Ikeda M, Kodama T, Miyoshi K, Obinata H, Mimura S, Kodera T, Kitagaki M, Sato M. Clinical characteristics of COVID-19 in 104 people with SARS-CoV-2 infection on the Diamond Princess cruise ship: a retrospective analysis. The Lancet Infectious Diseases. 2020 Sep 1;20(9):1043-50.

7- Sultan HI, Sultan AI, Maded ZK, Sultan HI. A descriptive study of COVID-19 infection among symptomatic patients in Al- Hawija district- Kirkuk- Iraq. International Journal of Psychosocial Rehabilitation.2020 Aug;24(10): 4403-4410.

8- Rahman MT. Potential benefits of combination of Nigella sativa and Zn supplements to treat COVID-19. Journal of herbal medicine. 2020 Jun 24:100382.

9- Kumar A, Kubota Y, Chernov M, Kasuya H. Potential role of zinc supplementation in prophylaxis and treatment of COVID-19. Medical hypotheses. 2020 Nov 1;144:109848.

10- Ghareeb OA. Pathological Changes in Liver Function Induced by Gold Nanoparticles and Protective Role of Tinospora Cordifolia: In Vivo. Annals of the Romanian Society for Cell Biology. 2021 Jan 31:660-5.

11- Ramadhan SA, Ghareeb OA. Clinicohematological Study of Gold Nanoparticles Toxicity and Ameliorative Effect of Allium Sativum. Annals of the Romanian Society for Cell Biology. 2021 Jan 31:597-602.

12- Gali-Muhtasib H, Roessner A, Schneider-Stock R. Thymoquinone: a promising anti-cancer drug from natural sources. The international journal of biochemistry & cell biology. 2006 Jan 1;38(8):1249-53.

13- Mollazadeh H, Afshari AR, Hosseinzadeh H. Review on the potential therapeutic roles of nigella sativa in the treatment of patients with cancer: Involvement of apoptosis:-black cumin and cancer. J Pharmacopuncture. 2017;20(3):158–172.

14- Kooti W, Hasanzadeh-Noohi Z, Sharafi-Ahvazi N, Asadi-Samani M, Ashtary-Larky D. Phytochemistry, pharmacology, and therapeutic uses of black seed (Nigella sativa) Chin J Nat Med. 2016;14(10):732–45.

15- Mashayekhi-Sardoo H, Rezaee R, Karimi G. Nigella sativa (black seed) safety: an overview. Asian Biomedicine. 2020 Sep 20;14(4):127-37.

16- Cascella M, Palma G, Barbieri A, Bimonte S, Amruthraj NJ, Muzio MR, Del Vecchio V, Rea D, Falco M, Luciano A, Arra C. Role of Nigella sativa and its constituent thymoquinone on chemotherapy-induced nephrotoxicity: evidences from experimental animal studies. Nutrients. 2017 Jun;9(6):625.

17- Mousavi SM, Sheikhi A, Varkaneh HK, Zarezadeh M, Rahmani J, Milajerdi A. Effect of Nigella sativa supplementation on obesity indices: A systematic review and meta-analysis of randomized controlled trials. Complementary therapies in medicine. 2018 Jun 1;38:48-57.

18- Sabzghabaee AM, Dianatkhah M, Sarrafzadegan N, Asgary S, Ghannadi A. Clinical evaluation of Nigella sativa seeds for the treatment of hyperlipidemia: a randomized, placebo controlled clinical trial. Med Arch. 2012 Jan 1;66(3):198-200.

19- Gheita TA, Kenawy SA. Effectiveness of Nigella sativa oil in the management of rheumatoid arthritis patients: a placebo controlled study. Phytotherapy research. 2012 Aug;26(8):1246-8.

20- Mahdavi R, Heshmati J, Namazi N. Effects of black seeds (Nigella sativa) on male infertility: A systematic review. Journal of Herbal Medicine. 2015 Sep 1;5(3):133-9.

21- Ulasli M, Gurses SA, Bayraktar R, Yumrutas O, Oztuzcu S, Igci M, Igci YZ, Cakmak EA, Arslan A. The effects of Nigella sativa (Ns), Anthemis hyalina (Ah) and Citrus sinensis (Cs) extracts on the replication of coronavirus and the expression of TRP genes family. Molecular biology reports. 2014 Mar;41(3):1703-11.

22- Kulyar MF, Li R, Mehmood K, Waqas M, Li K, Li J. Potential influence of Nagella sativa (Black cumin) in reinforcing immune system: A hope to decelerate the COVID-19 pandemic. Phytomedicine. 2020 Jul 10:153277.

23- Danzi GB, Loffi M, Galeazzi G, Gherbesi E. Acute pulmonary embolism and COVID-19 pneumonia: a random association?. European heart journal. 2020 May 14;41(19):1858-.

24- Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. Journal of pharmaceutical analysis. 2020 Apr 1;10(2):102-8.

25- Mashayekhi-Sardoo H, Rezaee R, Karimi G. Nigella sativa (black seed) safety: an overview. Asian Biomedicine. 2020 Sep 20;14(4):127-37.

26- Kulyar MF, Li R, Mehmood K, Waqas M, Li K, Li J. Potential influence of Nagella sativa (Black cumin) in reinforcing immune system: A hope to decelerate the COVID-19 pandemic. Phytomedicine. 2020 Jul 10:153277.

27- Goyal SN, Prajapati CP, Gore PR, Patil CR, Mahajan UB, Sharma C, Talla SP, Ojha SK. Therapeutic potential and pharmaceutical development of thymoquinone: a multitargeted molecule of natural origin. Frontiers in pharmacology. 2017 Sep 21;8:656.

28- Gomathinayagam R, Ha JH, Jayaraman M, Song YS, Isidoro C, Dhanasekaran DN. Chemopreventive and Anticancer Effects of Thymoquinone: Cellular and Molecular Targets. Journal of Cancer Prevention. 2020 Sep 30;25(3):136.

29- Mansour MA, Nagi MN, El- Khatib AS, Al- Bekairi AM. Effects of thymoquinone on antioxidant enzyme activities, lipid peroxidation and DT- diaphorase in different tissues of mice: a possible mechanism of action. Cell biochemistry and function. 2002 Jun;20(2):143-51.

30- Darakhshan S, Pour AB, Colagar AH, Sisakhtnezhad S. Thymoquinone and its therapeutic potentials. Pharmacological research. 2015 May 1;95:138-58.

31- Zhang DH, Wu KL, Zhang X, Deng SQ, Peng B. In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus. Journal of integrative medicine. 2020 Mar 1;18(2):152-8.

32- Bouchentouf S, Missoum N. Identification of compounds from Nigella sativa as new potential inhibitors of 2019 novel Coronasvirus (COVID-19): Molecular docking study.