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Review Article

Dietary Nitrate and Its Impact on Preserving Oral and Overall Health

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ABSTRACT

Recent years have seen a major shift in how the role of dietary nitrates is perceived, following extensive debate. Traditionally, low-nitrate diets were recommended due to epidemiological data linking nitrate-rich foods with cancer risk. However, newer research indicates that dietary nitrate, once converted to nitrite by oral microbiota, serves as a vital alternative source for nitric oxide (NO) production—a key molecule involved in regulating blood pressure, defending against pathogenic bacteria, and supporting a balanced gut and oral microbiome. This concise narrative review summarizes clinical and in vitro evidence highlighting the dual nature of dietary nitrates in systemic and oral health, and discusses how strategically incorporating nitrate-rich foods could offer novel, targeted approaches for managing caries and periodontal disease.

Keywords: Caries, Nitric oxide, Nitrite, Diet, Nitrate, Periodontitis

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Introduction

Nitrate (NO_3^-) represents the oxidized form of nitric oxide (NO) and nitrite (NO_2^-). As a component of soil, nitrate is vital for plant development, supplying nitrogen necessary for the synthesis of nitrogen-containing amino acids. Plants absorb nitrate through their roots, which originates either from microbial decomposition of organic matter or from certain soil bacteria that convert atmospheric nitrogen into ammonia, nitrite, and nitrate. Because nitrate availability often limits plant growth, it is commonly supplemented in agricultural soils through nitrate-based fertilizers [1–3].

Importance of the NO–NO_2–NO_3 cycle in human physiology

The NO–NO_2–NO_3 metabolic cycle is closely linked to numerous critical physiological processes in humans. In 1998, Robert F. Furchgott, Louis J. Ignarro, and Ferid Murad received the Nobel Prize in Physiology for identifying nitric oxide (NO) as a signaling molecule within the cardiovascular system. They demonstrated that the key mechanism for regulating blood pressure is the relaxation of vascular smooth muscle cells, mediated by NO produced in the endothelium through the oxidation of L-arginine to L-citrulline by nitric oxide synthase (NOS) [4]. Humans express three NOS isoforms, all of which generate NO via this L-arginine pathway [5]:

Endothelial nitric oxide synthase (eNOS)

eNOS is primarily found in endothelial cells but is also present in platelets, kidney epithelial cells, the placenta, and neurons. Its activity is mainly controlled by Ca^{2+}-dependent binding to calmodulin, although Ca^{2+}-independent pathways—such as fluid shear stress—also activate eNOS. Factors like plasma insulin, estrogen, and vascular endothelial growth factor (VEGF) can modulate eNOS activity. NO released by eNOS dilates blood vessels, inhibits platelet aggregation and adhesion, reduces MCP-1

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synthesis, and prevents leukocyte adhesion to vessel walls [6, 7]. In individuals with cardiovascular disease or risk factors, eNOS-mediated NO production is often impaired, accompanied by increased reactive oxygen species from NADPH oxidase, which promotes NO degradation. Chronic oxidative stress in aging vessels can also lead to eNOS uncoupling, shifting its function from NO production to oxygen radical generation [8, 9]. Dietary supplementation with ~3 g L-arginine daily has been shown to partially restore endothelial function in affected patients [10].

Neuronal nitric oxide synthase (nNOS)

nNOS is constitutively expressed in central and peripheral neurons and some other cell types. In the CNS, it supports synaptic plasticity, including long-term potentiation and depression, which are essential for learning and memory. nNOS also contributes to central blood pressure regulation, as animal studies show that hypothalamic nNOS inhibition leads to systemic hypertension [11]. In the peripheral nervous system, nNOS regulates smooth muscle tone in intestinal motility, penile erection, and peripheral blood pressure through nitrergic nerve activity, all mediated by NO. Like eNOS, nNOS is regulated by Ca^{2+}-dependent calmodulin binding.

Inducible nitric oxide synthase (iNOS)

iNOS is expressed in various immune and other cells in response to pro-inflammatory cytokines, bacterial lipopolysaccharides, or tissue stress. Its activation leads to Ca^{2+}-independent release of large NO quantities to destroy pathogens, tumor cells, or parasites through nitrosative stress. Unlike eNOS and nNOS, iNOS activity is not tightly regulated, and excessive activation can damage host tissues, contributing to periodontitis [12] and chronic inflammatory diseases such as cardiovascular disorders [13]. High levels of iNOS-derived NO entering circulation are a major trigger of septic shock [14].

Nitric oxide (NO)

Nitric oxide is a highly reactive signaling molecule due to its unpaired electron, acting through multiple pathways. Primarily, NO binds to the heme group of soluble guanylyl cyclase, increasing intracellular cyclic guanosine monophosphate (cGMP), which mediates effects such as vasodilation, nerve signaling, mitochondrial biogenesis, and angiogenesis [15]. NO is extremely short-lived, with a half-life of milliseconds, and is rapidly oxidized to nitrate by oxyhemoglobin or to nitrite by ceruloplasmin [16]. Normal plasma nitrate levels range from 20–40 μM and nitrite from 50–300 nM, maintained via renal excretion. In severe systemic inflammation, these levels can rise due to massive iNOS induction, whereas cardiovascular diseases with endothelial dysfunction and impaired eNOS activity usually show reduced plasma nitrate and nitrite concentrations [17].

NOS-independent nitric oxide production from dietary nitrate

For many years, it was assumed that NO production in humans occurred exclusively through NOS-mediated oxidation of L-arginine, with resulting plasma nitrate and nitrite considered mere byproducts without physiological significance. However, research over the past few decades has shown that NO availability is not solely dependent on NOS, but is also supported by an alternative pathway involving dietary nitrate and nitrite, particularly under acidic or hypoxic conditions [16]. Once ingested, dietary nitrate rapidly enters the bloodstream—approximately 75% is excreted via the kidneys, while 25% accumulates in the salivary glands at concentrations 20–100 times higher than in plasma [15]. Commensal bacteria on the tongue, such as Veillonella and Rothia species, possess nitrate reductases that convert salivary nitrate into nitrite for energy, reflecting a likely symbiotic relationship with the host [16].

Swallowed salivary nitrite is protonated by gastric acid to form nitrous acid (HNO_2), which subsequently decomposes into NO and other nitrogen oxides [18]. This NO formation is enhanced in the presence of antioxidants like ascorbic acid and polyphenols, abundant in fruits and vegetables. NO generated in the stomach improves mucosal blood flow and strengthens mucus barriers [16], while increased nitrite levels enhance the antimicrobial properties of gastric fluid [18, 19]. In vitro studies have demonstrated that 1 mM nitrite can effectively eliminate Helicobacter pylori, a bacterium linked to gastric ulcers and cancer [20]. In critically ill, intubation interrupts salivary nitrite delivery to the stomach, reducing intragastric NO formation and potentially promoting pathogen overgrowth and bacterial translocation, which may worsen patient prognosis [21].

Additionally, salivary nitrite in the acidic stomach environment facilitates the formation of S-nitrosothiols, organic compounds containing nitroso groups on thiols [22], which play crucial roles in blood pressure regulation and are explored as antihypertensive agents [23]. S-nitrosohemoglobin in red blood cells releases NO under hypoxia, promoting vasodilation [24]. Unreacted salivary nitrite is eventually absorbed into the bloodstream as inorganic nitrite, providing an important NO source when oxygen-dependent NOS activity is limited. Elevated

plasma nitrite has protective effects during ischemia and reduces reperfusion injury in conditions such as myocardial infarction [16, 25]. A transient rise in nitrate and nitrite has also been observed in elite breath-hold divers, counteracting hypoxia-induced oxidative stress during deep dives [26]. The pathways of the NO–NO_2–NO_3 cycle are illustrated schematically in **Figure 1**.

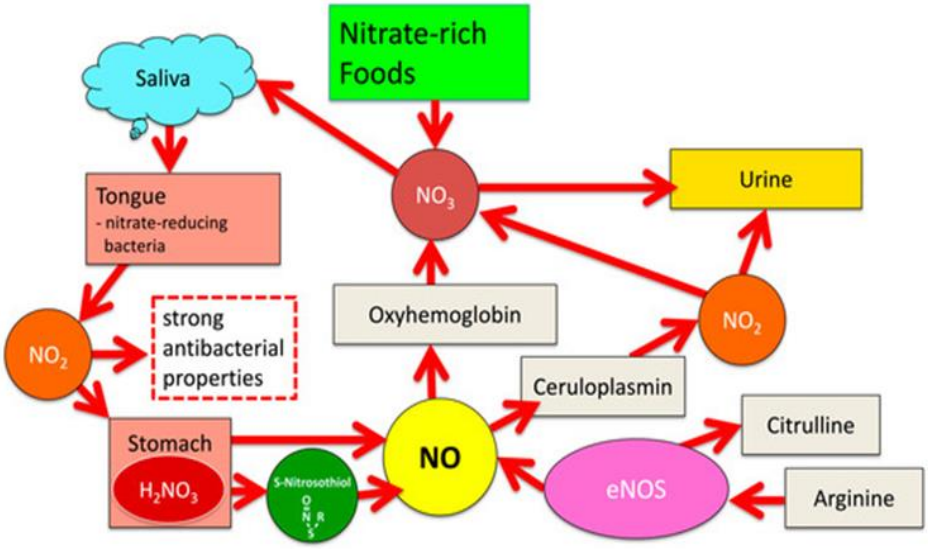

Figure 1. Pathways of the NO-NO_2-NO_3 cycle.

Dietary nitrate and oral health maintenance

While the role of the oral microbiota in converting nitrate-rich foods into nitrite and NO has been recognized for years, it is only recently that the potential preventive and therapeutic effects of a nitrate-rich diet have garnered attention from dental researchers.

Effects of dietary nitrate on caries formation

Salivary nitrite exhibits strong antibacterial activity, which intensifies under lower pH and can readily penetrate microbial biofilms [19]. Elevating salivary nitrite through nitrate-rich diets has therefore been proposed as a promising strategy for caries prevention. Scoffield *et al*. [27] studied nitrite effects in culture media containing Streptococcus mutans co-cultured with Streptococcus parasanguinis, finding a marked reduction in S. mutans growth and biofilm formation compared to controls without nitrite exposure. In an animal study, rats pre-inoculated with S. parasanguinis and given nitrite-supplemented water before S. mutans infection showed significantly fewer new carious lesions in enamel and dentin than control rats without nitrite supplementation.

These findings are further supported by Hohensinn *et al*. [28], who reported that healthy volunteers consuming nitrate-rich beetroot juice showed significant increases in salivary NO_3^-, NO_2^-, and NO, along with a rise in mean salivary pH from 7.0 to 7.5. Similarly, Burleigh *et al*. [29] observed that male endurance athletes experienced less pH reduction in saliva after consuming carbohydrate-rich snacks when nitrate-rich beetroot juice was ingested concurrently.

Huffines *et al*. [30] provided additional insights into salivary nitrate's role in fostering a balanced, non-cariogenic oral microbiome. Using a mixed in vitro biofilm model with S. parasanguinis, S. mutans, and Candida albicans, they found that S. parasanguinis was highly resistant to increased nitrosative stress and even amplified it through peroxide production, which converts to peroxynitrite in the presence of nitrite—a potent antibacterial agent. Conversely, S. mutans and C. albicans were highly susceptible to nitrosative stress, showing significant reductions in growth and biofilm formation.

Despite these promising results, controlled clinical trials confirming the effectiveness of nitrate-rich diets in preventing caries are still lacking.

Impact of dietary nitrate on gingivitis and periodontitis development

Historically, periodontology research primarily focused on the role of iNOS activation in periodontal tissue destruction and strategies to control it [31, 32]. As discussed earlier, salivary nitrite levels may reflect the activity of nitrate-reducing oral bacteria or the local release of iNOS-derived NO and NO_2 from inflamed gingival and periodontal tissues. Consequently, several studies have investigated NO and NO_2 concentrations in gingival crevicular fluid and saliva as potential markers of periodontal health, with mixed results. Topcu *et al*. [33] found significantly higher nitrite

levels in the gingival fluid of patients with gingivitis compared to healthy individuals. In vitro, Hussain *et al*. [34] exposed oral keratocytes to supernatants from various oral microorganisms, including Aggregatibacter actinomycetemcomitans, Campylobacter rectus, Porphyromonas gingivalis, Streptococcus salivarius, and Candida albicans, and observed differing nitrite release by the keratocytes, with A. actinomycetemcomitans and C. rectus inducing the strongest responses. In a subsequent study [35], the same group reported that the number of iNOS- and adrenomedullin-expressing cells in inflamed gingiva was three times higher than in healthy tissue, and salivary NO and AM levels were markedly elevated in patients with aggressive periodontitis compared to those with chronic periodontitis or gingivitis. Differences in gingival crevicular fluid NO levels were also significant between these patient groups. Similar trends were observed in elderly Korean patients with periodontitis [36], although Aurer *et al*. [37] reported lower salivary NO and NO_2 levels in periodontitis cases.

Only recently has the role of dietary nitrate in supporting periodontal health been investigated. In a controlled clinical trial, Jockel-Schneider *et al*. [38] examined the effect of daily consumption of a nitrate-rich lettuce juice on chronic gingivitis in periodontitis patients undergoing regular aftercare. Participants consuming 200 mg of dietary nitrate daily for two weeks following professional mechanical plaque removal (PMPR) exhibited a 50% reduction in gingival inflammation compared to baseline. In contrast, controls consuming nitrate-depleted lettuce juice showed only minimal, non-significant improvement. Whole-genome sequencing of periodontal pocket microbiota revealed a significant shift in bacterial composition in the nitrate-supplemented group: inflammation-associated genera such as Treponema and Prevotella decreased, while health-associated genera like Rothia and Neisseria increased. In the control group, microbiota composition remained largely unchanged despite PMPR, indicating that mechanical plaque removal alone may only address symptoms, whereas dietary nitrate can contribute to resolving dysbiosis and suppressing pathogenic oral bacteria [39].

These findings are partially supported by Woelber *et al*. [40], who reported that a diet rich in omega-3 fatty acids, antioxidants, and dietary nitrate reduced gingivitis in participants previously consuming a Western diet high in processed carbohydrates. However, the study combined multiple anti-inflammatory nutrients, making it difficult to isolate the specific contribution of nitrate. Despite promising preliminary evidence for the role of high-nitrate diets in preventing and mitigating periodontal inflammation, further research from larger controlled trials is required to confirm these effects.

Impact of oral antiseptics on salivary nitrite levels

In many industrialized nations, antibacterial mouthwashes are commonly used alongside daily toothbrushing. However, indiscriminate long-term use of oral antiseptics can be problematic, as they not only suppress pathogenic bacteria but may also disrupt beneficial oral microbes, including nitrate-reducing bacteria on the tongue. Kapil *et al*. [41] demonstrated that using a chlorhexidine-based mouthwash inhibited microbial nitrate reduction and led to a significant rise in systolic blood pressure in healthy young adults. Similar results have been confirmed by other studies [42], and epidemiological surveys have linked frequent mouthwash use to higher rates of hypertension [43] and type 2 diabetes [44], likely because dietary nitrate plays a key role in modulating insulin resistance in obese and metabolic syndrome patients [45, 46]. Therefore, while chlorhexidine and other proven antiseptics are generally considered safe, current guidelines recommend their use only as adjuncts to mechanical plaque control, for specific indications and limited durations [47, 48].

Nitrate-rich vegetables

Vegetables high in nitrate include common varieties such as lettuce, rocket, chard, spinach, cabbage, radish, and beetroot **(Figure 2)**. Nitrate content varies not only by plant type but also by factors such as fertilization, season, geographic location, and even the time of day of harvest [49]. This is because sunlight drives photosynthesis, which not only reduces carbon dioxide but also consumes inorganic nitrate absorbed from the soil [50]; consequently, nitrate accumulates in plants overnight and is utilized during the day, making it difficult for farmers to consistently standardize nitrate levels in harvested produce. Cooking or frying can further alter nitrate content [51], so intake from raw vegetables can only be roughly estimated using reference tables [49]. More precise monitoring of nitrate consumption requires either processed vegetables with defined nitrate content, as in Jockel-Schneider *et al*. [38], or direct measurement of salivary nitrite, which rises after nitrate-rich meals due to the activity of oral nitrate-reducing bacteria. Salivary nitrite testing is easily performed using commercially available strips, popular among athletes, since nitrate-rich diets can enhance endurance and high-intensity performance by improving coronary and muscular blood flow [52, 53].

Figure 2. Common nitrate-rich vegetables.

Diet and oral health—historical perspectives

The role of malnutrition and nutrient-poor diets in promoting bacterial dysbiosis and the development of caries and periodontal disease is further supported by findings from a unique archaeological study. Researchers examined human skulls from the late Neolithic to the early Industrial Revolution, assessing dental health and recovering microbial DNA from dental calculus [54]. Whole-genome sequencing allowed identification of specific microbial species and analysis of microbial diversity. The study linked the emergence of widespread caries and periodontal disease to the shift from a hunter-gatherer to an agricultural lifestyle. Hunter-gatherers consumed a highly varied diet that not only supported overall health but also provided substrates for a diverse, health-promoting oral microbiota. In contrast, the move to sedentary farming at the end of the Neolithic led to reduced dietary diversity, decreased oral microbial diversity, and a dysbiotic environment favoring disease-causing bacteria, contributing to periodontal disease. Comparisons of medieval dental calculus with samples from the Industrial Revolution showed further reductions in microbial diversity and widespread colonization by cariogenic bacteria, likely due to increased refined sugar consumption, which accelerated oral health deterioration. Although not directly assessed in the study, the regular intake of wild edible plants by hunter-gatherers likely supplied substantial dietary nitrate, as many wild plants naturally contain high nitrate levels [55].

Controversies surrounding the effects of dietary nitrate on general health

The evidence reviewed thus far highlights the important physiological role of dietary nitrate (NO_3^-) in supporting microbial balance and maintaining oral and systemic health; however, NO, NO_2, and NO_3 are inherently ambivalent molecules. While essential for normal physiological function, they can act as toxic agents when released by host defense cells during inflammation. In many countries, legal limits for nitrate and nitrite in drinking water have been established to prevent methemoglobinemia in newborns, as fetal hemoglobin is particularly vulnerable to oxidation by NO_2 due to a transient deficiency of methemoglobin reductase, which can lead to cyanosis [55]. Although contaminated water is an unlikely cause in industrialized nations, consumption of nitrate-rich foods contaminated with bacteria may still pose a risk to infants [56].

Another safety concern highlighted by toxicological and epidemiological studies is the potential formation of carcinogenic compounds following ingestion of nitrate-rich foods or water [57]. Epidemiological data have linked frequent consumption of processed meats—such as ham, bacon, salami, and hot dogs, often cured with nitrite- and nitrate-containing salts—to an increased cancer risk [58]; however, this association remains debated and has not been definitively confirmed in recent meta-analyses [59]. In the stomach, ingested nitrite can form reactive nitrosyl (NO^-) species under acidic conditions, which may react with biogenic amines from meat to produce carcinogenic nitrosamines. Yet, the clinical relevance of this pathway is questioned, as even in high red meat-consuming countries like Australia, only about 1% of total nitrate intake comes from processed meats, while over 80% is derived from vegetables [60]. Moreover, frequent consumption of nitrate-rich leafy greens is actually inversely associated with cancer risk [61, 62]. Thus, while the cancer-related effects of nitrates in processed meats remain debated, regular consumption of fresh nitrate-rich vegetables is generally considered safe. According to the European Food Safety Authority (EFSA), a daily intake of more than 400 g of mixed vegetables does not exceed the Acceptable Daily Intake (ADI) of 222 mg NO_3^-, as established by WHO/FAO for a 60 kg adult [49]. It is important to note that the ADI does not indicate a toxicity threshold but represents a level that can be consumed daily over a lifetime without significant health risks.

Dietary nitrates—clinical practice considerations

Although dietary deficiencies are recognized as significant contributors to the deterioration of systemic and oral health, current evidence-based guidelines for periodontal therapy do not emphasize targeted nutritional counseling. This is likely due to the limited long-term controlled clinical trial data demonstrating the efficacy of dietary interventions [63], while established mechanical plaque control methods are

well-supported and effectively limit disease progression in most patients [48]. Additionally, achieving lasting changes in patients' unhealthy dietary habits can be challenging, as indicated by a systematic review on long-term compliance with dietary recommendations among individuals with hypertension [64]. Nonetheless, in cases of severe caries or advanced periodontitis, particularly when accompanied by chronic systemic inflammation, mechanical plaque control alone may be insufficient, and addressing dietary deficiencies as an adjunct strategy can enhance disease management.

Conclusion

Dietary nitrate serves as a vital alternative source for nitric oxide, a critical signaling molecule involved in numerous essential physiological processes, including the maintenance of a health-promoting balance between the human microbiota and its host. Evidence from controlled clinical trials indicates that incorporating a varied, nitrate-rich diet as an adjunct to conventional therapeutic and preventive approaches may support the restoration and stabilization of oral health and microbial eubiosis.

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References

1. Murray JD, Liu CW, Chen Y, Miller AJ. Nitrogen sensing in legumes. J Exp Bot. 2017;68(8):1919–26.
2. Wang YY, Hsu PK, Tsay YF. Uptake, allocation and signaling of nitrate. Trends Plant Sci. 2012;17(8):458–67.
3. Wang YY, Cheng YH, Chen KE, Tsay YF. Nitrate transport, signaling, and use efficiency. Annu Rev Plant Biol. 2018;69(1):85–122.
4. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature. 1980;288(5789):373–6.
5. Förstermann U, Sessa WC. Nitric oxide synthases: Regulation and function. Eur Heart J. 2012;33(7):829–37.
6. Zeiher AM, Fisslthaler B, Schray-Utz B, Busse R. Nitric oxide modulates the expression of monocyte chemoattractant protein 1 in cultured human endothelial cells. Circ Res. 1995;76(6):980–6.
7. Kubes P, Suzuki M, Granger DN. Nitric oxide: an endogenous modulator of leukocyte adhesion. Proc Natl Acad Sci U S A. 1991;88(11):4651–5.
8. Yang YM, Huang A, Kaley G, Sun D. eNOS uncoupling and endothelial dysfunction in aged vessels. Am J Physiol Heart Circ Physiol. 2009;297(5):H1829–36.
9. Karbach S, Wenzel P, Waisman A, Münzel T, Daiber A. eNOS uncoupling in cardiovascular diseases: The role of oxidative stress and inflammation. Curr Pharm Des. 2014;20(22):3579–94.
10. Gambardella J, Khondkar W, Morelli MB, Wang X, Santulli G, Trimarco V. Arginine and endothelial function. Biomedicines. 2020;8(9):277.
11. Toda N, Ayajiki K, Okamura T. Control of systemic and pulmonary blood pressure by nitric oxide formed through neuronal nitric oxide synthase. J Hypertens. 2009;27(10):1929–40.
12. Wang Y, Huang X, He F. Mechanism and role of nitric oxide signaling in periodontitis. Exp Ther Med. 2019;18(5):3929–35.
13. Perez-Torres I, Manzano-Pech L, Rubio-Ruiz ME, Soto ME, Guarner-Lans V. Nitrosative stress and its association with cardiometabolic disorders. Molecules. 2020;25(11):2555.
14. Kirkeboen KA, Strand OA. The role of nitric oxide in sepsis—an overview. Acta Anaesthesiol Scand. 1999;43(3):275–88.
15. Lundberg JO, Weitzberg E. Biology of nitrogen oxides in the gastrointestinal tract. Gut. 2013;62(4):616–29.
16. Lundberg JO, Weitzberg E, Gladwin MT. The nitrate–nitrite–nitric oxide pathway in physiology and therapeutics. Nat Rev Drug Discov. 2008;7(2):156–67.
17. Khatri J, Mills CE, Maskell P, Odongerel C, Webb AJ. It is rocket science—why dietary nitrate is hard to 'beet'! Part I: Twists and turns in the realization of the nitrate–nitrite–NO pathway. Br J Clin Pharmacol. 2017;83(1):129–39.
18. Benjamin N, O'Driscoll F, Dougall H, Duncan C, Smith L, Golden M, et al. Stomach NO synthesis. Nature. 1994;368(6471):502.
19. Dykhuizen RS, Frazer R, Duncan C, Smith CC, Golden M, Benjamin N, et al. Antimicrobial effect of acidified nitrite on gut pathogens: importance of dietary nitrate in host defense. Antimicrob Agents Chemother. 1996;40(6):1422–5.

20. Dykhuizen RS, Fraser A, McKenzie H, Golden M, Leifert C, Benjamin N. Helicobacter pylori is killed by nitrite under acidic conditions. Gut. 1998;42(3):334–7.
21. Bjorne H, Govoni M, Tornberg DC, Lundberg JO, Weitzberg E. Intragastric nitric oxide is abolished in intubated patients and restored by nitrite. Crit Care Med. 2005;33(8):1722–7.
22. Abu-Alghayth M, Vanhatalo A, Wylie LJ, McDonagh ST, Thompson C, Kadach S, et al. S-nitrosothiols and other products of nitrate metabolism are increased in multiple human blood compartments following ingestion of beetroot juice. Redox Biol. 2021;43(101974):101974.
23. Oliveira-Paula GH, Tanus-Santos JE. Nitrite-stimulated gastric formation of S-nitrosothiols as an antihypertensive therapeutic strategy. Curr Drug Targets. 2019;20(4):431–43.
24. Diesen DL, Hess DT, Stamler JS. Hypoxic vasodilation by red blood cells: Evidence for an S-nitrosothiol-based signal. Circ Res. 2008;103(5):545–53.
25. Webb A, Bond R, McLean P, Uppal R, Benjamin N, Ahluwalia A. Reduction of nitrite to nitric oxide during ischemia protects against myocardial ischemia–reperfusion damage. Proc Natl Acad Sci U S A. 2004;101(37):13683–8.
26. Cialoni D, Brizzolari A, Samaja M, Bosco G, Paganini M, Pieri M, et al. Nitric oxide and oxidative stress changes at depth in breath-hold diving. Front Physiol. 2020;11(609642):609642.
27. Scoffield J, Michalek S, Harber G, Eipers P, Morrow C, Wu H. Dietary nitrite drives disease outcomes in oral polymicrobial infections. J Dent Res. 2019;98(9):1020–6.
28. Hohensinn B, Haselgrübler R, Müller U, Stadlbauer V, Lanzerstorfer P, Lirk G, et al. Sustaining elevated levels of nitrite in the oral cavity through consumption of nitrate-rich beetroot juice in young healthy adults reduces salivary pH. Nitric Oxide. 2016;60(1):10–5.
29. Burleigh MC, Sculthorpe N, Henriquez FL, Easton C. Nitrate-rich beetroot juice offsets salivary acidity following carbohydrate ingestion before and after endurance exercise in healthy male runners. PLoS One. 2020;15(12):e0243755.
30. Huffines JT, Stoner SN, Baty JJ, Scoffield JA. Nitrite triggers reprogramming of the oral polymicrobial metabolome by a commensal Streptococcus. Front Cell Infect Microbiol. 2022;12(833339):833339.
31. Parvu AE, Alb SF, Craciun A, Taulescu MA. Efficacy of subantimicrobial-dose doxycycline against nitrosative stress in chronic periodontitis. Acta Pharmacol Sin. 2013;34(2):247–54.
32. Kendall HK, Marshall RI, Bartold PM. Nitric oxide and tissue destruction. Oral Dis. 2001;7(1):2–10.
33. Topcu Ali O, Akalin FA, Sahbazoglu KB, Yamalik N, Kilinc K, Karabulut E, et al. Nitrite and nitrate levels of gingival crevicular fluid and saliva in subjects with gingivitis and chronic periodontitis. J Oral Maxillofac Res. 2014;5(1):e5.
34. Hussain QA, McKay IJ, Gonzales-Marin C, Allaker RP. Regulation of adrenomedullin and nitric oxide production by periodontal bacteria. J Periodontal Res. 2015;50(5):650–7.
35. Hussain QA, McKay IJ, Gonzales-Marin C, Allaker RP. Detection of adrenomedullin and nitric oxide in different forms of periodontal disease. J Periodontal Res. 2016;51(1):16–25.
36. Han DH, Kim MS, Shin HS, Park KP, Kim HD. Association between periodontitis and salivary nitric oxide metabolites among community elderly Koreans. J Periodontol. 2013;84(6):776–84.
37. Aurer A, Aleksić J, Ivić-Kardum M, Aurer J, Culo F. Nitric oxide synthesis is decreased in periodontitis. J Clin Periodontol. 2001;28(6):565–8.
38. Jockel-Schneider Y, Gossner SK, Petersen N, Stolzel P, Hagele F, Schweiggert RM, et al. Stimulation of the nitrate-nitrite-NO-metabolism by repeated lettuce juice consumption decreases gingival inflammation in periodontal recall patients: A randomized, double-blinded, placebo-controlled clinical trial. J Clin Periodontol. 2016;43(7):603–8.
39. Jockel-Schneider Y, Schlagenhauf U, Stolzel P, Gossner S, Carle R, Ehmke B, et al. Nitrate-rich diet alters the composition of the oral microbiota in periodontal recall patients. J Periodontol. 2021;92(11):1536–45.
40. Woelber JP, Gartner M, Breuninger L, Anderson A, Konig D, Hellwig E, et al. The influence of an anti-inflammatory diet on gingivitis: a randomized controlled trial. J Clin Periodontol. 2019;46(4):481–90.
41. Kapil V, Haydar SM, Pearl V, Lundberg JO, Weitzberg E, Ahluwalia A. Physiological role for nitrate-reducing oral bacteria in blood pressure control. Free Radic Biol Med. 2013;55(1):93–100.
42. Bondonno CP, Liu AH, Croft KD, Considine MJ, Puddey IB, Woodman RJ, et al. Antibacterial mouthwash blunts oral nitrate reduction and increases blood pressure in treated hypertensive men and women. Am J Hypertens. 2015;28(5):572–5.

43. Joshipura K, Munoz-Torres F, Fernandez-Santiago J, Patel RP, Lopez-Candales A. Over-the-counter mouthwash use, nitric oxide and hypertension risk. Blood Press. 2020;29(2):103–12.
44. Joshipura KJ, Munoz-Torres FJ, Morou-Bermudez E, Patel RP. Over-the-counter mouthwash use and risk of pre-diabetes/diabetes. Nitric Oxide. 2017;1(1):14–20.
45. Beals JW, Binns SE, Davis JL, Giordano GR, Klochak AL, Paris HL, et al. Concurrent beet juice and carbohydrate ingestion: Influence on glucose tolerance in obese and nonobese adults. J Nutr Metab. 2017;2017(1):6436783.
46. Hughan KS, Levine A, Helbling N, Anthony S, DeLany JP, Stefanovic-Racic M, et al. Effects of oral sodium nitrite on blood pressure, insulin sensitivity, and intima-media arterial thickening in adults with hypertension and metabolic syndrome. Hypertension. 2020;76(3):866–74.
47. Paris S, Banerjee A, Bottenberg P, Breschi L, Campus G, Domejean S, et al. How to intervene in the caries process in older adults: a joint ORCA and EFCD expert Delphi consensus statement. Caries Res. 2020;54(5):459–65.
48. Sanz M, Herrera D, Kebschull M, Chapple I, Jepsen S, Beglundh T, et al. Treatment of stage I–III periodontitis: the EFP S3 level clinical practice guideline. J Clin Periodontol. 2020;47(Suppl 22):4–60.
49. Chain E, PoCit F, Alexander J, Bedford D, Cockburn A, Cravedi JP, et al. Nitrate in vegetables: scientific opinion of the panel of contaminants in the food chain. EFSA J. 2008;6(6):698.
50. Sherameti I, Sopory SK, Trebicka A, Pfannschmidt T, Oelmuller R. Photosynthetic electron transport determines nitrate reductase gene expression and activity in higher plants. J Biol Chem. 2002;277(49):46594–600.
51. Salehzadeh H, Maleki A, Rezaee R, Shahmoradi B, Ponnet K. The nitrate content of fresh and cooked vegetables and their health-related risks. PLoS One. 2020;15(1):e0227551.
52. San Juan AF, Dominguez R, Lago-Rodriguez A, Montoya JJ, Tan R, Bailey SJ. Effects of dietary nitrate supplementation on weightlifting exercise performance in healthy adults: a systematic review. Nutrients. 2020;12(7):2227.
53. Nyakayiru J, Jonvik KL, Trommelen J, Pinckaers PJ, Senden JM, van Loon LJ, et al. Beetroot juice supplementation improves high-intensity intermittent type exercise performance in trained soccer players. Nutrients. 2017;9(3):314.
54. Adler CJ, Dobney K, Weyrich LS, Kaidonis J, Walker AW, Haak W, et al. Sequencing ancient calcified dental plaque shows changes in oral microbiota with dietary shifts of the Neolithic and Industrial revolutions. Nat Genet. 2013;45(4):450–5.
55. Herzog P, Feig SA. Methaemoglobinaemia in the newborn infant. Clin Haematol. 1978;7(1):75–83.
56. Sanchez-Echaniz J, Benito-Fernandez J, Mintegui-Raso S. Methemoglobinemia and consumption of vegetables in infants. Pediatrics. 2001;107(5):1024–8.
57. Hosseini F, Majdi M, Naghshi S, Sheikhhossein F, Djafarian K, Shab-Bidar S. Nitrate-nitrite exposure through drinking water and diet and risk of colorectal cancer: A systematic review and meta-analysis of observational studies. Clin Nutr. 2021;40(5):3073–81.
58. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Ingested nitrate and nitrite, and cyanobacterial peptide toxins. IARC Monogr Eval Carcinog Risks Hum. 2010;94(1):1–412.
59. Zhao Z, Yin Z, Zhao Q. Red and processed meat consumption and gastric cancer risk: a systematic review and meta-analysis. Oncotarget. 2017;8(19):30563–75.
60. Jackson JK, Patterson AJ, MacDonald-Wicks LK, Bondonno CP, Blekkenhorst LC, Ward NC, et al. Dietary nitrate and diet quality: an examination of changing dietary intakes within a representative sample of Australian women. Nutrients. 2018;10(8):1005.
61. Larsson SC, Bergkvist L, Wolk A. Fruit and vegetable consumption and incidence of gastric cancer: a prospective study. Cancer Epidemiol Biomarkers Prev. 2006;15(10):1998–2001.
62. Palli D, Russo A, Decarli A. Dietary patterns, nutrient intake and gastric cancer in a high-risk area of Italy. Cancer Causes Control. 2001;12(2):163–72.
63. Donos N, Calciolari E, Brusselaers N, Goldoni M, Bostanci N, Belibasakis GN. The adjunctive use of host modulators in non-surgical periodontal therapy: A systematic review of randomized, placebo-controlled clinical studies. J Clin Periodontol. 2020;47(Suppl 22):199–238.
64. Kwan MW, Wong MC, Wang HH, Liu KQ, Lee CL, Yan BP, et al. Compliance with the dietary approaches to stop hypertension (DASH) diet: a systematic review. PLoS One. 2013;8(10):e78412.