

Survey of the Effects of Ivy Leave Dry Extract and Bromhexine for Management of Cough and Shortness of Breath in COVID-19 Infected Patients

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SUMMARY. Coronavirus consists of a single-stranded RNA. The most common symptoms of COVID-19 are fever, dry cough and fatigue. Ivy leave extract, as a naturopathic therapy and bromhexine were chosen for the current study, to investigate the effectiveness of them for the treatment of cough and shortness of breath (SOB) associated with COVID-19 and if there is a relationship between patients' demographic data and their responses. A quantitative survey methodology was used to collect data, depending on face to face personal interview, in an internal hospital consultant in Iraq. The survey was contained on questions about the demographic data (age and gender) of the patients, specific symptoms of COVID-19 (cough and SOB) and if any OTC cough remedies; ivy leave dry extract syrup and bromhexinesyrup used for symptoms control and if the symptoms have been improved by the effect of the drugs. A total of one hundred COVID-19 patients were randomly participated in this study. It was found that there were significant associations between patients with cough and SOB COVID-19 symptoms took cough remedies and their responses, p-value 0.033 and 0.000, respectively. Also there were no significant associations between the demographic data (gender and age) of patients with cough and SOB COVID-19 symptoms and their responses to cough remedies. The current study concluded that ivy leave dry extract syrup and bromhexine syrup were effective against cough and SOB COVID-19 symptoms and there were no effect of demographic data on patients' responses to cough remedies.

RESUMEN. El coronavirus consiste en un ARN monocatenario. Los síntomas más comunes de COVID-19 son fiebre, tos seca y fatiga. El extracto de hojas de hiedra, como terapia naturopática, y la bromhexina fueron elegidos para el estudio actual, para investigar la efectividad de los mismos para el tratamiento de la tos y la falta de aire (SOB) asociadas con COVID-19 y si existe una relación entre los datos y sus respuestas. Se utilizó una metodología de encuesta cuantitativa para recopilar datos, dependiendo de la entrevista personal cara a cara, en un consultor interno de un hospital en Irak. La encuesta estaba contenida en preguntas sobre los datos demográficos (edad y sexo) de los pacientes, síntomas específicos de COVID-19 (tos y SOB) y si hay algún remedio para la tos de venta libre; jarabe de extracto seco de hiedra y jarabe de bromhexina utilizados para el control de los síntomas y si los síntomas han mejorado por el efecto de los fármacos. Un total de cien pacientes con COVID-19 participaron aleatoriamente en este estudio. Se encontró que existían asociaciones significativas entre los pacientes con tos y síntomas de SOB COVID-19 que tomaron remedios para la tos y sus respuestas, valor p 0.033 y 0.000, respectivamente. Además, no hubo asociaciones significativas entre los datos demográficos (sexo y edad) de los pacientes con tos y síntomas de SOB COVID-19 y sus respuestas a los remedios para la tos. El estudio actual concluyó que el jarabe de extracto seco de hojas de hiedra y el jarabe de bromhexina fueron efectivos contra la tos y los síntomas de SOB COVID-19 y no hubo ningún efecto de los datos demográficos en las respuestas de los pacientes a los remedios para la tos.

INTRODUCTION

At the end of December 2019, an onset of an indefinite disease known as pneumonia of an indefinite

reason taken place in Wuhan city, China ¹. After that, the major causative agent of this enigmatic pneumonia was identified as a well-known coronavirus by var-

KEY WORDS: bromhexine, COVID-19, cough, ivy leave dry extract, SOB.

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ious laboratories²⁻⁴. Temporarily, the corona virus has been called as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the infectious disease caused by this virus called as coronavirus disease 2019 (COVID-19) by the WHO (World Health Organization). Coronaviruses (CoVs) are a group of highly diverse, enveloped, positive sense and single stranded. It affects several body systems like respiratory, hepatic, enteric, and neurological with different seriousness among humans and animals⁵.

While the COVID-2019 major route of transportation is human to human, animal-to-human transport has not yet been verified. Unfortunately, virus carriers persons, asymptomatic carriers, are at high danger of being super infectors with this disease, because the large number of those infected persons may not develop the disease⁶. The droplets are main mode by which COVID-19 transmitted from human-to-human, this may occur during coughing, sneezing or talking, and may inhale by a healthy person⁷. The average incubation period of COVID-19 is approximately three days⁸. Fever, dry cough and fatigue are the most general symptoms of COVID-19. In a number of studies, the approximate age of infected patients ranged between 45 to 56 years. Nearly greater than 90% of infected patients with COVID-19 have abnormal chest radiographs^{8,9}.

Acute respiratory distress syndrome (ARDS) is considered to be the wide spread complication of the disease, which occurs in 3.4% of infected patients^{8,10}. There is no identified treatment approved for COVID-19. The treatment of infection is symptomatic, and oxygen therapy considered the first step for managing respiratory impairment¹¹. Bromhexine hydrochloride used for the management of less severe COVID-19 and it still has protective effect against acute lung injury induced by COVID-19 by inhibition of TMPRSS2 which was a host cell factor fundamental for viral spread¹². Ivy leave extract is indicated for some respiratory disease symptoms, its action as expectorant for productive coughs. Other most common indications include antispasmodic and management of flu¹². Therefore, ivy leave extract, as a naturopathic therapy, and bromhexine were chosen for the current study, to investigate the effectiveness of them for the treatment of cough and SOB associated

COVID-19 symptoms.

The aim of this study was to investigate the effectiveness of cough remedies (ivy leave dry extract and bromhexine) for treatment of cough and SOB COVID-19 symptoms and if there is a relationship between patients' demographic data and their responses.

METHODOLOGY

In the current study, a quantitative survey methodology was used to collect data, depending on face to face personal interview, in an internal hospital consultant in Iraq. Data collection took 21 days from September 27 and October 20, 2020. One hundred patients were randomly participated in the current study. The survey were contained on questions about the demographic data (age and gender) of the patients, specific symptoms of COVID-19 (cough and SOB) and if any OTC cough remedies; ivy leave dry extract syrup (in a dose of 35 mg three times daily) and bromhexine syrup (in a dose of 4 mg three times daily) used for symptoms control and if the symptoms have been improved by the effect of the drugs.

Statistical analysis

The results have been tested by SPSS-20 (IBM-USA). The data of this study were analyzed using descriptive statistics. The independency of variables was determined by nonparametric statistics chi-square test. The level of significance was considered for $p < 0.05$.

RESULTS

Cronbach alpha was used to determine the reliability of this study. Its value was (0.775), indicating that the survey study is highly reliable, stable and accurate. A total of one hundred patients were participated in this study; 86 (86%) patients suffered from cough while 59 (59%) patients suffered from SOB COVID-19 symptoms. A total of 49 (49 %) of patients with cough and SOB took OTC cough remedies. From whom, 30 (61.2 %) patients with cough responded while only 11 (22.4 %) patients with SOB responded, Table (1). Results of chi-Square test appeared that there were statistically significant association between patients with cough and SOB COVID-19 symptoms took cough remedies and their responses, since Chi-Square had p-value 0.033 and 0.000, respectively (Fig. 1).

Symptoms	patients	Patients took cough remedies, n (%)	Patients' responses to cough remedies, n (%)	X ²
Cough	86 (86)	49	30 (61.2)	0.033*
SOB	59 (59)		11 (22.4)	0.000*

Table 1. Chi-Square test results of patients with cough and SOB COVID-19 symptoms took cough remedies and their responses (n = 100). * p < 0.05.

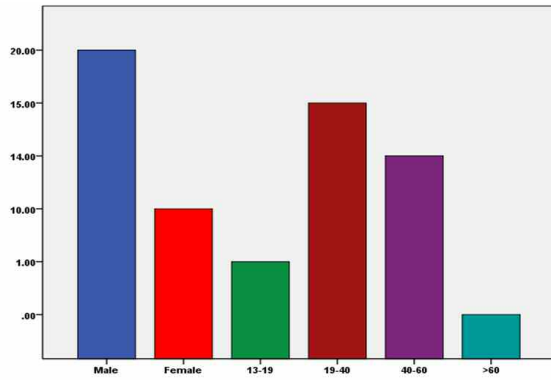


Figure 1. Chi-Square test results of patients with cough and SOB COVID-19 symptoms took cough remedies (ivy leave dry extract and bromhexine) and their responses. *p < 0.05 compared to patients took cough remedies.

Most of the patients included in this study were males; 72 (72%); while females were only 28 (28%). Also most of the patients 46 (46%) were aged 40-60

years while those with older age (> 60 years) constituted 6 (6 %) of all patients. In addition most of patients with cough and SOB were male 60 (83.3%), 41 (57%) respectively. It is found that there were higher responses rate to cough remedies among females with cough and SOB COVID-19 symptoms compared with males responses [10 (62.5%) and 4 (25%)], (20 (60.6) and 7 (21.2)], respectively. In addition, there were higher responses rate to cough remedies among patients with cough and SOB COVID-19 symptoms aged 40-60 year compared with younger age, 19-40 year, responses 14 (63.6) and 6 (27.3), 15 (62.5), and 5 (20.8), respectively, Table 2. Chi-Square test results showed that there were no statistically significant associations between the demographic data (gender and age) of patients with cough and SOB COVID-19 symptoms and their responses to cough remedies since chi-Square had p-value > 0.05 (0.068 and 0.366), (0.853 and 0.763), **Figs. 2 and 3.**

Variables	Patients, n (%)	Patients with cough, n (%)	Patients with SOB, n (%)	Patients took cough remedies, n (%)	Patients with cough responded to cough remedies, n (%)	Patients with SOB responded to cough remedies, n (%)
Male	72 (72)	60 (83.3)	41 (57)	33 (45.8)	20 (60.6)	7 (21.2)
Female	28 (28)	26 (92.8)	18 (64.3)	16 (57.1)	10 (62.5)	4 (25)
		X2			0.068	0.366
13-19	3 (3)	3 (3)	2 (66.7)	2 (66.7)	0 (0)	0 (0)
19-40	45 (45)	42 (93.3)	25 (55.6)	24 (53.3)	15 (62.5)	5 (20.8)
40-60	46 (46)	38 (82.6)	28 (60.9)	22 (47.8)	14 (63.6)	6 (27.3)
≥ 60	6 (6)	3 (50)	4 (66.7)	1 (16.7)	0 (0)	0 (0.0)
		X2			0.853	0.763

Table 2. Chi-Square test results of gender and ages of patients with cough and SOB COVID-19 symptoms and their responses to cough remedies (n=100).

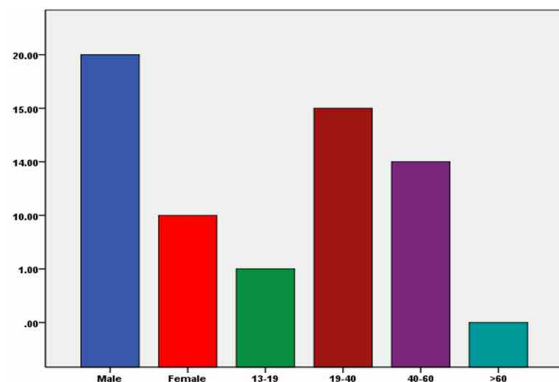


Figure 2. Chi-Square test results of gender and ages of patients with cough COVID-19 symptoms and their responses to cough remedies.

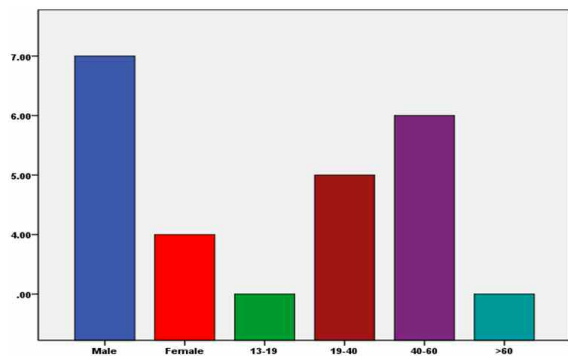


Figure 3. Chi-Square test results of gender and ages of patients with cough COVID-19 symptoms and their responses to cough remedies.

DISCUSSION

The prophylaxis use of herbal medicines/food supplementations to prevent or management of COVID-2019 has not been covered at a global level¹³. It is necessary and logical to develop effective intervention protocols from conventional medicine for its prevention¹⁴. Results of the current study indicated that there were significant effects of OTC cough remedies (ivy leave dry extract and bromhexine) in improving cough and SOB symptoms in patients with COVID-19. These results were compatible with results of a study when ivy leave extract applied three times daily, for seven days revealed a clinically related reduction in cough score and the intensity of symptoms associated with cough¹⁵. Also when ivy leave extract used in children for 7-10 days, the symptoms of (cough, sputum, shortness of breath) were improved after treatment¹⁶. In other study, bromhexine was founded to have a significant higher reduction of patients' symptom scores for symptoms of cough discomfort, cough frequency, easiness of expectoration and sputum volume¹⁷.

One of the widespread early COVID-19 infection symptoms is cough with dyspnea and increased sputum production. Also pulmonary oedema and pneumonia may be take place resulting in further aggravation of dyspnea. Ivy leaves preparations have a broncholytic and secretolytic effects that increase the surfactant production in the lungs and maintain alveolar function¹⁸. The well-known coronavirus mostly gets access the human body by angiotensin-converting enzyme 2/transmembrane protease serine 2 (TMPRSS2). Beforehand most studies on viruses that infect respiratory system have believed that TMPRSS2 takes part in the method of host cell access, maturation, and liberation of the virus, which intensify the viral infectivity. So, TMPRSS2 inhibition can be a hopeful therapeutic approach for COVID-19. Bromhexine, a well-known mucolytic agent, has ability to inhibit TMPRSS2 and considered to be effective against COVID-19¹².

In this study, most of patients with COVID-19; 72 (72%); and most of them presented with cough and SOB; 83.3% and 57% respectively, were males. Although the higher responses rate to cough remedies in patients with cough and SOB COVID-19 symptoms were among females compared to males but chi-Square test results revealed that there was no statistically significant association between the gender of patients with cough and SOB COVID-19 symptoms and their responses to cough remedies. This result was consistent with previous studies concluded that (73%) of patients admitted to the hospital with COVID-19 were males¹⁹. The lower vulnerability of

females to viral infections may be related to X chromosome and sex hormones that had protective effects and cover an important role in innate and adaptive immunity²¹.

Other study found that COVID-19 symptoms like cough and fever are experienced more by males. The same study explained that the causes of higher susceptibility of male to the H1N1 virus may be due to the differences in gender-based social stratifies which affect the modes of exposure to pathogens, vulnerability to disease and outcome of disease leading to differences in incidence, duration, severity and fatality rates²¹. There were no adequate studies about the effect of gender on responses to cough remedies. Moreover, the consumption of large doses of Vitamin C can lead to false blood glucose elevated levels²². In this study, most of the patients participated (46%) were aged 40-60 years while those with older age (> 60 years) constituted (6%) of all patients. In addition, there were higher responses rate to cough remedies among patients with cough and SOB COVID-19 symptoms aged (40-60) year compared with younger age, (19-40) year, responses. But chi-Square test results showed that there was no statistically significant association between the age of patients with cough and SOB COVID-19 symptoms and their responses to cough remedies since chi-Square had p-value > 0.05 (0.853 and 0.763). The available studies about the effect of age on the response to cough remedies among COVID-19 patients are limited. One study of the effect of ivy herbal extract in 268 children, with cough symptoms, aged 0-12 year concluded that the reduction of the symptom index did not show statistically significant differences between all age groups which means that all age groups benefited from similar effect size²³. This study is one of few studies that investigate the effect of ages and gender on COVID-19 patient's responses to cough remedies and may open the way for other future studies in this field.

CONCLUSION

The current study concluded that ivy leave dry extract syrup and bromhexine syrup were effective against cough and SOB COVID-19 symptoms and there was no effect of demographic data on patients' responses to cough remedies.

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