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REVIEW

Dietary Beetroot Juice – Effects in Patients with COPD: A Review

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Abstract: Chronic Obstructive Pulmonary Disease (COPD) exerts a severe toll on human health and the economy, with high prevalence and mortality rates. The search for bioactive components effective in the treatment of COPD has become a focal point of research. Beetroot juice, readily accessible and cost-effective, is noted for its ability to enhance athletic performance and for its preventive and therapeutic impact on hypertension. Beetroot juice is a rich source of dietary nitrates and modulates physiological processes via the nitrate-nitrite- nitric oxide pathway, exerting multiple beneficial effects such as antihypertensive, bronchodilatory, anti-inflammatory, antioxidant, hypoglycemic, and lipid-lowering actions. This paper provides a review of the existing research on the effects of beetroot juice on COPD, summarizing its potential in enhancing exercise capacity, lowering blood pressure, improving vascular function, and ameliorating sleep quality among patients with COPD. The review serves as a reference for the prospective use of beetroot juice in the symptomatic improvement of COPD, as well as in the prevention of exacerbations and associated comorbidities.

Keywords: chronic obstructive pulmonary disease, beetroot, nitrates, nitric oxide, exercise, vascular function

Introduction

Chronic obstructive pulmonary disease (COPD), a prevalent and major global public health issue, is characterized by a high incidence, mortality, and healthcare burden.[1,2] COPD is primarily caused by exposure to harmful particles or gases, especially cigarette smoke and pollutants, leading to partially reversible airflow limitation and progressive respiratory syndrome.[3,4] However, the etiology of COPD has not been fully elucidated. Known key mechanisms include oxidative stress, inflammatory response, protease/antiprotease imbalance, and excessive mucus secretion.[5–9] Currently, the search for safe and effective candidate drugs for treating COPD from natural products and their extracts, known for their antioxidant and anti-inflammatory activities, has become a prominent research focus.

Beetroot, also known as beet, is one of the few highly bioactive vegetables, containing bioactive components such as nitrates ($NO3^-$), betalains, carotenoids, flavonoids, phenolic acids, minerals, and ascorbic acid.[10] Recent research has revealed that beetroot juice and its bioactive constituents offer a variety of health benefits, particularly nitrates, including anti-inflammatory,[11] antioxidant,[11] lipid-lowering,[12] hepatoprotective,[13] blood sugar-lowering,[13] blood pressure-lowering,[14] regulation of gut microbiota imbalance,[15] anticancer,[16] kidney-protective,[17] and promotion of vascular regeneration.[18] Relevant studies have indicated that beetroot juice, rich in nitrates, can improve symptoms and prevent acute exacerbations in patients with COPD.[19] This article aims to review the research progress and underlying mechanisms of dietary nitrates in beetroot juice regarding their potential therapeutic effects on COPD. The findings of this review provide a reference for further research on the use of beetroot juice and its bioactive constituents in the treatment of chronic obstructive pulmonary disease.

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Materials and Methods

We conducted a comprehensive literature search using various databases, including PubMed, Cochrane Library, Embase, CNKI (China National Knowledge Infrastructure), and Wanfang Data, to identify relevant medical articles up until February 24, 2024. The search strategy incorporated the following keywords: COPD, beetroot, nitrate, betalains, anti-inflammatory, antioxidant, etc. We aimed to retrieve articles that examined the relationship between beetroot and COPD, particularly focusing on the effects of beetroot's bioactive components on inflammation and oxidative stress. In addition to the electronic database search, the reference lists of each retrieved article were manually searched to identify further relevant studies. This approach helped ensure the inclusion of any additional articles that might have been missed in the initial search.

Dietary Nitrate Metabolism

Traditionally, nitrate and its metabolic product nitrite ($NO2^-$) as additives in meat processing have been considered to pose risks to human health and the natural environment.[20] However, most experts now believe that dietary nitrates naturally present in vegetables may be harmless to the human body and offer benefits such as and prevention of cancer, cardiovascular diseases[21,22] and improvement of exercise capacity.[23] The beneficial effects of beetroot juice on the human body are largely attributed to its high nitrate content.[24] After consuming beetroot juice, dietary nitrates are rapidly and efficiently absorbed in the stomach and small intestine, with peak plasma nitrate levels reached within one hour.[21,25–27] Approximately 75% of the nitrates are eventually excreted through urine, while the remaining can be reabsorbed through the kidneys, intestines, and salivary glands.[21,28–30] Studies have shown that the reabsorption of circulating nitrate in the salivary glands is active, with over 25% of the nitrates eventually reduced to nitrite by commensal facultative anaerobic bacteria in the oral cavity.[21,31] Plasma nitrite levels increase within 30 minutes, and the high levels can be maintained for several hours due to the entero-salivary circulation of nitrates.[21,32] In the acidic gastric environment, nitrite can undergo protonation to form nitric oxide (NO).[33,34] Nitric oxide plays a crucial role in maintaining human physiological health. This recently discovered pathway, known as the nitrate-nitrite-NO ($NO3^-$ - $NO2^-$ - NO) pathway, functions as a supplementary system to the classical L-arginine/nitric oxide synthase (NOS) pathway in the body, contributing to the production of NO.[35,36] Nitric oxide plays a pivotal role in modulating various inflammation-associated signaling pathways, acting as an essential molecule for host defense mechanisms.[37] It impedes the activation of nuclear transcription factor κb (NF-κb), and concurrently attenuates the levels of multiple inflammatory cytokines within airway epithelial cells, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interferon-γ (IFN-γ). This activity contributes significantly to the mitigation of airway inflammation.[38] Moreover, NO triggers the activation of soluble guanylate cyclase upon its synthesis, facilitating the generation of cyclic guanosine monophosphate (cGMP) as a secondary messenger.[39] Through the stimulation of cGMP-dependent protein kinases (PKGs), phosphodiesterases (PDEs), and cGMP-sensitive ion channels, cGMP plays an instrumental role in orchestrating a wide array of physiological functions. These functions encompass, but are not limited to, the enhancement of airway clearance, promotion of bronchodilation, and the suppression of platelet aggregation (Figure 1).[40–43]

Plasma Nitrate and Nitrite

Presently, several studies have demonstrated that the consumption of beetroot juice significantly elevates the concentration of plasma nitrates in patients with COPD. A systematic review and meta-analysis that integrated eight studies showed that, compared to a placebo, a diet rich in nitrate from beetroot juice significantly increased the levels of plasma nitrates(*MD*=475.15; *95% CI* (137.52, 812.78), p=0.006) and nitrites(*MD*=235.82; *95% CI* (182.34, 289.29), $p< 0.00001$) in patients with COPD.[44] A double-blind, placebo-controlled, randomized study involving 13 subjects with mild to moderate COPD revealed that those who consumed beetroot juice rich in nitrates exhibited a significant increase in plasma nitrate concentration compared to participants who consumed beetroot juice depleted of nitrates.[45] A double-blind, placebo-controlled, crossover single-dose study involving 21 patients with COPD showed that after consuming nitrate-rich beetroot juice, plasma nitrate levels significantly increased from baseline(37.0 ± 16.4μM baseline vs 820.2 ± 187.7μM post dosing; $p<0.0001$), and plasma nitrite levels also rose by 1.57±0.98μM, an effect not observed in the

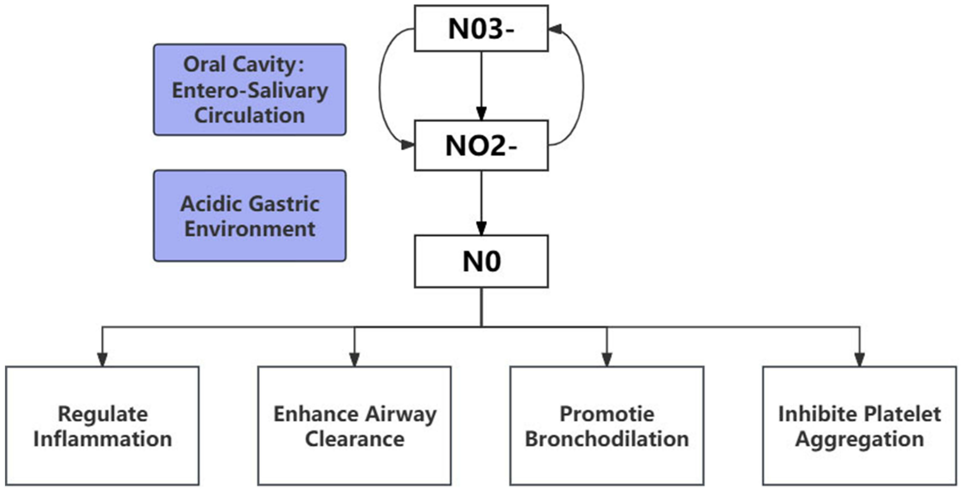

Figure 1 Dietary Nitrate Metabolism. The nitrates present in beetroot juice are reduced to nitrite by commensal facultative anaerobic bacteria in the oral cavity, participating in the entero-salivary circulation of nitrates. Nitrite undergoes protonation to form nitric oxide (NO) in the acidic gastric environment. NO plays a role in modulating inflammation, enhancing airway clearance, promoting bronchodilation, and inhibiting platelet aggregation, among other physiological functions.

control group.[46] A 14-day double-blind, randomized, placebo-controlled, crossover trial demonstrated that compared to the placebo group, nitrate-rich beetroot juice intervention significantly augmented the concentrations of plasma nitrates (+1007 vs −3.1µM; p=0.025) and nitrites(513.7 vs −17 nM; p=0.02) in patients with stable COPD.[47] This aligns with the findings from their preliminary research.[48] A single-blind, placebo-controlled, crossover study involving 15 elderly COPD patients showed that, compared to the intake of a placebo beverage, consuming beetroot juice significantly elevated levels of plasma nitrates and nitrites, with plasma nitrates levels increasing by 938% and nitrites levels by 379%.[49] Beijers et al conducted a 7-day double-blind, randomized, crossover, placebo-controlled trial involving 20 stable patients with mild to moderate COPD. On the seventh day of nitrate intervention, both plasma nitrate and nitrite levels significantly doubled, while there was no difference in plasma nitrate and nitrite levels between the first and seventh days in the placebo group.[50] In the study by Wisor et al on the effects of beetroot juice on the sleep quality of patients with COPD, it was observed that the plasma nitrate concentration after waking was significantly higher(269±17 µM vs 27±3 µM; p<0.05) in patients with COPD who received beetroot juice intervention compared to the placebo group, although nitrite concentration was unaffected.[51] In a double-blind, randomized crossover study by Pavitt et al on hypoxic patients with COPD, supplementation with nitrate-rich beetroot juice led to an 887% increase in plasma NO3- and an 84% increase in plasma NO2- after 180 minutes.[52] Although Friis et al did not directly measure nitrate levels, an increase in nitrite concentration was observed following the intervention with beetroot juice(538.5±186.6 nM vs 140.0±68.9 nM; p<0.01).[19] The latest randomized controlled study results show that after consuming beetroot juice, which is rich in nitrates, patients with COPD experienced an increase in plasma nitrate levels, a phenomenon not observed in the placebo group.[53] The details of each trial can be found in Table 1.

Exercise Performance and Symptoms

Patients with COPD commonly experience dysfunction of limb muscle function, accompanied by breathlessness, resulting in a significant reduction in exercise performance. This, in turn, leads to a loss of physical function and limitations in activities of daily living.[54,55] Studies have indicated that regular exercise training can ameliorate symptoms of dyspnea and exercise tolerance in patients with COPD.[56] Given that beetroot juice, which is rich in nitrates, has been observed to enhance the exercise capacity of healthy individuals, a number of studies have focused on whether beetroot juice can serve as a dietary therapeutic agent to improve exercise performance and symptoms in patients with COPD.[57] Research by Berry et al found that acute intake of $NO3^-$ rich beetroot juice could prolong the time-to-exhaustion during submaximal constant work rate exercise in patients with COPD without increasing their oxygen consumption. The study population included in this research meets the criteria of forced expiratory volume in 1 s / forced vital capacity (FEV_1

Table 1 The Details of Referenced Trials

Trial	Type of Trial	No. Patients	Dosage	Length (days)	Nitrate	Nitrite
Alshafie S et al (2021)[44]	Systematic review and Meta-analysis	-	-	-	↑	↑
Shepherd AI et al (2015)[45]	Double-blind, placebo-controlled, randomized study	13	6.77 mmol	2.5	↑	-
Curtis KJ et al (2015)[46]	Double-blind, placebo-controlled, crossover single-dose study	21	12.9 mmol	-	↑	↑
Kerley CP et al (2019)[47]	Double-blind, randomized, placebo-controlled, crossover trial	8	12.9 mmol	14	↑	↑
Kerley CP et al (2015)[48]	Randomized, placebo-controlled, double-blinded, crossover study	11	140 mL	-	↑	↑
Berry MJ et al (2015)[49]	Single-blind, placebo-controlled, crossover study	15	-	-	↑	↑
Beijers RJHCG et al (2018)[50]	Double-blind, randomized, crossover, placebo-controlled trial	20	~8 mmol	7	↑	↑
Wisor JP et al (2021)[51]	Double-blind, counterbalanced design	15	~6.2 mmol	-	↑	None
Pavitt MJ et al (2022)[52]	Double-blind, randomized crossover study	20	12.9 mmol	-	↑	↑
Friis et al (2017)[19]	Randomized, double-blinded, PL-controlled, crossover study	15	600 mg	7	-	↑
Alasmari AM et al (2024)[53]	Prospective, double-blind, parallel group, randomised, placebo-controlled trial	70	400 mg	84	↑	↑

Notes: None, No increase in the levels of the substance was detected in the plasma; "-", not specified; ↑, An elevated level of the substance has been detected in the plasma.
Abbreviation: No. patients, Number of patients.

/FVC) > 70% and FEV_1 < 20% of predicted. However, the study found no significant difference in dynamic lung hyperinflation, dyspnea, and leg discomfort scores between beetroot juice and placebo, either isotime or at the end of exercise.[49] A multicenter, double-blind, placebo-controlled, randomized parallel-group study in patients with COPD grades II–IV who meet the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) showed that, after an 8-week pulmonary rehabilitation course, the nitrate-rich beetroot juice active treatment group showed significant improvements in the Incremental Shuttle Walk Test (ISWT) walking distance and daily step count compared to the nitrate-depleted placebo group. However, there were no differences in Medical Research Council (MRC) dyspnea scores, COPD Assessment Test (CAT), and Hospital Anxiety and Depression Scale (HADS) scores.[58] These findings are consistent with the outcomes of two double-blind, randomized controlled trials conducted by Kerley et al[47,48] Research by Pavitt et al also confirmed that nitrate-rich beetroot juice could enhance the exercise capacity of hypoxic patients with COPD.[52] The population involved in this study also consisted of COPD patients meeting the GOLD stages II–IV. In the most recent Oral Nitrate for Blood pressure in COPD (ON-BC) study, Alasmari et al assessed the exercise capacity of stable patients with COPD through the 6-min walk test (6MWT), and results showed improvement in the 6MWT distance in the active treatment group, but no significant improvements were observed in the CAT score and MRC dyspnea score.[53] This aligns with the perspective of Webb AJ et al. In his study, an intervention with beetroot juice for 90 days in 81 patients with COPD significantly increased walking distance and improved exercise capacity.[59]

Certain investigations have yielded contradictory outcomes. The study conducted by Shepherd et al demonstrated that the consumption of beetroot juice did not result in significant enhancements in the walking distance during the 6MWT or the oxygen consumption during cycling exercise among patients with mild–moderate COPD.[45] In the double-blind, randomized controlled trial by Curtis et al, despite a reduction in isotime oxygen consumption following the intake of nitrate-rich beetroot juice, there was no improvement in the endurance exercise duration for stable patients with COPD.[46] Similarly, a double-blind, randomized controlled trial by Leong et al failed to prove that beetroot juice could enhance the exercise tolerance in patients with COPD who meet the criteria for GOLD Stage II stable chronic obstructive pulmonary disease (moderate severity: $FEV_1/FVC < 0.7$, FEV_1 50–79% predicted). Compared to the placebo group, the patients with COPD who consumed beetroot juice showed an 11% and 6% improvement in the average walking distance and fatigue time, respectively, in the Endurance Shuttle Walk Test (ESWT). However, these differences were not statistically significant. Moreover, no difference was observed in the dyspnea scores between the two groups.[60] In the study of Friis et al, the intervention with beetroot juice did not enhance the exercise capacity of patients with moderate-severe COPD (FEV_1<80% of predicted), nor was there a significant reduction observed in oxygen consumption.[19]

Studies have indicated that dietary nitrates abundant in beetroot juice can enhance mitochondrial oxidative phosphorylation efficiency, augment skeletal muscle contractile function, ameliorate skeletal muscle blood circulation, modulate calcium homeostasis, regulate glucose stability, and increase NO bioavailability through the ($NO3^-$ - $NO2^-$ - NO) pathway.[23,61–64] This, in turn, enhances exercise capability and reduces oxygen consumption. The P/O ratio, denoting the amount of ATP generated per molecule of oxygen consumed, is commonly utilized to assess the efficiency of mitochondrial oxidative phosphorylation.[65] Dietary nitrates can improve the P/O ratio by regulating mitochondrial proton leak, proton slip, oxygen affinity, mitochondrial biogenesis, and thermodynamic coupling, thereby decreasing the oxygen consumption during physical activity.[61] Furthermore, the reduction in oxygen consumption is also related to muscle energy metabolism.[23] NO can activate guanylate cyclase and modify cysteines in proteins to produce S-nitrosothiols, and directly regulate striated muscle myosin, sarcoplasmic reticulum Ca^{2+}-ATPase, and the actin-myosin ATPase, thereby influencing muscle contraction.[66–68]

However, some studies have not observed a reduction in exercise oxygen consumption, which may be associated with oxidative stress in COPD.[7] Following exposure to cigarette smoke, airway inflammatory and epithelial cells generate reactive oxygen species.[8] Due to the lack of histones, mitochondrial DNA is more susceptible to oxidative damage compared to nuclear DNA, leading to mitochondrial dysfunction.[69,70] Mitochondrial dysfunction results in alterations in skeletal muscle structure and function and decreased oxidative phosphorylation efficiency. Under oxidative stress conditions, nitric oxide synthase uncoupling occurs, and the L-arginine-NO metabolic pathway is impaired, thereby reducing NO production and decreasing NO bioavailability, affecting exercise performance and oxygen consumption.[71] Moreover, skeletal muscles in patients with COPD may be affected by various factors such as hypoxia, systemic inflammation, and malnutrition, potentially causing variable responses to dietary nitrates in these individuals.

Vascular Function

Patients with COPD are at an increased risk of developing cardiovascular diseases, with a greater disease burden and higher mortality rates.[72] Vascular endothelial dysfunction is considered an early marker for the onset and progression of cardiovascular diseases.[73] Studies have indicated that dietary nitrates and their endogenous conversion to NO can reduce platelet aggregation and improve vascular endothelial dysfunction induced by ischemia.[74] A systematic review and meta-analysis incorporating 13 high-quality original studies revealed that dietary nitrate supplementation in the form of beetroot juice improves vascular endothelial function in subjects.[75] Similar conclusions have been observed in recent studies involving patients with COPD. In the ON-BC study by Alasmari et al, vascular function and arterial stiffness were assessed by calculating the Reactive Hyperemia Index (RHI) score and measuring the augmentation index normalized to a heart rate of 75 beats per minute (AIx75). The results demonstrated that, compared to placebo, 12 weeks of dietary nitrate intake in the form of beetroot juice was associated with improvements in endothelial RHI scores and AIx75, without leading to any changes related to platelet aggregation. They proposed that the increased bioavailability of supplemented dietary nitrates and their reduction to NO improved vascular function. A long-term dietary nitrate regimen could potentially enhance vascular structural properties, thereby reducing the incidence of cardiovascular diseases in patients with COPD.[53] The Effect of Dietary Nitrate Supplementation on Exercise Performance in Hypoxia (EDEN-OX) study by Pavitt et al, which assessed vascular function through brachial artery flow-mediated dilatation (FMD) 3 hours post-intervention, also indicated that dietary nitrates improved vascular function.[52] This is consistent with their earlier Oral Nitrate to Enhance Pulmonary Rehabilitation in COPD (ON-EPIC) study, which also used FMD to assess vascular function.[58]

Oxidative stress and inflammatory responses are pivotal pathophysiological features of COPD.[8,76] A variety of cells, including inflammatory cells such as neutrophils and macrophages, as well as tissue cells like endothelial cells, airway epithelial cells, and fibroblasts, participate in the pathogenesis of COPD.[5,6] Under hypoxic conditions, patients with COPD exhibit neutrophilic inflammation, where neutrophils degranulate in response to platelet-activating factor stimulation, increasing the release of cytotoxic proteins and causing endothelial damage.[77] Dietary nitrates are reduced in the body to NO, which subsequently forms S-nitrosothiols. These compounds improve COPD-related vascular dysfunction and respiratory symptoms through mechanisms such as downregulating the pro-inflammatory activity of macrophages, neutrophils, and lymphocytes,[78] inhibiting platelet aggregation,[79] relaxing bronchial smooth muscles,[80] and reducing airway hyperreactivity.[37,81] Previous animal studies have indicated that vascular dysfunction is mediated by excessive superoxide production due to oxidative stress, such as the increased activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. The increased superoxide reacts with NO to form peroxynitrite and oxidized tetrahydrobiopterin (BH4). Dietary nitrates improve vascular endothelial function by inhibiting the production of superoxide by NADPH oxidase and enhancing the bioactivity of BH4.[82,83]

Blood Pressure

The incidence of hypertension is elevated in patients with COPD compared to healthy individuals, with a significant impairment observed in vascular reactivity among patients with COPD.[58] Studies have shown that dietary nitrates have antihypertensive effects. In the inaugural study examining the impact of dietary nitrates on patients with COPD, Kerley et al supplemented nitrates in the form of concentrated beetroot juice. The results demonstrated that, compared to the placebo beverage group, beetroot juice intervention for one week significantly lowered the resting systolic and diastolic blood pressures, as well as the mean arterial pressure in patients with COPD.[48] However, subsequent randomized double-blind controlled trials conducted by the same research team over a period of two weeks showed that beetroot juice intervention did not improve the blood pressure in patients with COPD.[47] Although this study had a smaller sample size than others, it utilized a rigorous placebo control, where the placebo was matched in all aspects except nitrate content. This suggests that the antihypertensive effects of beetroot juice may not be solely attributed to its nitrate content, but possibly also to other bioactive components. Subsequent studies yielded varying conclusions. Leong et al observed a decrease in blood pressure in patients with stable moderate COPD after nitrate supplementation.[60] Shepherd's study, involving patients with mild to moderate COPD, found no significant decrease in blood pressure compared to the placebo group after two days of beetroot juice intervention.[45] Several factors affecting blood pressure in the participants were noted in this study: the subjects had a higher BMI index than those in other studies; they were on antihypertensive medications during the study period; and there were variations in age—all of which should not be overlooked. In the research by Berry et al, the intake of beetroot juice led to a significant decrease in resting systolic blood pressure, diastolic blood pressure at isotime, and post-exercise, as well as a downward trend in resting diastolic pressure.[49] Pavitt's findings showed that compared to the placebo group, the nitrate-rich beetroot juice group exhibited statistically significant reductions in systolic and diastolic blood pressure, and mean arterial pressure at the end of the intervention, with a significant antihypertensive effect that lasted at least eight weeks.[58] However, their subsequent single-center, randomized double-blind controlled study showed no statistical difference in any blood pressure changes.[52] The study by Curtis et al indicated that nitrate-rich beetroot juice significantly lowered the resting diastolic blood pressure in patients with COPD, although a further reduction in mean arterial pressure was noted, it did not reach statistical significance.[46] Friis's research also observed that nitrate-rich beetroot juice significantly reduced diastolic blood pressure in patients with COPD but had no effect on systolic pressure.[19] A systematic review and meta-analysis incorporating eight original studies found no significant effect of beetroot juice on blood pressure in patients with COPD.[44] In the latest randomized controlled trial specifically examining the impact of dietary nitrates on cardiovascular risk markers in patients with COPD with elevated blood pressure, Alasmari et al found that compared to placebos, supplementing the diet with nitrates significantly reduced systolic and mean arterial pressures, with no statistically significant effect on diastolic pressure.[53] Nevertheless, this antihypertensive effect can still serve as a primary and secondary prevention for cardiovascular diseases in patients with COPD. This concurs with the viewpoint of Webb et al. His study indicated that a 90-day beetroot juice intervention in 81 patients with COPD could significantly reduce systolic blood pressure.[59] Although the precise mechanism by which beetroot juice lowers blood pressure is not yet clear, the rich nitrate content and the resultant production of NO are most likely the underlying basis for its blood pressure-lowering effect.

Sleep

Patients with COPD often experience varying degrees of sleep disturbances.[84] One possible pathophysiological mechanism for the occurrence of sleep disorders in patients with COPD may be the compromised pulmonary function leading to a decline in blood oxygen saturation, resulting in difficulty breathing during sleep.[85,86] Additional factors such as coughing, excessive mucus production, hypercapnia, and impaired respiratory muscle function may also cause frequent nocturnal awakenings in patients with COPD.[87–89] Previous research has indicated that nitrates can improve blood oxygen levels in non-COPD individuals,[90] increase cerebral blood flow,[91] enhance oxygen utilization and tissue oxygen delivery,[92] and improve cognitive function.[93] Beetroot juice is known to be a substance rich in dietary nitrates. Currently, there is only one study on the effect of beetroot juice on the sleep of patients with COPD.

Wisor et al recruited fifteen COPD subjects for a 4-week randomized double-blind, balanced inpatient pulmonary rehabilitation trial.[51] Subjects consumed beetroot juice rich in nitrates or a nitrate-depleted placebo before sleep, and a bedside computer continuously recorded multiple sleep graphs and other signals for three nights, including electroencephalography (F4-M1, C4-M1, O2-M1), left and right electrooculography, submental electromyography, anterior tibial electromyography, thoracoabdominal respiratory movement, nasal airflow pressure, oxygen saturation, body position changes, and more. The results showed that beetroot juice reduced the frequency of direct awakenings to non-rapid eye movement (NREM) sleep transitions and awakenings to moderate-depth N2 sleep transitions, and increased the frequency of transitions from NREM sleep to rapid eye movement (REM) sleep. This implies that beetroot juice intervention may normalize the sequence of events within the sleep cycle of patients with COPD. Beetroot juice also promoted a decrease in N3 slow-wave activity and an increase in the percentage of time spent in REM sleep, but it did not have a significant effect on the total duration of each sleep stage. Furthermore, researchers observed an increase in oxygen saturation in the patients with COPD of the beetroot juice group during the wakeful period after sleep onset. This suggests that beetroot juice may improve brain oxygenation and inhibit delta waves, thus having a potential therapeutic effect on the treatment of sleep disorders in patients with COPD.

During sleep in patients with COPD, respiratory muscle drive is weakened, affecting oxygen delivery and utilization, leading to hypoventilation and causing frequent sleep awakenings.[94] In the body, beetroot juice is reduced to produce NO. Studies have shown that NO can reduce pulmonary vascular resistance and dilate the bronchial smooth muscle, improving severe hypoxemia.[95,96] Previous research has confirmed that NO, as a cellular signaling molecule, acts on soluble guanylate cyclase, thereby triggering the production of cGMP, regulating neuronal activity and homeostasis, acetylcholine release, and thus modulating the initiation and maintenance of sleep as well as the occurrence of REM sleep.[97] Regardless, the intake of beetroot juice before sleep by patients with COPD increases the duration of deep sleep and the frequency of healthy sleep events, indicating that beetroot juice can improve their nocturnal sleep quality. This offers a new perspective for the treatment of sleep disorders in patients with COPD.

Dosage of Treatment

Beetroot juice, enriched with dietary nitrates, has multiple benefits for patients with COPD, yet this does not imply that more is necessarily better. The role of dietary nitrates in the human body is complex and can be likened to a double-edged sword. Although dietary nitrates have been proven to have several beneficial effects, such as lowering blood pressure and improving vascular function, the intake of high concentrations of nitrates can lead to the production of nitric oxide as well as potentially stimulate the formation of nitrosamines and other nitrosyl compounds.[98] These nitrosyl compounds have potential carcinogenic, teratogenic, and mutagenic effects on the human body.[99] The European Food Safety Authority (EFSA) has set the Acceptable Daily Intake (ADI) for nitrates and nitrites at 3.7 mg and 0.07 mg per kilogram of body weight, respectively.[100,101] Similar to other clinical pharmacotherapies, nitrates have a specific dose-response range that defines their pharmacological activity. A dose that is too low may not reach the threshold to exert pharmacological effects, while exceeding a certain dose may lead to toxicological effects. In existing research on the impact of dietary beetroot juice on COPD, most supplementation regimens involve 140 mL (12.9 mmol) of beetroot juice per day.[46–48,50,52,57] Some studies have employed a regimen of 70 mL per instance, twice daily, in the morning and evening.[19,45,58] Although not every study has yielded entirely positive results, the evidence suggests that a daily intake of approximately 140 mL of beetroot juice can significantly improve the exercise capacity, blood pressure, vascular function, and sleep quality of patients with COPD.

Conclusion

In summary, our investigation furnishes invaluable reference for the utilization of beetroot juice in the treatment of COPD. Our review encompasses the metabolic pathways of dietary nitrates following the ingestion of beetroot juice and delineates the contributions of beetroot juice to various aspects such as exercise capacity, vascular function, blood pressure, and sleep in patients with COPD. Beetroot juice, as a natural dietary nitrate supplement, emerges as a favorable therapeutic alternative for patients who exhibit intolerance to exercise rehabilitation, antihypertensive medications, or sleep-improving drugs. Moreover, it may be synergistically coupled with other pharmacological treatments to enhance therapeutic outcomes. Nevertheless, there remain challenges to be addressed. The clinical phenotypic heterogeneity among COPD patients makes the diagnosis and treatment of COPD complex. Beetroot juice contains not only nitrates but also other bioactive constituents, whose roles in COPD are yet to be fully understood. Additionally, the regulation of physiological functions by dietary nitrates is dichotomous, necessitating a judicious intake of beetroot juice. While the dosages in most current studies are closely aligned, the optimal pharmacologically effective dose remains to be ascertained. Future high-quality research targeting specific phenotypes of COPD patients is crucial to overcoming these challenges and confirming the clinical application of beetroot juice in the management of COPD, aiming for more accurate results and providing more targeted reference.

In Supplementary Data Table 1, we provide an overview of the studies used in this review.

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Disclosure

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