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Original Research Paper

Effects of antioxidant supplement on immune health and physical wellbeing: A randomized, controlled trial

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ABSTRACT

Background: Maintaining a healthy immune system came to the forefront of people's minds as SARS-CoV-2 (COVID-19) was introduced. Antioxidants contained in dark berries have been shown to support the physical wellbeing of otherwise healthy adults. Adding a supplement rich in dark berries and citrus essential oils contributes antioxidants to the body and serves as an aid to reduce free radicals.

Aim: We evaluated the effects of an antioxidant rich supplement on immune health and overall physical wellbeing compared to a control group.

Method: Participants were otherwise healthy adults, aged 18–60 years old, and were placed in either the antioxidant supplement group or control group using adaptive randomization. Data was collected at day 1 and 60. The Physical Health Questionnaire was used to measure the primary outcomes of this study. The immune health was reflected through the Jackson Symptom Scale.

Results: 155 participants were analyzed. Participants who consumed the antioxidant beverage saw improvements to overall health which dramatically exceeded those of the control group. The sleep domain produced improvements which represented disturbances in sleep habits as they pertain to general health. Those in the supplement group who reported illness, had illnesses lasting 1–2 days while those in the control group had illnesses lasting from 1 to 9 days.

Conclusion: Length of illness was shorter and sleep duration improved in the supplement group compared to the control group. Daily consumption of 60 ml of the antioxidant drink NingXia Red® showed significant improvement after 60 days.

1. Introduction

1.1. Background

Fruits and vegetables are high in antioxidants that serve to aid in eliminating free radicals from the body, giving the immune system more opportunity to deal with other foreign invaders coming from airborne pathogens rather than food sources [1]. Antioxidants have long been touted as healthy additions to a preventive diet for those in search of more natural foods and supplements to support their immune health and overall wellbeing. Strengthening and maintaining a healthy immune system through nutrient-rich diet is central in preventing infection, which was prioritized with the introduction of SARS-CoV-2 (COVID-19) to the United States in 2020 [2]. Ingredients such as wolfberry, blueberry, aronia, cherry, prune, and pomegranate contain high levels of antioxidants that have been shown to promote protection against

disease and immunomodulation [3–9]. Citrus essential oils have been used for culinary use for decades and continue to increase in popularity both in ingestion and inhalation [10]. Essential oils can be pressed and extracted from the peels of the citrus fruit. The peels have been found to contain various antioxidants that can contribute to free radical reduction within the body [11,12]. While many of these berries and citrus essential oils have been studied alone, there is a gap in the research on combining antioxidant-bearing fruits. Yet, the majority of dietary supplements available for consumers are developed using a combination of antioxidant-rich ingredients. This study will provide more evidence that dark berries provide support to the body's overall physical wellbeing, and consumption of a proprietary blend of berry juices and citrus essential oils successively allows the body to stay in optimal immune health for both men and women.

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1.2. Objective

The purpose of this study was to evaluate the real-world effects of an antioxidant rich supplement on immune health and overall physical wellbeing, as measured by multiple outcome measures and compared to a control group.

This study is reported using the CONSORT checklist for reporting clinical trials with the Herbal Medicinal Interventions extension.

2. Methods

2.1. Trial Design

This study is part of the Antioxidant Beverage (AOB) Trial, a randomized controlled trial assessing the effects of an antioxidant rich supplement beverage on immune health and physical wellbeing. In order to control for age as well as sex and region during analysis, adaptive randomization was used. Participants were placed in either an intervention group who consumed the antioxidant beverage or a control group who continued their daily routines without the intervention.

No changes in the design were made during the study period. Data was collected by each participant throughout the study through a secure survey platform. On-line surveys were used for data collection at day 0 and day 60 through a secure portal. All participants, in both the supplement group or the control group, were instructed to not change their routine for 60 days.

2.2. Participants

Participants were eligible to participate if they met the following inclusion criteria, screened through an online survey for eligibility: aged 18–65 years of age, healthy adults, living in the United States at the start of the study. Exclusion criteria included: if they were currently trying to conceive or pregnant, smokers, those who have experienced allergic reactions to citrus fruit, berries, or stevia, or had a past or present positive COVID-19 diagnosis. All participants gave informed consent before starting the study and verified they understood the study instructions in English and would comply with the study procedures at time of consent.

A quasi-snowball method of recruiting participants was used in South Carolina, Alabama, and Tennessee. A secure data entry portal was used in collecting participant information which required each participant to have access to the internet through a computer or smart device on day 0 and day 60.

The study was conducted in accordance with the Declaration of Helsinki and adhered to Good Clinical Practice guidelines. Ethical approval for the study and the informed consent documents were obtained. Approval for the protocol was obtained by a central IRB, Advarra, prior to the recruitment of the first participant. The trial was also registered at ClinicalTrials.gov (NCT04499560). All participants provided written informed consent prior to any intervention procedures being assigned by the research team or performed by the participant.

2.3. Intervention

The dietary supplement for this study was NingXia Red®, a proprietary blend of dark berry juices and citrus extracts. The supplement contains extracts from dark pigmented fruits rich in antioxidants, including ningxia wolfberry (*Lycium barbarum*), blueberry (*Vaccinium corymbosum*), plum (*Prunus domestica*), cherry (*Prunus avium*), aronia (*Aronia melanocarpa*), and pomegranate (*Punica granatum*). It also includes a proprietary blend of orange (*Citrus sinensis*), yuzu (*Citrus junos*), lemon (*Citrus limon*), and tangerine (*Citrus reticulata*) essential oils. This antioxidant beverage is marketed as a dietary supplement in the United States and is available worldwide.

Participants in the supplement group consumed 60 ml of the product each day for 60 total days. They could drink it at any point in their day,

at a time they would take any other supplement. Those in the control group did not consume the product. Participants in both groups agreed to delay any changes to lifestyle, fitness, medications, diet, and supplements until after the study concluded. Compliance was monitored in both groups through routine check-ins via phone, text, or email confirming that each participant was maintaining their pre-intervention lifestyles. Compliance was also included for the intervention group in each data collection segment by asking participants to report on their intervention supply levels.

2.4. Outcomes

The prespecified primary endpoint to measure efficacy was the Physical Health Questionnaire (PHQ), which is a modified version of Spence's behavioral scale, was used to measure the primary outcomes of this study. The original measure was not intended to measure physical health; this scale utilizes only the physical health questions which have been found to have significant validity [13]. The PHQ provides measures on four domains of health, including gastrointestinal health, headaches, sleep disturbance, and respiratory health. Possible scores for these domains range from 3 to 21 (headache domain) and 4–28 (gastrointestinal health and sleep domains) with higher scores indicating better health. Respiratory measures did not have a predetermined range.

The PHQ has been validated in multiple populations. Cronbach's alpha from tests on internal consistency are .83 (gastrointestinal domain), .88 (headaches domain), .80 (sleep disturbance domain), and .66 (respiratory domain) (Ruddle, 2005). The PHQ was administered at baseline, and at the end of month 2.

Immune health was also measured as incidence, severity, and duration of upper respiratory infections during the trial. These outcomes were measured through the Jackson Symptom Scale (JSS) (Jackson, 1958).

2.5. Sample size

A power analysis was conducted using G*Power. To achieve a power of .9 and significance level of .05, the minimum number of participants required to observe a small effect size is 144, with 72 in each group. To allow for participants who would be disqualified due to the COVID-19 pandemic and who would be lost to follow-up, a total of 160 participants were recruited.

2.6. Randomization and blinding

Participants were adaptively randomized, controlling for region, sex, and age. Adaptive randomization prevents bias and allows balanced treatment assignments within the demographics of sex and age. Participants were randomly assigned to a group after they were screened and qualified to participate based on their inclusion criteria. They were consented by the research team in person. After they agreed to participate, the participants were given their study instructions and study materials if they were a part of the intervention group and study instructions only if in the control group. Randomization was also assessed through t-tests of participant demographics. There were no statistical differences between groups on educational attainment, income, marital status, race, and employment status.

Participants were not blinded in this study due to the nature of having a control group. The intervention group were not told the name or ingredients of the product they were consuming other than it was an antioxidant beverage.

2.7. Statistical analyses

Demographics and randomization were assessed using Fisher's exact test. Outcomes were grouped by domains and assessed using analysis of covariance (ANCOVA) with baseline scores as a covariate. Levene's test

was used to confirm the assumption of homogeneity of variance. Shapiro Wilk’s test was used to confirm normality of residuals. The potential for interactions for sex, age, and underlying health status was also assessed. All data were analyzed using STATA v16.

3. Results

3.1. Participant flow

Participants were recruited from August 2020 to October 2020 from participating centers in Tennessee, Alabama, and South Carolina. Participants were informed of the study procedures and provided informed consent from regional centers. If they were randomized into the supplement group, they were given the drink after they signed their consent form. A total of 463 participants were screened for participation. Of those screened, 160 met the inclusion criteria and agreed to provide informed consent. During the study, 3 participants became pregnant and were withdrawn and an additional 2 were removed for protocol violations. A total of 155 participants were analyzed for the primary outcomes. See Image 1: Flow Chart.

the control group. Almost half (49.06 %) of all participants held a college degree. See Table 1.

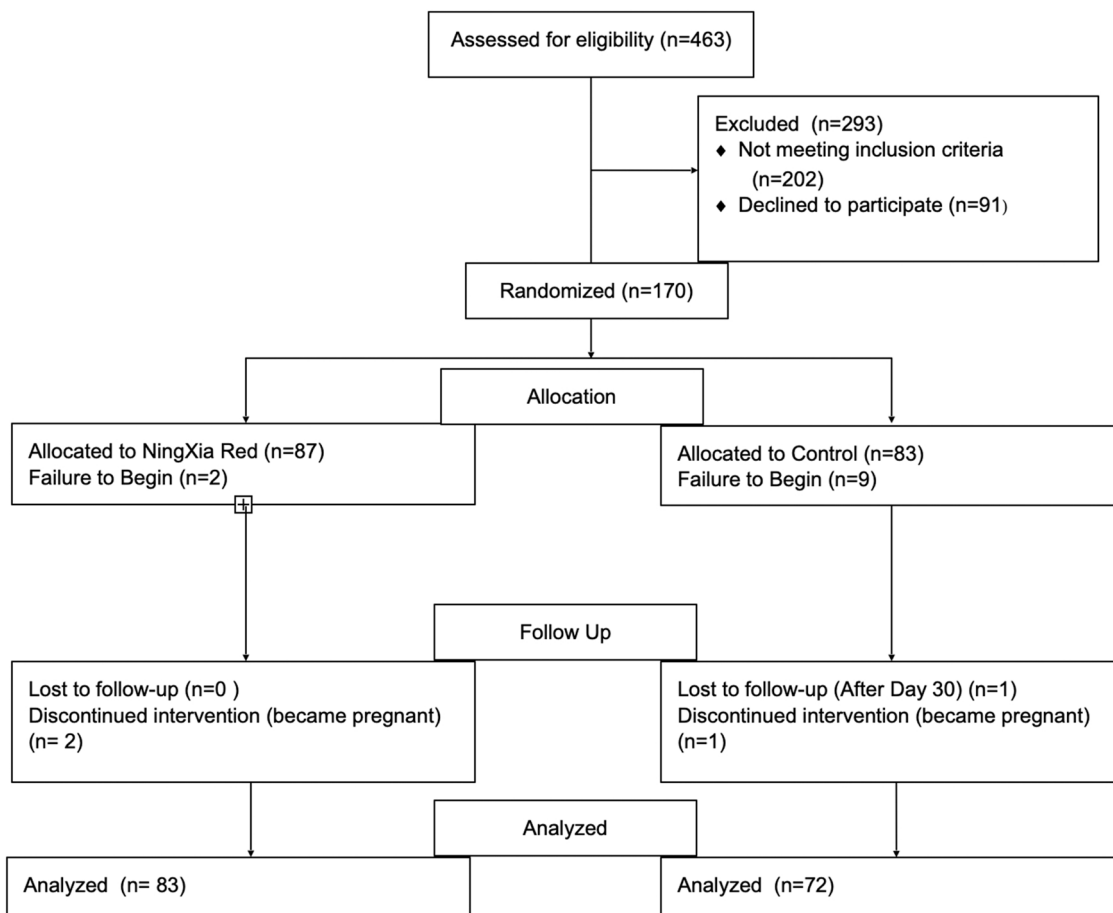
3.3. Numbers analyzed

In the final numbers analyzed, 72 individuals were in the control group and 83 individuals in the drink group. Participants were analyzed on an intent-to-treat basis.

3.4. Physical health outcomes

At the start of the study, average scores for the control group on the global PHQ measure were 19.16 (SD=9.40) and those in the NingXia Red group were 23.09 (SD=11.45). Preliminary analysis identified significant differences between the two groups ($t(157) = -2.34, p = .021$). To fully capture the change caused by NingXia Red, endpoint change scores were calculated by subtracting baseline scores from outcome scores. These scores were then compared between groups for significant differences.

On day 60, scores had decreased by 3.49 (SD=6.96) in the control group and the supplement’s improvement at 6.30 (SD=8.81) in the



3.2. Baseline data

In this study, participants were predominantly white, married and female (92.45 %, 74.21 %, and 76.73 %, respectively) in the age range of 20–65 years. Age distribution was approximately normal. Mean age for the intervention group was 40.88 (SD:11.47) and 39.70 (SD: 11.42) for

supplement group. After confirming assumptions of equality of variance, an independent samples t test was conducted to assess the size of the change. These changes were statistically significant, ($t(153) = 2.21, p = .029$). These changes were also statistically significant with a Cohen’s *d* of .36. Those who consumed the antioxidant beverage saw improvements to overall health which dramatically exceeded those of the control group. To identify the specific areas of improvement, each domain was evaluated individually. The sleep domain was the only domain to

Table 1
Participant Demographics.

Demographics	NingXia Red	Control	Total	p
Sex				.454
Male	22	15	37	
Female	64	58	122	
Race				.401
White	80	67	147	
Black	1	3	4	
Other	5	3	8	
Marital Status				.772
Married	63	55	118	
Single/Never Married	16	13	29	
Widowed, Divorced, Separated	7	5	12	
Employment Status				.663
Employed, full time	40	28	68	
Employed, part time	18	15	33	
Homemaker	21	22	43	
Part-time, Student, Retired	7	8	15	
Educational Attainment				.840
High School	3	2	5	
Some College	23	16	39	
Bachelor's Degree	40	38	78	
Advanced Degree	20	17	37	
Income				.920
< \$50k	29	21	50	
\$50k-\$99k	34	31	65	
\$100k-\$150k	17	17	34	
> \$150k	6	4	10	

produce statistically significant improvements (See Table 2).

3.5. Sleep domain

The sleep domain measures disturbances to sleep habits related to general health. Scores range from 0 to 24, with higher scores indicating greater interruptions to sleep habits. At the start of the study, the average sleep domain score for those in the control group was 8.48 (SD=4.06), which was similar to the average for the NingXia Red group of 9.77 (SD=4.70). The scores were not significantly different ($t(157) = -1.83, p = .069$).

The improvements were statistically significant on day 60. In the NingXia Red group, sleep change scores averaged -2.77 (SD=4.37) as compared to the control group change scores of -0.90 (SD=3.67). These changes were also statistically significant ($t(153) = 2.857, p = .005$) with a Cohen's d of .54. Those who consumed the supplement saw improvements to sleep habits which dramatically exceeded those of the control group.

3.6. Immune health

3.6.1. Incidence and duration of respiratory infection symptoms

There was a total of 23 respiratory illnesses during the trial; 11 occurred in the control group and 12 occurred in the NingXia Red group. Incidence in illness between groups was not statistically significant ($X^2(1, N = 155) = 0.02, p = .886$). Mean duration of illness, however, was substantially longer in the control group. Most illnesses in the supplement group were 1 or 2 days in duration while those in the control group experienced illnesses ranging from 1 to 9 days.

Mean duration of symptoms in the control group was 3.09 days (SD=2.84) compared to a mean duration of 1.58 days in the supplement group (SD=1.44). Those in the control group experienced upper respiratory infections that were nearly twice as long as those in the supplement group. However, this difference was not statistically significant, ($t(21) = 1.624, p = .119$), likely due to the small number of illnesses in the overall sample ($n = 23$).

3.6.2. Severity of respiratory infection

To evaluate the severity of the respiratory infections among groups,

Table 2
Change Scores From Baseline to Days 30 and 60.

Measure	NR Mean (SD)	CT Mean (SD)	t (155)	Cohen's d	p
Global PHQ, day 30	6.17(7.76)	2.52 (5.26)	3.39	.55	< 0.001
Global PHQ, day 60	6.30 (8.81)	3.49 (6.96)	2.21	.36	.029
Sleep Domain, day 30	2.82 (3.79)	0.90 (2.72)	3.59	.66	< 0.001
Sleep Domain, day 60	2.77 (4.37)	0.90 (3.67)	2.86	.54	.005

Guide: Values shown as mean(standard deviation)

NR: NingXia Red Group; CT: Control Group

respiratory illness was classified into “mild” representing symptoms lasting less than a day and “moderate-to-severe” representing symptoms lasting 2–9 days. Logistic regression was used to assess the impact of supplement consumption on severity of respiratory illness. The model was statistically significant at the .10 level ($X^2(1, N = 23) = 3.58, p = .059$) indicating that the model was able to distinguish between those who did and did not consume the antioxidant beverage. Supplement consumption was associated with an odds ratio of 5.25, indicating that participants who did not consume NingXia Red were over 5 times more likely to develop moderate-to-severe respiratory illness than those who did consume the supplement (90 % CI: 1.17, 23.65). While the .10 level of significance is not traditionally used for large sample sizes, it is an appropriate tool for assessing significance of small samples, such as this ($n = 23$).

3.7. Adverse events

Participants were monitored for adverse events. One individual in the supplement group noted that the product caused “vivid dreams” approximately 1 week after the study began. No other effects were noted. The dark fruit and essential oil supplement was well tolerated among the participants and is able to boost health without posing significant risk of side effects.

4. Discussion

4.1. Limitations

This study was conducted during the COVID-19 pandemic which caused underlying stress due to its unpredictability in spread [14]. Global stress is known to be related to altered sleep patterns [15]. With this evidence, the potential effect size of NingXia Red on sleep duration could be greater than found in this study due to the sporadic negative effects of the pandemic on sleep and overall health dependent on time and region of COVID-19 surges.

Additionally, participants were evaluated for 60 days. Certain populations could require a longer intervention time for effects to be documented. For example, older adults often exact larger doses of supplements due to pharmacokinetic differences compared to younger adults [16]. In the future, studies should examine the effects of an antioxidant beverage for periods of 4–6 months or longer to determine whether the benefits continue to increase.

4.2. Generalizability

This study population reflects demographics more likely to consider the use of dietary supplements in their daily lives. College educated, white women have a higher prevalence toward purchasing and using herbal supplements in the United States [17].

4.3. Interpretation

With the surge of the COVID-19 pandemic came a renewed vigor toward pursuing tools to support immune health and overall wellness as people searched for ways to balance healthy lifestyle choices, social distancing, washing hands, and wearing masks in order to promote optimal health [18]. Many populations made dietary changes such as consuming more fruits and vegetables to aid in the betterment of their health [19]. Fruits and vegetables contain antioxidants that can reduce oxidative stress on the body's systems. Reducing oxidative stress promotes wellness and strengthens the immune system [2]. Taking supplements rich in antioxidants as an addition to other healthy habits promotes better health to fight infection and disease [20]. NingXia Red's proprietary formula containing dark berries and essential oils, pressed from the peels of citrus fruit, provide antioxidants that perform the key tasks of reducing oxidative stress within the body [21].

4.4. Conclusion

Daily consumption of 60 ml of NingXia Red resulted in an increase in sleep duration when used consistently for 60 days. Length of illness was shorter in the supplement group compared to the control group. The supplement improved both immune response and overall health through a safe and healthy method of use.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki and adhered to Good Clinical Practice guidelines. Ethical approval for the study and the informed consent documents were obtained. Approval for the protocol was obtained by a central IRB, Advarra, prior to the recruitment of the first participant.

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CRedit authorship contribution statement

Jessie Hawkins: Conceptualization, Supervision, Formal analysis, Writing – original draft. **Christy Y Hires:** Methodology; Investigation; Writing – original draft, any Editing for reviewers during publication process as Corresponding Author. **Elizabeth Dunne:** Investigation; Writing – review & editing. **Lindsey Keenan:** Writing – review & editing; Visualization.

Disclosures

All authors of this study confirm there are no conflicts of interest to declare. This was an investigator-initiated study and the design, management, and analysis of this trial was completely independent of the research sponsor. Additionally, the sponsor has no influence in the interpretation, reporting, or dissemination of the trial results.

Registration

The Antioxidant Beverage Trial was registered at ClinicalTrials.gov

Identifier: NCT04499560. All participants provided written informed consent prior to any intervention procedures being assigned by the research team or performed by the participant.

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