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Effects of Nitrite on the Acidogenic and Antimicrobial Activities of *Streptococcus mutans*: A Systematic Review

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ABSTRACT

Nitrite has attracted interest for its potential to modulate the acidogenic and antimicrobial activities of *Streptococcus mutans*, a major cariogenic bacterium associated with dental caries. However, evidence regarding these effects remains scattered across experimental studies conducted under varying nitrite concentrations and experimental conditions. This systematic review aimed to evaluate the effects of nitrite exposure on the acidogenic and antimicrobial activities of *S. mutans* in *in vitro* studies. A systematic literature search was conducted in PubMed, Scopus, and ScienceDirect up to August 15, 2026. Five eligible *in vitro* studies were included and narratively synthesized. Study quality was assessed using the Quality Assessment Tool for In Vitro Studies (QUIN), with all five studies demonstrating a moderate risk of bias. Collectively, the findings suggested that nitrite may suppress the acidification process and exert antimicrobial effects against *S. mutans*, including inhibition of bacterial growth and reduced viability, particularly under acidic conditions. The included studies also provided evidence of the potential role of nitrite in the ecological interactions between oral microorganisms and cariogenic bacteria. Overall, nitrite may have potential anti-acidogenic and antimicrobial effects against *S. mutans* under certain experimental conditions. However, differences in nitrite concentrations, bacterial strains, experimental conditions, and outcome measurements limit direct comparisons across studies. Further standardized research is needed to clarify these effects and determine their relevance to the complex oral environment.

Keywords: nitrites; streptococcus mutans; acidogenicity; antimicrobial activity; environmental pH

INTRODUCTION

Dental caries is a biofilm-mediated disease characterized by localized demineralization of dental hard tissues and is one of the most prevalent oral diseases worldwide that affects approximately 537 million children and 2.5 billion adults [1,2]. This condition is common and arises due to interaction between the host, the environment, and the oral microbiome [3]. Dental caries develops when a dysbiotic biofilm repeatedly ferments dietary carbohydrates and produces acids that lower the local pH [4]. *Streptococcus mutans* also contributes to cariogenic biofilm formation through glucosyltransferase-mediated glucan synthesis from sucrose, which facilitates bacterial adherence and biofilm development [5]. The accumulation of such acids provokes a decrease in pH plaque in the oral cavity to below the critical threshold of 5.5 systematically causes demineralization in enamel hydroxyapatite crystals and initiates the formation of lesions on the enamel surface [6,7].

This cariogenic biofilm is composed of acidogenic and aciduric microorganisms such as *Lactobacillus spp., Scardovia wiggsiae, Actinomyces spp*., and *Streptococcus mutans*, one of the primary cariogenic pathogens [8]. As the primary pathogen, *Streptococcus mutans* exhibits high acidogenicity by fermenting dietary carbohydrates through glycolysis to produce pyruvate, which is subsequently converted into lactic acid by lactate dehydrogenase (LDH) [9,10]. Previous studies have demonstrated the important role of *Streptococcus mutans* in dental caries and its ability to form biofilms and produce acid. For instance, this bacterium was detected in 94% of children with dental caries, supporting its frequent association with cariogenic conditions [11].

Biofilm formation plays a critical role in oral disease [12], and its adherence can be further influenced by the availability of carbohydrates such as sucrose and lactose [13]. One potential natural compound that is now widely studied is nitrite (NO_2^-). Nitrite is an inorganic ion generated within the oral nitrate–nitrite pathway and has been investigated for possible antimicrobial effects under acidic conditions [14]. Previous studies have suggested that nitrite may inhibit the growth and acid production of *Streptococcus mutans* and may therefore influence plaque pH [15]. Mechanistically, nitrite can be converted into nitric oxide (NO), which disrupts DNA synthesis and inhibits important metabolic enzymes of cariogenic bacteria [16].

Several experimental studies have investigated the effects of nitrite exposure on *Streptococcus mutans*, particularly its acid production and environmental pH. However, these studies have been conducted under different experimental conditions, including variations in nitrite concentration, exposure time, culture media, and pH. These variations may contribute to differences in the reported effects of nitrite on bacterial acid production and environmental pH. Despite the growing interest in the potential role of nitrite in modulating cariogenic bacterial activity, the available evidence has not yet been systematically synthesized. Therefore, this systematic review aimed to evaluate the effects of nitrite exposure on the acidogenic and antimicrobial activities of *Streptococcus mutans* in *in vitro* studies.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Three electronic databases, namely PubMed, Scopus, and ScienceDirect, were used to conduct a comprehensive systematic search for eligible studies from their inception until August 15, 2026.

Selection criteria

A population, intervention, comparison, and outcomes (PICO) strategy was used to define the following eligibility criteria (P) cariogenic bacteria, particularly *Streptococcus mutans*, including studies involving alone or in combination with other oral or cariogenic microorganisms; (I) exposure to nitrite (NO_2^-), including sodium nitrite, potassium nitrite, acidified nitrite or nitrite ions; (C) no nitrite exposure, untreated or vehicle control, placebo, or a lower concentration of nitrite; and (O) acidogenic and antimicrobial activity of *Streptococcus mutans*/ including acid production, acidogenicity, environmental pH, bacterial growth, bacterial viability, growth inhibition, and acid-related metabolic activity. (T) Studies published from database inception until the date of the final literature search were considered, with no restriction on publication year.

Inclusion criteria

The inclusion criteria were studies investigating *Streptococcus mutans* or cariogenic bacteria containing a relevant *S. mutans* component; studies in which nitrite (NO_2^-), including sodium nitrite, potassium nitrite, acidified nitrite, or nitrite ions, was the intervention or exposure of interest; and studies reporting at least one outcome related to acidogenic or antimicrobial activity, including acid production, acidogenicity, environmental pH, bacterial growth, bacterial viability, growth inhibition, or acid-related metabolic activity.

Exclusion criteria

The exclusion criteria were studies investigating non-cariogenic bacteria without a relevant *S. mutans* component; studies in which nitrite was not the intervention or exposure of interest; and studies that did not report any outcome related to the acidogenic or antimicrobial activity of *S. mutans*, including acid production, acidogenicity, environmental pH, bacterial growth, bacterial viability, growth inhibition, or acid-related metabolic activity.

Search strategies

The search strategy was developed using combinations of medical subject headings (MeSH) terms and free-text keywords related to the intervention and the target microorganism. The primary keyword combinations included: ("Nitrite" OR "Nitrites" OR "Sodium Nitrite" OR "Acidified Nitrite") AND ("*Streptococcus mutans*" OR "*S. mutans*" OR "Cariogenic Bacteria") AND ("Acid Production" OR "pH" OR "Acidogenicity"). The detailed searching strategies for each database are listed in Table 1. In addition, the reference lists of the fully retrieved eligible articles were manually screened (citation chasing) to identify any additional relevant publications. (TABLE 1).

Study selection

After eliminating duplicates, the remaining studies were screened based on their titles and abstracts. Studies that were not available in full-text form or did not meet the eligibility criteria were excluded. The remaining full-text studies were thoroughly evaluated to ensure strict compliance with the predefined inclusion criteria. One investigator screened the studies that manage the retrieved reports using Microsoft Excel Office 2019.

Risk of bias assessment

The methodological quality and risk of bias of the final five included studies were assessed independently by the author. Since all included papers were laboratory experimental designs, the Quality Assessment Tool for *In Vitro* Studies (QUIN) was utilized for critical appraisal. The author scored each study across the QUIN domains to determine whether it fell into the low, moderate, or high risk of bias category.

Data extraction

The author extracted primary data from the five eligible studies using a standardized extraction form. The extracted data components included: author and publication year, study design, concentrations of nitrite NO_2^- utilized, methods for measuring acidity, and the specific outcomes regarding *Streptococcus mutans* acid production and environmental pH alterations.

TABLE 1: Details of the Search Strategy and Results Based on Electronic Databases.

Database	Keyword / Search String
PubMed	("Nitrite"[All Fields] OR "Nitrites"[All Fields]) AND ("*Streptococcus mutans*"[MeSH Terms] OR "*Streptococcus mutans*"[All Fields] OR "*S. mutans*"[All Fields] OR "Cariogenic Bacteria"[All Fields]) AND ("Acid Production"[All Fields] OR "pH"[All Fields] OR "Acidogenicity"[All Fields])
Scopus	TITLE-ABS-KEY (("Nitrite" OR "Nitrites" OR "Sodium Nitrite" OR "Acidified Nitrite") AND ("*Streptococcus mutans*" OR "*S. mutans*" OR "Cariogenic Bacteria") AND ("Acid Production" OR "pH" OR "Acidogenicity"))
ScienceDirect	"Nitrite" AND "*Streptococcus mutans*" AND ("pH" OR "Acid Production")

RESULTS

Study selection

One reviewer screened titles and abstracts, assessed full-text eligibility, extracted data, and performed the risk-of-bias assessment. The PubMed database provided 21 studies; Scopus provided 13 studies; and 25 studies were from ScienceDirect. After removing the duplicates based on their titles, 54 studies were obtained. During the title and abstract screening phase, 49 records were excluded for specific reasons: 18 records lacked an abstract, and 31 records did not discuss Streptococcus mutans or meet the topic criteria. Consequently, 5 reports were sought and successfully retrieved for full-text eligibility assessment. Following a rigorous full-text review, all 5 studies met the predefined inclusion criteria and were finally included in the systematic review (Figure 1).

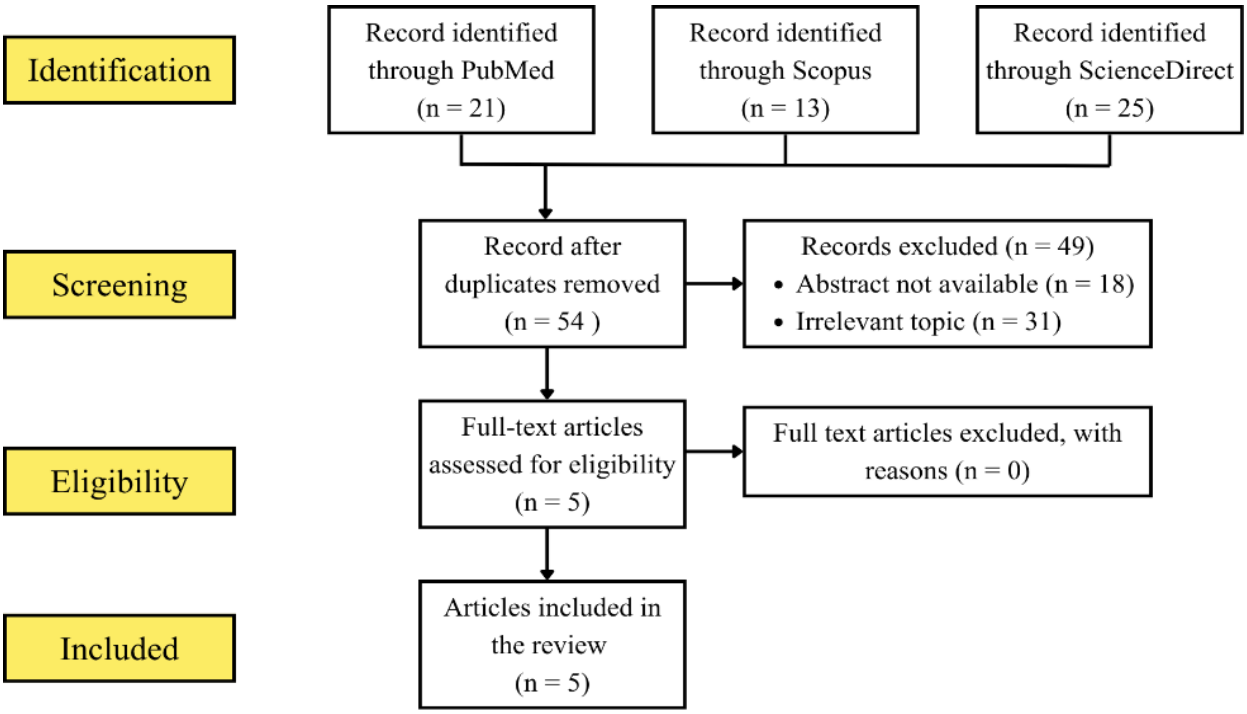

FIGURE 1: Flowchart of the Process of Screening and Selection of Articles.

Data Extraction

This systematic review synthesized data from five selected *in vitro* laboratory studies. The primary outcomes extracted from the eligible studies focused on changes in the acid production capacity and acidogenicity of *Streptococcus mutans*, as well as alterations in environmental pH following exposure to nitrite (NO_2^-). Related indicators of cariogenic activity, including bacterial growth, bacterial viability, growth inhibition, and acid-related metabolic activity, were also extracted when reported. The extracted data from the five studies were systematically organized according to the nitrite concentration used, bacterial species or strain, experimental methodology, exposure conditions, measured outcomes, and reported values of environmental pH, acid production, bacterial growth, or viability (Table 2).

TABLE 2: Data Extraction.

Variable	Xia et al. 2006	Radcliffe et.al 2003	Radcliffe et al. 2002	Silva Mendez et al. 1999	Wicaksono et al. 2020
Author and year	Xia D-S, Liu Y, Zhang C-M, Yang S-H, Wang S-L, 2006	Radcliffe CE, Lamb R, Blinkhorn AS, Drucker DB, 2003	Radcliffe CE, Akram NC, Hurrell F, Drucker DB, 2002	Silva Mendez LS, Allaker RP, Hardie JM, Benjamin N, 1999	Wicaksono DP, Washio J, Abiko Y, Domon H, Takahashi N, 2020
Country	China	UK	UK	UK	Japan
Study design	*In vitro* experimental study	*In vitro* experimental study (short communication)	*In vitro* experimental study	*In vitro* experimental study (short communication)	*In vitro* experimental study
Bacterial species	*S. mutans*, *L. acidophilus*, *P. gingivalis*, Capnocytophaga gingivalis, *F. nucleatum, C. albicans*	*S. mutans* only	*S. mutans* (primary); *A. naeslundii* ATCC 27038 and *L. casei* ATCC 4646 (comparators)	*S. mutans, A. naeslundii, L. casei*	Veillonella atypica ATCC 17744, Veillonella parvula ATCC 10740, *S. mutans* NCTC 10449
***Streptococcus mutans* strain**	NCTC 10449	NCTC 10449(T) and NCTC 10832	NCTC 10449(T); also, NCTC 10832 and R9 (strain-specificity control)	NCTC 10499	NCTC 10449
Nitrite compound/source	Sodium nitrite (NaNO2); sodium nitrate (NaNO3) tested separately	Sodium nitrite (NaNO2)	Sodium nitrite (NaNO2); sodium nitrate (NaNO3) tested for comparison	Sodium nitrite (NaNO2)	Potassium nitrite (KNO2); potassium nitrate (KNO3) tested separately
Initial pH / pH condition	Acidified with HCl to final pH 3.0, 4.0, 4.5, 5.0, 6.0, 7.0	NR	Fixed at pH 2.0-7.0 (independent variable)	pH 7 (buffered)	
Initial pH / pH condition	Acidified with HCl to final pH 3.0, 4.0, 4.5, 5.0, 6.0, 7.0	NR	Not preset acid; natural starting pH approx. 7.1-7.5	Fixed at pH 2.0-7.0 (independent variable)	pH 7 (buffered)
Initial pH / pH condition	Acidified with HCl to final pH 3.0, 4.0, 4.5, 5.0, 6.0, 7.0	NR	Not preset acid; natural starting pH approx. 7.1-7.5	Fixed at pH 2.0-7.0 (independent variable)	pH 7 (buffered)
Final pH/change in pH	NR	NCTC 10449: 0 mM=4.39+/-0.01 vs 200 mM=6.53+/-0.01; NCTC 10832: 0 mM=4.42+/-0.01 vs 200 mM=6.63+/-0.00 (varies slightly by ascorbic acid level, see Table 2)	*S. mutans* NCTC 10449: 0 mM=4.6+/-0.00; 0.2 mM=4.6+/-0.04; 2.0 mM=4.7+/-0.05; 20 mM=5.4+/-0.04*; 200 mM=6.6+/-0.03*. Nitrate: all approx. 4.6 (NS)	NR	NR
Growth outcome	OD decreased dose-dependently with nitrite; effect increased with acidity; nitrate had no effect at any concentration	Viable at 4.5x10^8-7.9x10^9 cfu/ml without nitrite (any ascorbic acid level); not detected (0 cfu/ml) with 200 mM nitrite at all ascorbic acid concentrations, both strains	cfu/ml fell dose-dependently: 0 mM=4.49x10^9; 0.2 mM=4.11x10^7; 2.0 mM=1.45x10^7; 20 mM=4.38x10^6; 200 mM=1.79x10^6. R9 completely inactivated at 200 mM; NCTC 10832 ~50% reduction. Nitrate: no growth effect at any concentration	Growth (OD540) inhibited by more acid pH (P<0.001) and by increasing nitrite dose-dependently (P<0.001); effect seen even at 0.2 mM; at pH<7, 0.2 mM caused complete killing on recovery testing (P<0.001)	KNO3 had no effect on *S. mutans* growth except at 100 mM (P<0.05); KNO2 reduced *S. mutans* growth dose-dependently, inhibition evident from 0.5 mM (P<0.01)

Variable	Xia et al. 2006	Radcliffe et.al 2003	Radcliffe et al. 2002	Silva Mendez et al. 1999	Wicaksono et al. 2020
Acid production/ acidogenicity outcome	NR	138-fold (NCTC 10449) and 162-fold (NCTC 10832) reduction in [H+]; ascorbic acid had little independent effect and did not block nitrite's action (possible synergism for NCTC 10449)	200 mM NO_2^-= 99% reduction in [H+]; 20 mM = 84% reduction; effect persisted anaerobically (pH 6.9 vs 5.1 without nitrite); not due to salt/osmotic stress or glucose limitation	NR	NR
Other relevant outcomes	MIC/MBC per pH, e.g. at pH 5.0: MIC=0.5, MBC=1 mmol/L; at pH 7.0: MIC=2, MBC=10 mmol/L. Susceptibility ranking: *S. mutans* most sensitive of the 6 organisms	Detection limit = 50 cfu/ml (stated explicitly)	Harvested/biofilm cells produced acid immediately, but nitrite still blocked pH fall at all time points; broth cells showed effect mainly after 24 h	Recovery (bactericidal) assay showed nitrite-concentration-dependent reduction in recovery ($P<0.05$); similar effects in *A. naeslundii* and *L. casei*	Veillonella required >=20 mM $NO_2^-$to be inhibited (much more resistant than *S. mutans*); Veillonella produces NO_2^- from NO_3^-via lactate-linked metabolism
Main result	Acidified nitrite (0.5-10 mmol/L) inhibited/killed *S. mutans* dose- and pH-dependently; nitrate had no antimicrobial effect	200 mM NaNO2 completely killed *S. mutans* and abolished acid production regardless of ascorbic acid presence	Nitrite at 20-200 mM is bactericidal and anti-acidogenic for *S. mutans* (and other acidogenic species); nitrate ineffective at 0.2-200 mM	Acidified nitrite as low as 0.2 mM (near salivary levels) caused dose- and pH-dependent inhibition and complete killing of *S. mutans*	NO_2^- inhibits *S. mutans* growth at low concentration (0.5 mM); NO_3^- has no effect on *S. mutans* except at very high concentration (100 mM)

Risk of Bias assessment

Quality assessment was carried out on the five included studies, all of which utilized a laboratory experimental design (*in vitro*). The Quality Assessment Tool for *In Vitro* Studies (QUIN) was employed to evaluate the methodological quality and critical appraisal of these selected papers. Based on the QUIN criteria, all five studies [12,13,14,15] were classified as having a moderate risk of bias (Table 3).

TABLE 3: Risk of Bias Assessment.

Author, year	1	2	3	4	5	6	7	8	9	10	11	12
Xia, 2006	Y	N	Y	Y	Y	N	N	Y	N	N	Y	Y
Radcliffe, 2003	Y	N	Y	Y	Y	N	N	Y	N	N	Y	Y
Radcliffe, 2002	Y	N	Y	Y	Y	N	N	Y	N	N	Y	Y
Silva Mendez, 1999	Y	N	UC	Y	Y	N	N	Y	N	N	UC	Y
Wicaksono, 2020	Y	N	Y	Y	Y	N	N	Y	N	N	Y	Y

1, Were the aims and objectives of the study clearly stated? **2**, Was a detailed evaluation of the sample size calculation provided? **3**, Was the sampling methodology described in detail? **4**, Were the details of the intervention or group descriptions clearly presented? **5**, Was there detailed clarity regarding the procedures applied? **6**, Was the operator calibration or standardization adequately described? **7**, Were the randomization details clearly described? **8**, Was the method of blinding explicitly described? **9**, Was the outcome measurement method described in a valid and reliable way? **10**, Was the blinding of the outcome assessment clearly described? **11**, Were the statistical analysis details fully described? **12**, Was the presentation of the results or outcomes comprehensive and clear? *N, no; UC, unclear; Y, yes*

DISCUSSION

Evidence Summary

Five *in vitro* studies into nitrite's effect on *Streptococcus mutans* acidogenicity and growth were synthesized in this systematic review. Four of these studies matched the PICO directly [12,13,14,15], while the remaining study supported the mechanism indirectly [21].

A study by Radcliffe et al. (2002) showed the effects of sodium nitrite and nitrate at different concentrations on the ability of *S. mutans* NCTC 10449 to lower the pH were studied and whether these two compounds exerted bactericidal or bacteriostatic effects against *S. mutans.* The study used concentrations of 0.0, 0.2, 2.0, 20, and 200 mM, with Fastidious Anaerobe Broth (FAB) selected for its low buffering capacity to allow significant changes in pH to occur. The results showed that nitrite significantly inhibited the ability of S. mutans to lower the pH, with highly significant effects observed at concentrations of 20 and 200 mM. In the group with 0.2 mM nitrite, the pH decreased to 4.6; at 2.0 mM nitrite, the pH decreased to 4.7; at 20 mM nitrite, the pH decreased to 5.4; and at 200 mM nitrite, the pH decreased to 6.6. These findings indicate that nitrite can inhibit the acidification process caused by *S. mutans*. This effect was also reflected in the reduction in hydrogen ion concentration ($[H^+]$), which was 84% at 20 mM and 99% at 200 mM compared with the group without nitrite. The study concluded that nitrite exhibited bactericidal and anti-acidogenic effects against *S. mutans*, indicating that nitrite not only reduces bacterial viability but also inhibits the acidification process.

Potential risks associated with nitrosamine formation during nitrite exposure led Radcliffe et al. (2003) to analyzed the combined treatment against *S. mutans*. In this study, 200 mM sodium nitrite prevented the environmental pH from falling below the critical pH associated with enamel demineralization in both *S. mutans* NCTC 10449 and NCTC 10832. In NCTC 10449, the final pH remained between 6.53 and 6.69 in the presence of nitrite, compared with 4.32–4.39 without nitrite. Similarly, NCTC 10832 showed final pH values of 5.55–6.71 with nitrite, compared with 4.36–4.60 without nitrite. The study also reported substantial reductions in hydrogen ion concentration, corresponding to approximately 138-fold and 162-fold reductions for the two strains. Importantly, the inhibitory effect of nitrite was maintained across the concentrations of ascorbic acid tested, indicating that ascorbic acid did not prevent the anti-acidogenic and bactericidal effects of nitrite.

Evidence from Silva Mendez et al. (1999) and Xia et al. (2006) provides further support for the inhibitory effect of nitrite on *S. mutans*, and these studies primarily evaluated bacterial growth and viability rather than acid production or environmental pH directly. Silva Mendez et al. (1999) found that acidic conditions inhibited the growth of *S. mutans*, while the addition of nitrite produced a greater, dose-dependent reduction in bacterial numbers. Notably, 0.2 mM nitrite resulted in complete killing of *S. mutans* at pH values below 7. Expanding on this acid-enhanced susceptibility, Xia et al. (2006) confirmed that acidified nitrite exerts potent antimicrobial effects across multiple oral pathogens, with *S. mutans* proving exceptionally sensitive. Because the magnitude of bacterial inhibition scaled directly with the medium's acidity in both investigations, these data collectively highlight environmental pH as a decisive regulator of nitrite's antibacterial potency.

The relationship between nitrite and environmental acidity can also be understood from the ecological perspective provided by Wicaksono et al. (2020). This study primarily investigated nitrate reduction and nitrite production by oral Veillonella species rather than directly examining acid production by *S. mutans*. The study demonstrated that nitrite production increased under conditions associated with oral biofilm metabolism, including acidic and anaerobic environments and the presence of lactate, and also showed that nitrite inhibited the growth of *S. mutans* at concentrations lower than those required to inhibit the Veillonella species investigated. These findings suggest that nitrite production within the oral microbial community may contribute to an ecological interaction in which nitrite-producing bacteria can suppress more nitrite-sensitive cariogenic bacteria.

Strength and limitations

Overall, the studies identified provided strong evidence for the inhibitory effect of nitrite on *S. mutans*. Despite differences in nitrite concentrations, pH conditions, bacterial strains, and experimental approaches, the studies generally demonstrated inhibitory effects of nitrite against *S. mutans*, either through reduced bacterial growth and viability or reduced acidogenic activity. Radcliffe et al. (2002), for example, directly demonstrated that nitrite at 20 and 200 mM significantly inhibited the ability of *S. mutans* to lower environmental pH, while Radcliffe et al. (2003) similarly reported suppression of bacterial growth and acid production. Xia et al. (2006) further supported these findings by showing that nitrite inhibited several oral pathogens, with its antimicrobial activity increasing under more acidic conditions. In addition, Wicaksono et al. (2020) provided a broader mechanistic perspective by demonstrating the relationship between nitrate reduction, nitrite production, and lactate metabolism in oral Veillonella species.

However, several limitations should be considered when interpreting these findings. All included studies were conducted *in vitro*, meaning that the experimental conditions do not fully reproduce the complexity of the oral environment, particularly mature dental biofilms and interactions among multiple microbial species. There was also considerable variation in nitrite concentrations, with some studies using concentrations as high as 200 mM, which may have limited physiological relevance.

Furthermore, most studies focused on *S. mutans* or a limited number of oral microorganisms, and outcomes differed between studies, making direct comparison difficult. Xia et al. (2006) mainly evaluated antimicrobial effects, whereas Radcliffe et al. (2002, 2003) specifically assessed pH and acidogenicity. Therefore, although the findings consistently support antimicrobial and anti-acidogenic potential, their direct translation to clinical caries prevention remains uncertain.

Implication for practices and future research

The findings suggest that nitrite showed *in vitro* effects on selected *S. mutans* outcomes; however, its clinical efficacy and safety for caries prevention remain undetermined.

Radcliffe et al. (2002) demonstrated that nitrite could significantly inhibit the ability of *S. mutans* to reduce environmental pH, while Xia et al. (2006) showed that nitrite had antimicrobial activity at concentrations of 0.5–10 mM under acidic conditions. These findings provide a rationale for further consideration of nitrite-related strategies, including dietary nitrate pathways and nitrite-containing oral care products. Wicaksono et al. (2020) showed that oral Veillonella can convert nitrate to nitrite and that nitrite production is associated with lactate metabolism, suggesting a possible link between dietary nitrate, oral microbial metabolism, and nitrite availability. However, these findings are not sufficient to recommend nitrite as an established clinical treatment or replacement for conventional caries-preventive measures. At present, nitrite should be considered a potential adjunct to established strategies such as fluoride use, plaque control, and dietary sugar reduction until its clinical efficacy and safety are confirmed.

Future research should focus primarily on translating the current *in vitro* evidence into more clinically relevant models. *In vivo* studies and randomized clinical trials are needed to determine whether nitrite can produce similar antimicrobial and anti-acidogenic effects within dental plaque and whether these effects can reduce caries development. Further studies should also investigate physiologically achievable nitrite concentrations, dose–response relationships, activity against mature multispecies biofilms, and differences between *S. mutans* strains. The nitrate–nitrite pathway also warrants further investigation, particularly because Wicaksono et al. (2020) demonstrated that nitrite production by Veillonella is influenced by lactate availability, acidic conditions, and anaerobic metabolism. In addition, future research should evaluate the long-term safety of nitrite exposure, its effects on the overall oral microbiome, and the feasibility of incorporating nitrite-related mechanisms into oral care products. Radcliffe et al. (2003) also showed that ascorbic acid did not prevent the antibacterial action of nitrite, providing a basis for further investigation of potential combinations while ensuring their safety and clinical effectiveness.

CONCLUSIONS

These five studies suggest that nitrite may influence cariogenic activity through two mechanisms, by inhibiting *S. mutans* viability or growth, and suppressing the acidification process. The strongest direct evidence comes from Radcliffe et al. (2002) and Radcliffe et al. (2003), whereas Silva Mendez et al. (1999), Xia et al. (2006), and Wicaksono et al. (2020) provide complementary evidence concerning bacterial inhibition and the ecological relationship between nitrite and acidic oral environments. However, the included studies differed considerably in nitrite concentration, bacterial strains, experimental conditions, and outcome measurements. Therefore, the findings should be interpreted primarily as evidence of a potential anti-acidogenic and antimicrobial effect of nitrite rather than as evidence for a single effective nitrite concentration. Furthermore, because the available evidence is predominantly derived from *in vitro* experiments, the extent to which these findings translate to the complex and dynamic oral environment requires further investigation.

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