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Original Article

Efficacy of honey -Nigella Sativa oil mixture as an adjuvant therapy against COVID-19 in randomized patients in Libya

Souad Elghamoudi[1], *Nasrien Elfarrah[2], Nesren Jaaida [3], Hana Smeda[4]

1. Department of analysis, Abu slim Clinic, Tripoli,
2. National Medical research Center,
3. Department of pharmaceutics, faculty of pharmacy Az-Zawia University:
4. Department of pharmacology, faculty of pharmacy Az-Zawia University:

h.smeda@zu.edu.ly

ABSTRACT

Introduction: Since 2020, the spread of a novel beta coronavirus has resulted in a high morbidity and mortality rate. As the infectious disease spread throughout the world, it mutated and evolved several times. Since there is no definite therapeutic strategy for COVID-19, it is the responsibility of all researchers to develop a safe therapeutic approach for coronavirus treatment. Despite the widespread use of medicinal herbs during the corona epidemic period in Libya, there has been little research in this area. This study aimed to assess the efficacy of a honey -*Nigella Sativa* oil mixture (HNSOM) against the coronavirus.

Methods: An open-label randomized controlled clinical trial (RCT) was conducted on 107 adult patients with mild to moderate COVID-19 symptoms at the Abu Slim clinic in Tripoli. Patients were randomly divided into control and treated groups. Both groups received the standard treatment protocol, with the test subject group receiving 10 mL of HNSOM. A chi-square statistical test was used for data analysis.

Results: There were a significant positive results associated with HNSOM as an adjunctive treatment against the coronavirus. It was found that the percentage of patients' recovery in the treated group was significantly higher (86%) compared to the control group (27%), (P-value < 0.00001). Furthermore, viral clearance (negative PCR test) was 94% higher in the tested group than in the control group (36 %), with the chi-square statistics value being 39.08 (P-value < 0.00001).

Conclusion: The therapeutic efficacy of HNSOM supplementation was proved in this study. Further clinical trials should be conducted to ensure the beneficial therapeutic response obtained in this study.

Keywords: Coronavirus, clinical trial, HNSM, Libya.

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Introduction

The novel corona virus detected in china December 2019 has shortly changed to be global pandemic and caused numerous health and economic concerns that have impacted human quality of life. [1 ,2] A global interest was generated after the widespread and mutation of corona virus disease which described later by the world health organization (WHO) as pandemic. To date, as of September 24, 2022 world health organization has counted 611,421,786 confirmed cases and 6,512,438 confirmed deaths worldwide. [3] In Libya, the National Center for Disease Control has recorded 507,005 cases and 6,437 deaths. [4]

This infectious disease is highly contagious, caused by SARS-CoV-2 and resulted in high morbidity and mortality among the public, which in particularly effects the lower respiratory system [5] [6]. Cough, dyspnea, fatigue, and fever have been described as the most common symptoms. More health complication and sever symptoms appearance are associated with those patients of all age group suffering other chronic disease. [7, 8]

Developing of effective therapy has challenged the medical and nutritional researchers. Several clinical trials have been conducted to develop vaccines or drugs for prevention or treatment of COVID-19. Currently, despite the availability of several vaccines, no specific antiviral treatment against corona viruses is available, especially after the identification of new corona virus strains (α, β, γ, δ, Omicron). [9,10] Furthermore, supplemental herbal drugs are being researched and studied as a possible treatment for COVID-19.[11] Numerous research has shown the potential use of natural supplements like ginger, garlic, honey, Nigella sativa and honey in the prevention and treatment of COVID-19. [12, 13, 14] In particular, honey and Nigella sativa contain active biocompounds that have the potential to exert many different properties, such as anti-inflammatory, antiviral, and immunostimulant effects. [15, 16, 17]

Honey is a natural product that contains many ingredients and bioactive molecules that possess potential therapeutic effects against several diseases. [18] It has been used in medicine since ancient times and is mentioned in holy Quran as a healing agent. [19, 20]

Many studies have proven the role of honey in boosting and activating the immune system due to its phyto-chemical, anti-inflammatory, antimicrobial, and antioxidant properties. [18]

Several honey health benefits have been reported due to its opulent natural composition, which includes many substances such as vitamins, minerals, protein, [21,22] glycosides, flavonoids, alkaloids, polyphenols, reducing compounds, anthraquinone, volatile

compounds, and monosaccharides. [23, 24, 25]

Nigella sativa (called black cumin or black seed this is in debate with the other plant) is a medicinal herb that provides antiviral and immunomodulatory effects. [26] It contains different ingredients, including proteins, fiber, carbohydrates, flavonoids, minerals and vitamins. These numerous ingredients have a variety of beneficial effects as anti-inflammatory, anti-viral, anti-microbial, analgesics, anti-nociceptive, and anti-epileptic. [27, 28, 29, 30] The mechanism of antiviral activity of Nigella sativa is accomplished either via targeting viral sites or viral-host interactions. [31]

The objective of this study is to examine the efficacy of honey and Nigella sativa oil mixture as an adjunctive therapy against corona virus.

Methodology

Study design and setting

To evaluate the therapeutic efficacy of honey and Nigella Sativa oil mixture against coronavirus, an open-label randomized controlled trial (RCT) was conducted on COVID-19-infected outpatients visiting an Abu slim clinic in Tripoli, Libya. The research was conducted during May and June, 2020. The research trial was approved by the University of Zawia - Libya. What you mean here; ethical approval??

Study participants

A total of 107 male and female adult patients aged between 25 and 65 years with mild to moderate COVID-19 symptoms and a positive PCR test were recruited for the study. The participants were divided into two groups at random: the treatment (HNSOM) group and the control group. The trial excluded patients with renal impairment and those with severe diseases requiring hospitalization in a critical care unit. All participants were clearly informed of the study's objectives, and their verbal consent was obtained.

Procedures for intervention and randomization

Participants were randomly allocated into two groups: the HNSOM (test) group (subject number 52) and the control group (subject number 55). Random assignment of participants into groups was conducted using the research randomizer online resource. Both groups received the recommended protocol for treatment care of COVID-19 patients (vitamin C, zinc, and aspirin for mild patients; vitamin C, zinc, aspirin, and azithromycin for patients with moderate symptoms). An oral supplement of honey and Nigella sativa oil mixture was included as adjunctive therapy for the test group. The HNSOM is a combination of honey and Nigella-sativa oil mixed in the same proportion. The local honey used in the mixture was a mix of 6 different local honey types (thyme honey, Sider, Willow, Harem, Kind, and the legacy honey) obtained from a honey markets at Alkums city. The used cold-extracted Nigella sativa oil was produced by WPO® Company in Libya.

The oil is licensed by the industrial and economic ministry with a license number of 36120. The test subject group received 10 ml of the mixture dissolved in warm water orally on a daily basis over 14 days. The mixture and dose administration were given as mentioned in the holy Quran and Prophetic Hadith. [32.33, 34]

Outcome measures and follow-up. The two main primary outcomes measured for each patient were the percentage of patient recovery (defined as three days without symptoms) and viral clearance (negative PCR test result). An additional outcomes were measured including duration of clinical symptoms and adverse drug reactions caused by disease complications. Asthma, fatigue, cough, nasal congestion, sore throat, and fever were among the clinical symptoms monitored in patients. Data is collected and recorded every day via telecommunication and electronic mail.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) Software version 25 was used to analyze the data. For data analysis, descriptive statistics were used. A Chi-square test was used to analyze the differences between the HNSOM group and the control group. All categorical variables were expressed as frequency and percentages. A p-value less than 0.05 was set as the level of significance with a 95 % confidence interval.

Result

Baseline characteristics of study participants

The trial included 107 patients with mild to moderate symptoms who had confirmed positive PCR test results. The participants were randomly assigned to one of the two groups: a test group (n=52) and a control group (n=55). More than half of those who took part were female, 57.9% (n=62). Males made up 42.1% (n=45). Table 1 shows all baseline characteristics reported.

Table 1: summarizes the baseline characteristics of the participants.

Parameters	Total number (n=107)	HNSOM group (n=52)	Control group (n=55)
Age	**25-65**	**26-55**	**25-65**
Sex Male Female	 **45** **62**	 **17** **35**	 **28** **27**
Smoking	**25**	**10**	**5**
Obesity	**30**	**17**	**13**
Allergic rhinitis	**28**	**15**	**13**
Hypertension	**35**	**12**	**13**

Diabetes	**10**	**4**	**6**
Asthma	**3**	**2**	**12**
Migrain	**6**	**4**	**2**

Percentage of patient recovery during the study period (14 days)

Among 52 patients in the HNSOM group, 45 recovered during the study period. The percentage of recovery for HNSOM-received patients was 86%, which was significantly higher compared to the control group (27%) (P-value < 0.00001).Figure 1 and 2 shows the results.

Table 2: Percentage of patients' recovery over the study period

Outcome	Recovered	Non recovered	Total	% of recovery	P -value
Control group	**15**	**40**	**55**	**27%**	**P<0.00001**
HNSOM group	**45**	**7**	**52**	**86%**	**P<0.00001**

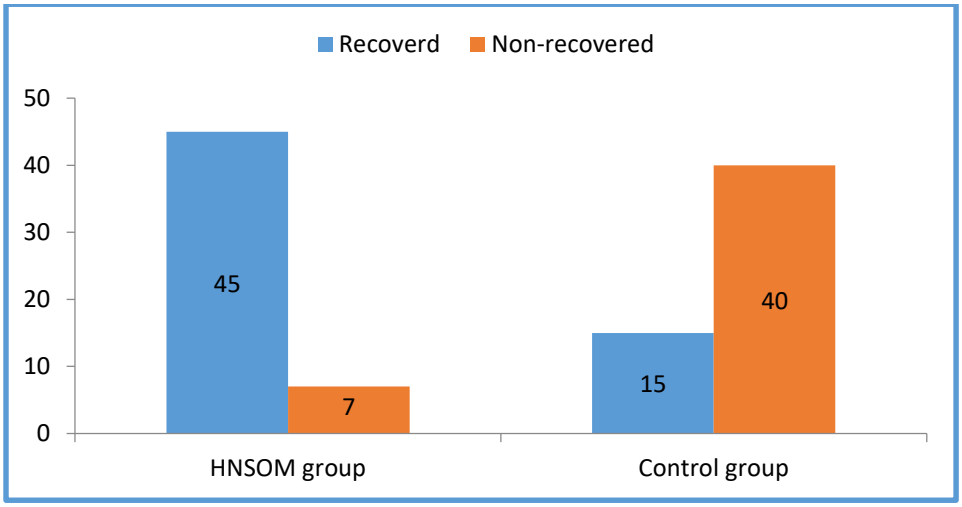

Figure 1: Number of patients' recovery among control and test groups

Viral clearance

Positive results were accompanied by HNSOM supplementation, whereas the vast majority of HNSOM patients (n= 49) showed negative PCR tests in contrast to the control subject group. The percentage of viral-free recovery was 94.2% higher

than the control group (36.4%).The chi-square statistic is 39.08 (P< 0.00001).Table and Figure 3 show the results.

Table 3: Percentage of viral clearance after 14 days of honey supplementation for treated (HNSOM) group compared to control group.

Outcome	Negative PCR test	Positive PCR test	Total	%of viral clearance	P -value
Control group	**20**	**35**	**55**	**36.40%**	**P<0.00001**
HNSOM group	**49**	**3**	**52**	**94.20%**	**P<0.00001**

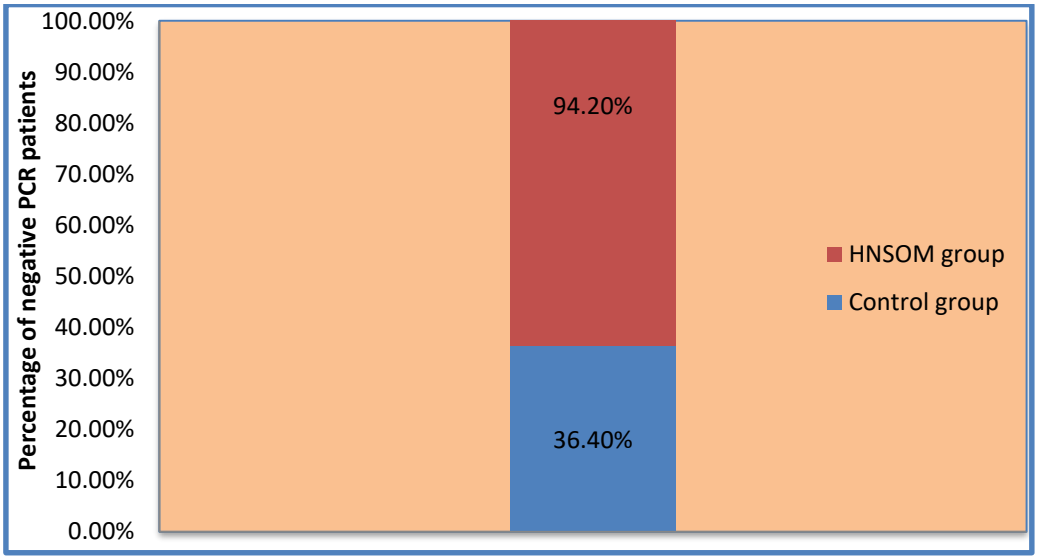

Figure 3: Percentage of viral clearance among control and test groups

Reported clinical symptoms of participants

In table 4, the significance of clinical symptoms and their duration (days) were evaluated to assess clinical improvement and to be considered as additional outcome measures. Headache (96%), fatigue (95%), insomnia (90%), sore throat (84%), and nasal congestion (81%) were the most common symptoms among participants. Excluding loss of appetite, nausea, vomiting, and sneezing, all the COVID-19 symptoms were relieved earlier in the HNSOM groups than in the control groups, and the differences were significant. Furthermore, no adverse drug reactions were reported, and neither the control

nor test groups' participants were hospitalized.

Table 4: Prevalence and duration of clinical symptoms experienced by participants.

Symptoms	HNSOM group No of subject (52)		Control group No of subject (55)		Total	P value
	Frequency		**Frequency**			
		2.48±1.57		±		
	50	**3.2 ± 1.07**	**50**	±		
	50	**2.76±1.16**	**53**	±		
	35	±	**45**	±		
	45	±	**42**	±		
	30	±	**40**	±		
Sore throat	**51**	±	**39**	±		
	40	±	**35**	±		
loss of appetite	**31**	±	**19**	±		
	22	±	**18**	±		
	29	±	**26**	±		
	22	±	**23**	±		
		±	**23**	±		
	20	±	**15**	±		
	19	±	**21**	±		
	20	±	**15**	±		
	13	±	**17**	±		
	15	±	**20**	±		
	12	±	**8**	±		
	43	±	**42**	±		

Discussion

Results in present study showed that the HNSOM supplementation had a significant positive impact. After 14 days of treatment, 86.5% of test patients recovered, and 94.2% had negative PCR results. In contrast, only 27.3% of the

control group recovered, and 36.4% had negative PCR test results. Patients' rapid recovery and the short duration of some clinical symptoms confirm HNSOM's therapeutic efficacy as an adjunctive therapy against the coronavirus.

Previous clinical studies on the coronavirus investigated the potential effect of honey and Nigella sativa alone or in combination with other herbal components. Remarkably, many of these trials produced positive clinical effectiveness results that were similar to the present study.

In Pakistan, a 2020 clinical randomized parallel trial was conducted among moderate and severely COVID-19 infected patients to evaluate the effectiveness of natural honey and grinded powder of Nigella sativa mixture against the coronavirus. They found a significant decrease in the time required for symptom alleviation. Furthermore, improved viral clearance and a mortality rate were associated with the honey-Nigella sativa treatment. [35]

Different studies were conducted to evaluate the mechanism of immunodulatory honey effect and its action on antibody engenderment. The results found that the natural honey increases the generation of immune cells (T and B lymphocytes), antibodies, eosinophils, neutrophils, monocytes, and natural killer cells. [36] In addition, the presence of fermentable sugars and non-sugar ingredients contained substantial amounts of endotoxin and induced interleukin-6, which are responsible for immunomodulation. [37]

Other studies focused on the potential effect of honey as adjunctive therapy for COVI-19 have shown that the potential antiviral properties of honey are due to the presence of bioactive compounds, namely polyphenols. [38, 39] In addition, biological properties of honey (anti-inflammatory and antioxidant properties) reduce inflammation and play an important role in promoting the immune system against any pathogenic attack. [40, 41] More recent study indicated the ability of honey to prevent viral entry and viral replication within the host cell. [42]

Likewise, several studies considered Nigella sativa treatment against coronavirus. In Iraq a clinical trial conducted among COVID-19 infected patients whom received Nigella sativa seed as an oral dose of 40mg/kg daily concurrently with standard treatment of corona infection. Positive results were found concerning the severity and complications of COVID-19 infection. [43]. Interestingly, an Indian study found that Nigella sativa components had a higher binding affinity to the coronavirus's key enzyme SARS-CoV-2 Mpro, which is involved in virus replication and transcription [44]. In Saudi-Arabia 2021, an open randomized controlled trial concluded fast COVID-19 symptoms recovery and shorter duration of some symptoms were accompanied by Nigella-sativa oil supplementation. [13]

Moreover, previous in-vivo investigations proved the role of Nigella-sativa oil in enhancing immunity, where it increases lymphocyte count and is effective in immunity regulation. [45]

Overall, HNSOM administration as an adjuvant therapy against COVID-19 demonstrated evident clinical efficacy with a significant improvement concerning patient recovery and time taken for viral clearance compared to non-treated group. Further investigation and clinical monitoring are required and recommended.

STUDY LIMITATION

In this study, we exclude the potential beneficial effect of honey-Nigella Sativa oil mixture in patients with renal impairment and those with severe diseases as they required hospitalization in a critical care unit. However, the potential efficacy of the HNSOM mixture as an adjuvant therapy against COVID-19 improves patient recovery and viral clearance time.

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