

Effects of Cranberry on Outpatients with Mild to Moderate COVID-19 Infection

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Abstract

COVID-19 disease is an acute viral infection illness of the airway system resulting from the SARS-CoV-2 virus. Cranberry is an evergreen group of dwarf shrubs of the Vaccinium Oxycoccus. The most important pharmacological effects of cranberry are related to its composition liking of quercetin, flavonols, and proanthocyanidins. Cranberry had numerous pharmacological activities encompassing antioxidant, cardioprotective, antibacterial, anticancer, antiviral, and regulated glucose levels. This research aimed to estimate the potential activity of cranberry to enhance the efficacy of standard therapy for COVID-19 infection. This study was an open-label multicenter clinical trial. Simple randomized, and observation were conducted from Nov. 2021 to Feb. 2022 in Imam Al Hussein hospital, Imam Zain-ul-Abdeen hospital, and Alkafeel Super Specialty Hospital. A total of ٦0 patients with age \geq 18 years suffering from mild to moderate COVID-19 pneumonia were volunteered to do this study, allocated into two groups. The first group managed standard treatment only according to the Russian Ministry of Health, while the second group managed standard treatment plus cranberry 1000 mg capsule per day for 7 days. Each patient was assessed individually and followed up for 10 days. Cranberry significantly enhanced the effect of standard COVID – 19 therapies by rapidly relieving clinical symptoms of COVID – 19 infections and significantly lowered the count of WBC, CRP, D-Dimer, and ferritin in comparison with patients who only received STD therapy at $P < 0.05$. In conclusion, Cranberry significantly improved STD therapy by reducing inflammatory response and enhancing lung function via maintaining normal SPO2% level and relieving clinical symptoms of COVID-19 infection.

Keywords: COVID-19, Cranberry, Headache, Cough, WBC, D-Dimer.

تأثير التوت البري على المرض المصابين بعدوى خفيف الى متوسطة من مرض كوفيد ١٩

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الخلاصة

كوفيد – ١٩ هو التهاب فيروسي حاد ومعدي يصيب الجهاز التنفسي والذي يسببه فيروس المتلازمة التنفسية الحادة الوخيمة كورونا ٢ (سارس-كوف-٢). التوت البري هو مجموعة دائمة الخضرة من الشجيرات القزمية من مجموعة عنبية حادة الخباء. تعزى أهم التأثيرات الدوائية للتوت البري لامتلاكه الكيرسيتين، والفلافونول، والبروانثوسيانيدين. يمتلك التوت البري العديد من الأنشطة العلاجية التي تشمل كمضاد الأكسدة، والجراثيم، والسرطان، والفيروسات، وحماية القلب وتنظيم مستوى السكر في الدم. هدفت الدراسة الحالية إلى تقدير النشاط المحتمل للتوت البري لتعزيز فعالية العلاج القياسي لعدوى كوفيد – ١٩. كانت هذه الدراسة عبارة عن تجربة سريرية متعددة المراكز حيث تم إجراءها باختبار المرضى عشوائياً من نوفمبر ٢٠٢١ إلى فبراير ٢٠٢٢ في مستشفى الإمام الحسين (ع) التعليمي ومستشفى الإمام زين العابدين (ع) ومستشفى الكفيل التخصصي. تطوع ٦٠ مريضاً بعمر يتراوح ١٨ عام أو أكثر يعانون من الالتهاب الرئوي كوفيد -١٩ الخفيف إلى المتوسط الشدة لإجراء هذه الدراسة، وتم تقسيمهم إلى مجموعتين. حيث تم معالجة المجموعة الأولى بالعلاج القياسي فقط وفقاً لوزارة الصحة الروسية، بينما تم معالجة المجموعة الثانية إضافة لعلاج القياسي بالتوت البري ١٠٠٠ مجم كبسول يومياً لمدة ٧ أيام. ثم تم معاينة ومتابعة كل مريض على حدة لمدة ١٠ أيام. عزز التوت البري بشكل كبير من تأثير علاج كوفيد – ١٩ القياسي من خلال سرعة تخفيف الأعراض السريرية لعدوى كوفيد – ١٩ وخفض بشكل ملحوظ تعداد خلايا الدم البيضاء واختبار البروتين المتفاعل (CRP) ومؤشر تجلط الدم (الذي دايمر) ومؤشر مخزون الحديد (الفرتين) مقارنة بالمرضى الذين تلقوا العلاج القياسي فقط عند قيمة $P < 0.05$. إشارة النتائج بأن التوت البري يقوم بتحسين فعالية العلاج القياسي لعدوى كوفيد – ١٩ بشكل ملحوظ من خلال تقليل الاستجابة الالتهابية المناعية وتعزيز وظائف الرئة من خلال الحفاظ على مستوى نسبة تشبع الاوكسجين SPO2 % الطبيعي وتخفيف الأعراض السريرية لمرض كوفيد – ١٩.

الكلمات المفتاحية: كوفيد -١٩، توت بري، صداع، السعال، خلايا الدم البيضاء، الذي دايمر.

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Introduction

Coronavirus disease 2019 (COVID-19) is an acute viral infection illness of the airway system resulting from the SARS-CoV-2 virus. This virus may infect the upper airway tracts like sinuses, nose, and throat or the lower airway tract like bronchus and lungs. There are three species of coronaviruses that have been developed and transmitted from animal species, like bats, to human populations in the last two decades resulting in a large-scale pandemic ⁽¹⁾. The main problems in the management of COVID-19 were that specific antiviral agents were not available and different drugs were tested to overcome this pandemic infectious disease ⁽²⁾. Despite, many cases of COVID-19 infections have been mild, severe cases can fast progress to severe acute respiratory syndrome (SARS), damage to multiple organs, and finally death. Therefore, it is important to find potent therapy against COVID-19 that is essential to delay or halt disease progression ⁽³⁾.

Cranberry is an evergreen group of dwarf shrubs of the *Vaccinium Oxycoccus* ⁽⁴⁾. It is got from nature and handled as sauce and juice in municipal America due to it being abundant with vitamins and minerals. It is also made medicinally as syrup, capsules, chewable tablets, and dispersed powder ^(5,6). The most important pharmacological effects of cranberry are related to its composition liking of quercetin, flavonols, and proanthocyanidins ^(7,8).

Many studies interested in antibacterial properties of cranberry which are mainly confirmed for the treatment of urinary tract infection and gastrointestinal tract infection ^(9,10). The antiviral activity of cranberry is also evaluated in-vitro against the influenza virus and exhibited as a potent inhibitor of viral adhesion to cells ⁽¹¹⁾. Cranberries rich with antioxidant constituents made it a cardiovascular protective medicine by halting the oxidation of LDL and increasing the HDL level, prohibiting platelet aggregation, ameliorating vascular endothelial function, and then declining blood pressure ^(12,13).

Cranberry had anticancer activity trapped metastasis of tumor via necrosis and apoptosis, reduce the generation of the reactive oxygen species and changed cytokine and signal transduction pathway ⁽¹⁴⁾, and regulated glucose levels by suppression of carbohydrate digestive enzymes like α -glycosidase and α -amylase resulting in reducing glucose absorption and enhancement of peripheral insulin sensitivity ⁽¹⁵⁾. This research is aimed to estimate the potential activity of cranberry to enhance the efficacy of standard therapy for COVID-19 infection.

Material and Methods

Patients

The adult-aged patients or older were estimated for competence, given permission with informed consent, and the symptoms of COVID-19 infection were initially considered within 3 days. COVID-19 was diagnosed according to the Chinese Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia with a positive real-time polymerase chain reaction (PCR) assay or a positive chest computerized tomography (CT) scan, significant clinical symptoms like cough, breathing difficulty, pyrexia, and other symptoms of viral airway infection, and lymphopenia considered desired laboratory investigation ⁽¹⁶⁾. Thus, this study included both genders who suffered from mild to moderate symptoms of confirmed COVID-19 infections. Patients with a history of renal stones were excluded.

Study design

This study was an open-label multicenter clinical trial. Simple randomized, and observation were conducted from Nov. 2021 to Feb. 2022 in Imam Al Hussein hospital, Imam Zain-ul-Abdeen hospital, and Alkafeel Super Specialty Hospital in Kerbala province/Iraq. A total of 60 outpatients with age ≥ 18 years suffering from mild to moderate COVID-19 pneumonia were volunteered to do this study, sectioned into two groups. The first group received standard therapy only composed of Favipiravir 1600 mg twice daily on day 1 and 600 mg twice daily for the next 4 days plus supportive therapy according to the Russian Ministry of Health, while the second group received standard therapy plus cranberry 1000 mg capsule (Cranrx of Nature's Way company – USA) per day for 7 days ⁽¹⁷⁾.

Each patient was assessed individually and followed up for 10 days with aiding a case sheet that consisted of age, current disease, and full medical history. Body temperature measurement was done a daily long period of study by digital thermometer recording. Blood Pressure measurement was done by mercurial sphygmomanometer recording. Blood oxygen level (SpO₂) was measured using a digital fingertip pulse oximeter. The severity of cough scored from 0 to 4 as follows: 0, none; 1, infrequently cough; 2, mild cough with the absence of other traditional symptoms; 3, moderate paroxysmal cough with the absence of other traditional symptoms; 4, sharp exhausted cough associated with chest discomfort and sore throat ⁽¹⁸⁾.

The severity of headache is also scaled according to patient's descriptor and activity on the score from 0 to 4 as follows: 0, 0, none (no headache); 1, mild (headache may inhibit few daily activities); 2, moderate (headache probably inhibit some daily activities); 3, severe (headache inhibits daily activities but does not prohibit activities); 4, extremely (headache prohibits daily activities) ⁽¹⁹⁾.

Assessment of white blood count, CRP, ferritin, and D-Dimer level

Complete blood count was tested on day 1, 7, 10 and done by taking a blood sample (about 2 ml) from the vein and transporting it to the laboratory using an anticoagulant Ethylenediaminetetraacetic acid (EDTA) tube and sodium citrate tube. White blood count including lymphocytes was measured using an auto-hematology analyzer (Mindary company – China). C-reactive protein (CRP), Ferritin, and D-dimer level were measured according to ichroma biotechnology technic using ichroma d-dimer kit and apparatus (Boditech Med Inc. – Korea).

Statistical analysis

Statistical Package for Social Sciences (SPSS 22) was used for performing the statistical analysis. The mean and standard error of the mean (Mean \pm SE) were used to present the numerical data and number and percentage (n (%)) were used to present non-numerical data. Independent t test was used to analyze numerical data (like age, body temperature, severity of cough, severity of headache, SpO₂, CRP, D-dimer, and ferritin) after tested normality of distribution of data and Chi-square test was used to analyze non-numerical data (like gender, hypertension, and diabetes). The P values < 0.05 were considered statistically significant ⁽²⁰⁾.

Result

Demographic factors and concomitant chronic disease

There is no significant difference between patients only received STD therapy and patients received STD therapy plus cranberry regarding age, gender, concomitant chronic disease at P < 0.05 as show in Table 1.

Clinical parameter associated with the COVID – 19 infections

Body temperature

Cranberry significantly enhanced the effect of standard COVID – 19 therapies by rapidly lowered body temperature (37.8 C^o) within first 3 days of treatment in comparison with patients' group only received STD therapy as show in Figure 1.

Oxygen saturation

Cranberry significantly improved lung function by elevated SpO₂ level (96.11%) within first 5 days of treatment in comparison with

patients group only received STD therapy as show in Figure 2.

Severity of headache

Cranberry significantly lowered severity of headache within 2nd day to occasional suffered from headache in 5th day of treatment in comparison with patients' group only received STD therapy as show in Figure 3.

Severity of cough

Cranberry significantly lowered severity of cough (mild, isolated cough without additional symptoms) within 3rd day to no cough in 6th day of treatment in comparison with patients group only received STD therapy as show in Figure 4.

Effects of cranberry on complete blood count

Cranberry significantly lowered count of white blood count from 11.23 X 10⁹ to 9.8 X 10⁹ within 7th day of treatment in comparison with patients only received STD therapy at P < 0.05 as show in Figure 5 - A. Cranberry also significantly elevated count of lymphocyte from 0.46 X 10⁹ to 1.22 X 10⁹ and platelet from 90.97 X 10⁹ to 137.23 X 10⁹ in comparison with patients only received STD therapy at P < 0.05 as show in Figure 5 – B & C.

Effects of cranberry on C-reactive protein, D-Dimer, and Ferritin

Cranberry significantly lowered CRP, D-Dimer, and ferritin in comparison with patients with patients only receiving STD therapy at P < 0.05 as show in Table 2.

Discussion

Many mixtures and kinds of nutraceuticals like garlic, cranberries, Fish oil, and broccoli had been exhibited vital activities in enhancing and maintaining the immune system during viral and other microbial infections ⁽²¹⁾.

In this study, cranberry significantly enhanced the effect of standard COVID – 19 therapies by rapidly lowering body temperature (37.8 C^o) within the first 3 days of treatment in comparison with patients who only received the STD therapy group. These results corresponded with another study that suggested consuming polyphenols-rich cranberries promoting the human $\gamma\delta$ -T cell propagation and relieving many symptoms of colds and influenza-like fever ⁽²²⁾.

In this study, cranberry significantly lowered the severity of headache within the 2nd day to occasional suffered from headache on the 5th day of treatment in comparison with patients who only received STD therapy group. The same result was observed in another study that mentioned Vaccinium macrocarpon had the ability to relieve headaches ⁽²³⁾.

The present study showed that cranberry significantly reduced COVID-19 symptoms including the severity of cough and shortness of

breathing in comparison with patients who only received the STD therapy group. Konowalchuk, et al. demonstrated that cranberry juice had antiviral activity against a variety of viruses, such as human enteric virus surrogates, murine norovirus, feline calicivirus, bacteriophage MS2 (ssRNA), and bacteriophage phiX-174 (ssDNA) (24). Another study mentioned that cranberry could reduce the virus titers within one hour of viral contact with cranberry juice (25).

This study exhibited that cranberry significantly reduced white blood cells count, CRP, Ferritin, and D-Dimer and significantly elevated count of lymphocyte and platelet in comparison with patients who only received the STD therapy group. Many studies reveal that cranberry exhibited important roles in enhancing anti-inflammatory markers mainly reducing CRP levels, soluble vascular cell adhesion molecule-1, and plasma IL-1 β in patients prone to deep vein thrombosis (26). Cranberry exerted antiviral activity against some enveloped viruses like Herpes simplex virus 1&2 and influenza virus may be through changing virus envelope glycoproteins and thus, reduced virus abilities to adsorption and entry to host cells (27). Some studies approved that the severity of COVID-19 symptoms including a thrombotic state associated with a degree of lymphopenia and thrombocytopenia which can be improved by polyphenol – containing plants like cranberry that inhibits the signaling pathway of nuclear factor-kappa β (NF- $\kappa\beta$), thus prevent the generating and releasing of the pro-inflammatory cytokine TNF- α and enhance the proliferation and activation of lymphocytes resulting in increased antibody titer against some viruses (28, 29, 30).

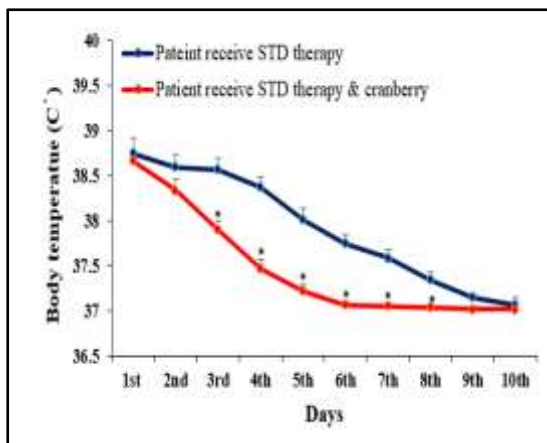


Figure 1. Effect of cranberry on severity of body temperatures.

* Significant effect ($P<0.05$) compared to patients' group only received STD therapy

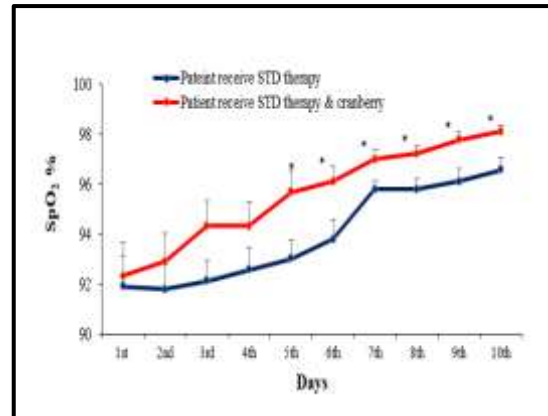


Figure 2. Effect of cranberry on oxygen saturate level.

*Significant effect ($P<0.05$) compared to patients' group only received STD therapy

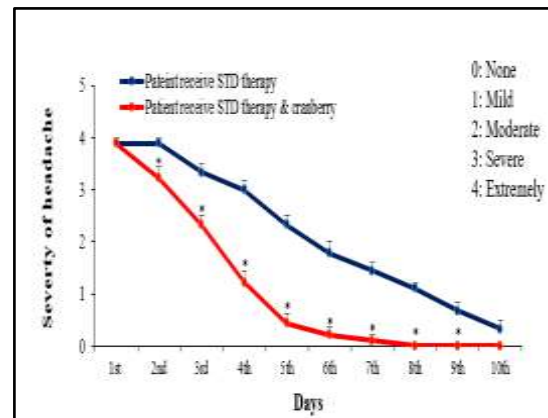


Figure 3. Effect of cranberry on severity of headache.

*Significant effect ($P<0.05$) compared to patients' group only received STD therapy

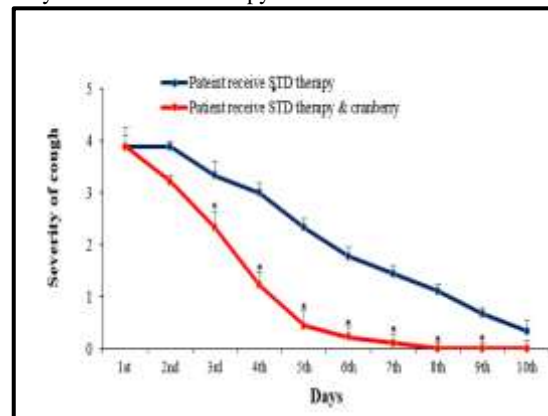


Figure 4. Effect of cranberry on severity of cough.

0: None 1: Infrequently cough 2: Mild, cough with the absence of other traditional symptoms 3: Moderate paroxysmal cough with the absence of other traditional symptoms. Sharp exhausted cough associated with chest discomfort and sore throat. *: Significant effect ($P<0.05$) compared to patients' group only received STD therapy

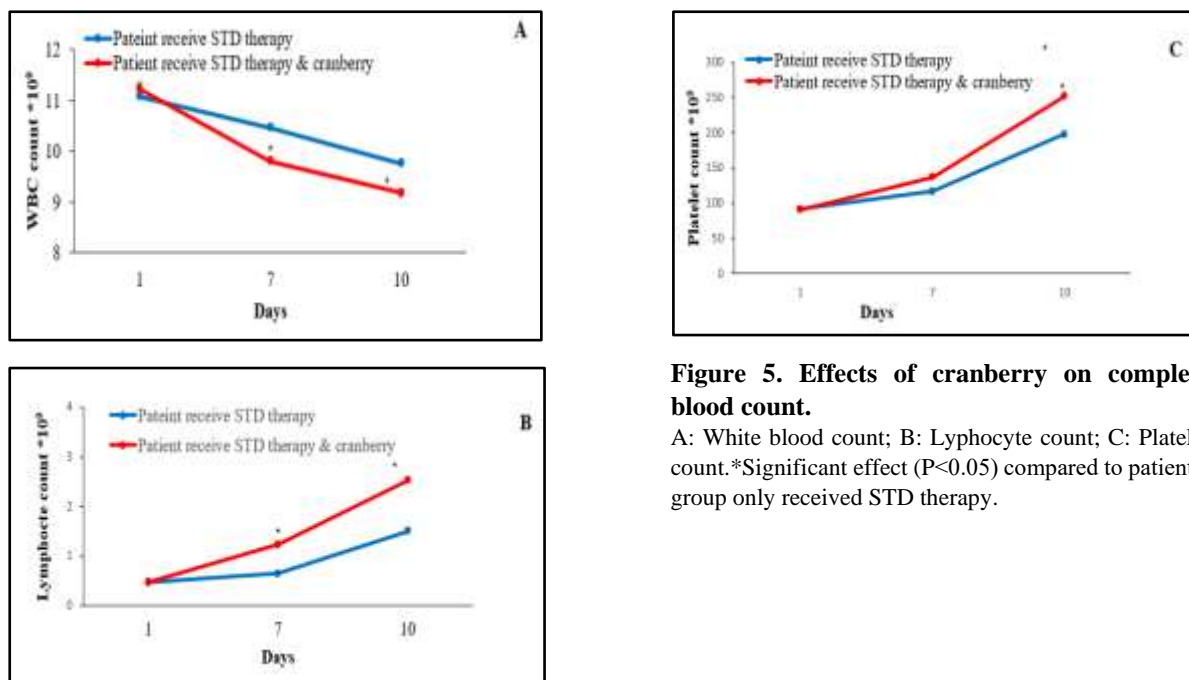


Figure 5. Effects of cranberry on complete blood count.

A: White blood count; B: Lymphocyte count; C: Platelet count. *Significant effect (P<0.05) compared to patients' group only received STD therapy.

Table 1. Demographic factors and concomitant chronic disease of patient groups on admission.

Variable	Patient received STD therapy groups		P value
	Without cranberry	With cranberry	
Age, mean ± SE	46.4 ± 3.44	45.8 ± 3.03	0.897
Gender, n (%)	Male	5 (33.3%)	0.409
	Female	12 (80%)	
Hypertension, n (%)	No	4 (26.7%)	0.690
	Yes	11 (73.3%)	
Diabetes, n (%)	No	13 (86.7%)	0.624
	Yes	2 (13.3%)	

Table 2. Effects of cranberry on CRP, D-Dimer, and Ferritin.

Variable	Patient received STD therapy groups		P value	
	Without cranberry	With cranberry		
CRP (mean ± S.E)	Before	15.43 ± 1.17	16.96 ± 1.07	0.469
	After	8.17 ± 0.5	6.22 ± 0.32	0.027
D-Dimer (mean ± S.E)	Before	689.53 ± 98.3	636.13 ± 93.92	0.696
	After	438.07 ± 41.94	223.7 ± 22.32	0.0001
Ferritin (mean ± S.E)	Before	218.95 ± 23.08	199.1 ± 23.01	0.732
	After	131.77 ± 11.04	101.15 ± 4.4	0.002

Conclusion

In conclusion, Cranberry significantly improved STD therapy by reducing inflammatory response and enhancing lung function via maintaining normal SPO2% level and relieving clinical symptoms of COVID-19 infection.

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This study was conducted in Imam Al Hussein hospital, Imam Zain-ul-Abdeen hospital, and Alkafeel Super Specialty Hospital. Therefore, we extend our thanks and appreciation to all members of the said department, including nurses,

service workers, resident doctors, and statistics employees.

Conflicts of Interest

There is no conflict of interest, according to the authors.

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Ethics Statements

The study was approved by the scientific and ethical committee, Kerbala University, college

of pharmacy with the project being assigned No: 2021HU7 in addition to patient approval.

Author Contribution

Atheer Majid Rashid Al-juhiashi designed the study; Munaf Aal-Aaboda performed, collected data; Atheer Majid Rashid Al-juhiashi, discussed the results and strategy and made statistical analysis; Amal U mosa, writing the manuscript; and Atheer Majid Rashid Al-juhiashi, approved of the version to be published.

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