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Review

Impact of Mouthwash-Induced Oral Microbiome Disruption on Alzheimer's Disease Risk: A Perspective Review

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ABSTRACT

The widespread use of mouthwashes, particularly those containing chlorhexidine (CHX), has raised concerns about their impact on the oral microbiome and potential systemic health effects. This perspective review examines the current evidence linking CHX mouthwash use to disruptions in the oral microbiome and explores the potential indirect implications for Alzheimer's disease (AD) risk. CHX mouthwash is effective in reducing dental plaque and gingival inflammation, but it also significantly alters the composition of the oral microbiome, decreasing the abundance of nitrate-reducing bacteria critical for nitric oxide (NO) production. This disruption can lead to increased blood pressure, a major risk factor for AD. Given the established connection between hypertension and AD, the long-term use of CHX mouthwash may indirectly contribute to the onset of AD. However, the relationship between CHX mouthwash use and AD remains largely indirect, necessitating further longitudinal and cohort studies to investigate whether a direct causal link exists. The review aims to highlight the importance of maintaining a balanced oral microbiome for both oral and systemic health and calls for more research into safer oral hygiene practices and their potential impacts on neurodegenerative disease risk.

Introduction

Alzheimer's disease (AD) is the main leading cause of dementia, accounting for approximately 60%-80% of cases,[1] and is rapidly becoming one of the most costly, deadly, and burdensome diseases of this century.[2] This progressive neurodegenerative disorder is characterized by cognitive decline, memory loss, and behavioural changes, primarily affecting the elderly. As the global population ages, the prevalence of AD is expected to rise significantly, posing a substantial public health challenge. The etiology of AD is multifactorial, involving genetic, environmental, and lifestyle factors.[3] Despite extensive research, the precise mechanisms underlying AD remain elusive, necessitating a comprehensive understanding of all potential risk factors.

Recent research has underscored the significance of oral health in systemic diseases, including cardiovascular diseases and diabetes. Emerging evidence suggests that poor oral hygiene and periodontal disease may be linked to an increased risk of AD.[4] One of the primary pathogens implicated in this connection is *Porphyromonas gingivalis* (*P. gingivalis*), a bacterium associated with chronic periodontitis. Studies have detected this bacterium in the brains of AD patients, suggesting its potential role in neuroinflammation and neurodegeneration by migrating from the oral cavity to the brain and releasing neurotoxic substances such as gingipains.[5] Additionally, periodontal disease has been shown to be associated with a 1.45-fold increase in the risk of developing AD and an increase in amyloid-β load, further emphasizing the importance of oral health in preventing cognitive decline.[6]

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Mouthwashes, particularly those containing antimicrobial agents like chlorhexidine, are widely used to maintain oral hygiene by reducing microbial load in the mouth. However, these mouthwashes can disrupt the balance of the oral microbiome, which plays a crucial role in the enterosalivary nitrate-nitrite-nitric oxide (NO) pathway.[7] This pathway is essential for cardiovascular health, as NO is a key signalling molecule involved in vasodilation and blood pressure regulation. Disruption of this pathway by antiseptic mouthwashes can lead to decreased NO production and elevated blood pressure—a recognized risk factor for AD.[8]

The Lancet Commission on dementia prevention, intervention, and care has identified several modifiable risk factors for dementia, including hypertension, obesity, smoking, physical inactivity, and diabetes, which together account for approximately 40% of worldwide dementia cases.[3] Hypertension, in particular, has been shown to increase the risk of cognitive decline and dementia. Given the potential link between mouthwash use, disruption of the oral microbiome, and increased blood pressure, it is imperative to investigate whether these common oral hygiene practices could contribute to the onset of AD.

This review aims to explore the potential link between the use of mouthwashes, particularly those with strong antimicrobial properties, and the increased risk of AD (Figure 1). By examining current evidence on how these products affect the oral microbiome and systemic health, we hope to shed light on the mechanisms that may underlie this association and highlight the importance of balanced oral hygiene practices in preventing cognitive decline.

Oral health and neurodegeneration

Oral health has long been recognized as an integral component of overall systemic health.[9,10] Recent studies have increasingly pointed to its significant impact on systemic conditions, including neurodegenerative diseases such as AD.[11] Poor oral health, particularly periodontal disease caused by pathogens like *P. gingivalis*, has been linked to an elevated risk of AD.[11,12] Some studies are epidemiological investigations,[13-16] while others explore the connection between periodontitis and serum levels of beta-amyloid[17] or utilize brain imaging to detect amyloid deposits[6]. *P. gingivalis* can migrate to the brain through the bloodstream, where it releases neurotoxic enzymes called gingipains that contribute to neuroinflammation and neuronal damage, exacerbating the formation of amyloid-β plaques and tau tangles, thereby contributing to the onset and progression of AD.[5,11] Clinical studies have demonstrated that poor oral health, indicated by a higher number of missing teeth and greater periodontal probing depth, is associated with lower cognitive scores and an increased risk of cognitive decline.[4] For instance, a systematic review and meta-analysis revealed that patients with AD have a significantly higher risk of tooth loss and edentulism compared to healthy controls.

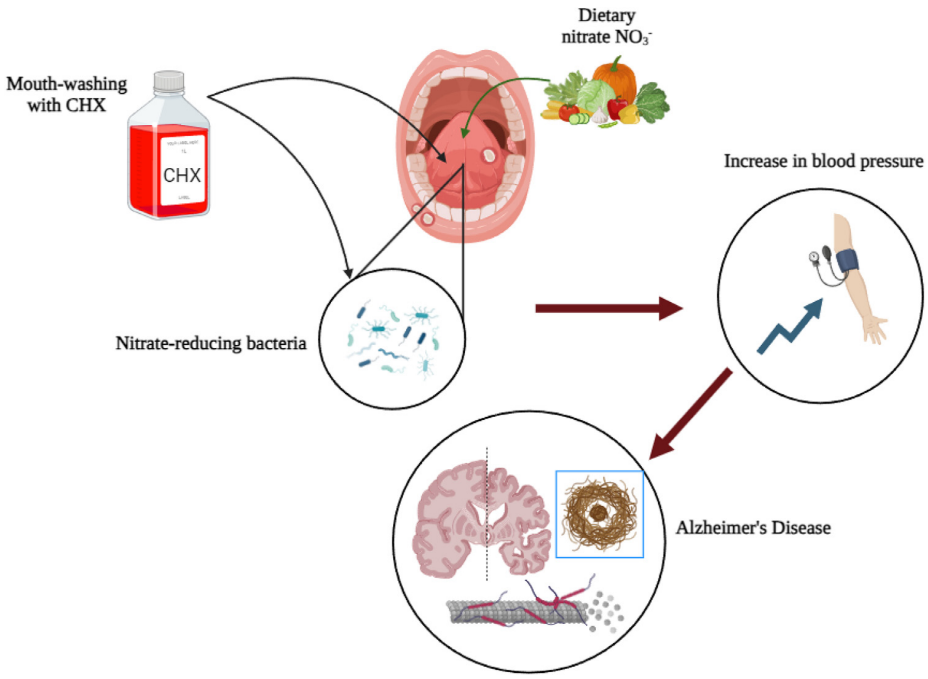

Fig. 1 – This graphical abstract illustrates the impact of oral microbiome disruption on Alzheimer's disease (AD) risk. *Porphyromonas gingivalis*, associated with periodontal disease, migrates to the brain, releasing neurotoxic substances and contributing to neuroinflammation and amyloid-β plaque formation in AD. The nitrate-nitrite-nitric oxide (NO) pathway, where dietary nitrates are converted by oral bacteria to nitrite and then, to NO, is crucial for vasodilation and blood pressure regulation. Chlorhexidine (CHX) mouthwash reduces nitrate-reducing bacteria, leading to decreased NO production and increased blood pressure, a risk factor for AD. (Created with BioRender.com, accessed on July 1, 2024).

Table 1 – Summary of evidence linking oral health, mouthwash use, and Alzheimer's disease.

Aspect	Evidence	Reference
Oral health and AD	Poor oral health and periodontal disease linked to elevated risk of AD; *P. gingivalis* found in AD patients' brains.	5,6,11,12,17
	Higher incidence of hypodontia and greater periodontal probing depth associated with lower cognitive scores and increased risk of cognitive decline.	4,18
	Animal studies show *P. gingivalis* infection leads to brain colonization and cognitive impairment.	5,20
Oral microbiome and cardiovascular health	The nitrate–nitrite–NO pathway is essential for cardiovascular health; disrupted by antimicrobial mouthwashes.	21-23
	NO is recognized as a vital signalling molecule in the cardiovascular system; higher NO levels are associated with lower CVD risk.	
	Pathological conditions like pulmonary arterial hypertension and other forms of pulmonary hypertension exhibit reduced NO signalling bioavailability and impaired endothelial responsiveness.	24,25
	Vascular diseases, CVD, and metabolic syndrome are characterized by significant NO functionality loss.	26,27
	The ingestion of nitrates, abundant in vegetables like beetroot and spinach, is crucial for the nitrate–nitrite–NO pathway, with oral bacteria playing a key role in converting nitrates to nitrites	28-33
	Humans rely on oral commensal bacteria for the nitrate-to-nitrite conversion, emphasizing the symbiotic relationship and its importance in maintaining vascular health.	32,33
	NO has a short half-life, making continuous production essential for vascular health.	21,34
Effects of mouthwash on oral microbiome	CHX mouthwash significantly alters the salivary microbiome, leading to more acidic conditions and lower nitrite availability.	21,36
	CHX mouthwash increases blood pressure, which is correlated with reduced plasma nitrite levels.	7,30,38_40
	Gargling with CHX mouthwash significantly reduces nitrate-reducing bacteria by approximately 80%.	30
Smoking and oral microbiome	Smoking is associated with microbial dysbiosis, increased pathogenic bacteria, and decreased beneficial bacteria.	41
	Smoking contributes to conditions like periodontitis, linked to systemic inflammation and AD.	41
Hypertension and AD	Midlife hypertension is strongly associated with an increased risk of late-life dementia.	3,43,44
	Persistent hypertension contributes to vascular damage, which can impair blood flow to the brain, and promote neuroinflammation and neurodegeneration, key processes in the development of AD.	44,45

AD: Alzheimer's Disease, CHX: Chlorhexidine, CVD: Cardiovascular Diseases, NO: Nitric Oxide, *P. gingivalis: Porphyromonas gingivalis*.

Specifically, the hazard ratio (HR) for dental loss was 1.52 (95% CI 1.00-2.30), and for edentulous conditions, it was 2.26 (95% CI 1.70-3.01).[18] Hypodontia was also shown to be associated with hypertension, a major risk factor for AD.[19] Furthermore, animal studies have shown that oral infection with *P. gingivalis* can lead to brain colonization and cognitive impairment, while treatment with gingipain inhibitors reduces the bacterial load of an established *P. gingivalis* brain infection, blocks Aβ1–42 production, reduces neuroinflammation, and rescues neurons in the hippocampus.[5,20] Given these associations, maintaining good oral hygiene may be a crucial strategy in preventing cognitive decline and neurodegenerative diseases (Table 1). The association between poor oral health and neurodegenerative diseases like AD is supported by a growing body of evidence. While these studies indicate a strong correlation, direct causative studies are still lacking.

Effects of the oral microbiome on nitric oxide production and vascular health

The human oral microbiome, particularly the tongue microbiome, plays a significant role in cardiovascular health through the enterosalivary nitrate-nitrite-nitric oxide (NO) pathway. This pathway is essential for converting dietary nitrates, predominantly found in vegetables and in water, into nitrite and subsequently into NO, which is crucial for maintaining vascular health.[21] NO was first recognized in 1998 as a vital signalling molecule in the cardiovascular system and is involved in regulating vascular tone, inhibiting platelet aggregation, and maintaining endothelial function.[22] Higher circulating concentrations of NO are associated with a lower risk of cardiovascular diseases (CVD).[22,23] Pathologically, conditions like pulmonary arterial hypertension and other forms of pulmonary hypertension exhibit reduced NO signalling bioavailability and impaired endothelial responsiveness to vasodilatory triggers.[24,25] Similarly, vascular diseases, CVD, and metabolic syndrome are all characterized by significant NO functionality loss.[26,27]

The nitrate–nitrite–NO pathway begins with the ingestion of nitrates, which are abundant in vegetables like beetroot and spinach,[28] accounting for 80% of daily nitrate intake.[29] These dietary nitrates are reduced to nitrite by nitrate-reducing bacteria in the mouth, primarily residing on the dorsum of the tongue.[30,31] Most of these bacteria are found on the surface of the tongue and around the teeth, where a millilitre of saliva can contain up to 10^7 to 10^8 microorganisms.[32] This conversion is crucial because humans cannot complete this process without these bacteria.[32] A symbiotic relationship exists between the host and the oral commensal bacteria, where the bacteria utilize nitrate for respiration and, in return, produce nitrite required by the host. Approximately 80% of nitrates swallowed and present in the stomach are produced by these oral commensals.[21,33]

Once produced in the endothelial cells *via* the endogenous pathway, NO rapidly diffuses to the underlying smooth muscle layer, mediating blood vessel vasodilation. The NO that remains in the circulation is quickly converted to nitrate by oxyhaemoglobin or superoxide before entering the enterosalivary pathway. Therefore, NO has a relatively short half-life, lasting only seconds to minutes, emphasizing the importance of continuous NO production for maintaining vascular health[21,34] (Table 1).

Given the significant role of the oral microbiome in managing blood pressure through NO homeostasis, it is essential to maintain a balanced oral microbial community, ensuring a diet rich in nitrates, such as those from green leafy vegetables and beetroot.

Effects of chlorhexidine mouthwash on the oral microbiome

Mouthwashes are commonly used to maintain oral hygiene by reducing the microbial load in the mouth or to treat oral pathogens and diseases. A study on 3,022 humans revealed that 17.5% used mouthwash less than once a month, 19.4% used mouthwash once every few days, and 25.1% used mouthwash daily.[35] These products, especially those containing antimicrobial agents like chlorhexidine (CHX), are effective in controlling dental plaque, gingival inflammation, and bleeding. However, their impact on the oral microbiome is a subject of growing concern. The effectiveness of mouthwashes in eliminating oral microbiomes varies depending on their composition. CHX-based mouthwashes, such as Corsodyl, have been found to be more effective at reducing *Veillonella dispar*, a nitrate-reducing bacterium, in the oral cavity compared to other mouthwashes like Listerine, which contains a mixture of essential oils, and other antibacterial mouthwashes like Isodine and Cepacol.[21,36]

CHX has been widely used since the 1970s as an antiseptic due to its long-lasting antibacterial activity. Its effects have been extensively studied in animal models.[37] Fewer studies on humans have investigated the impact of CHX mouthwashes on mixed bacterial communities (microbiome) in the oral cavity. These studies demonstrate that mouthwash containing CHX is associated with a major shift in the salivary microbiome, leading to more acidic conditions and lower nitrite availability in healthy individuals. One study by Bescos et al.[7] showed that a 7-day use of CHX mouthwash significantly altered the composition of the salivary microbiome, increasing the abundance of *Firmicutes* and *Proteobacteria* while reducing the presence of *Bacteroidetes, TM7, SR1* and *Fusobacteria*. This shift resulted in decreased salivary pH, indicating more acidic conditions, and increased saliva lactate and glucose levels. The second study by Tribble et al.[38] using 16S rRNA gene sequencing and analysis, found that the introduction of CHX mouthwash for one week was associated with a significant increase in systolic blood pressure. However, recovery from use resulted in an enrichment of nitrate-reducing bacteria on the tongue. Individuals with relatively high levels of bacterial nitrite reductases had lower resting systolic blood pressure.

Furthermore, it has been proven that gargling with 10 ml of CHX mouthwash twice for 1 minute reduces the bacterial count of nitrate-reducing bacteria by approximately 80% and virtually abolishes the oral nitrate-reducing capacity compared to no mouthwash in healthy subjects.[30] Additionally, using 0.2% CHX twice daily for 7 days significantly increased systolic and diastolic blood pressure by approximately 3 and 2 mmHg, respectively, in 19 healthy normotensive subjects. This rise in blood pressure was evident after just a single use and maintained for the following six days, correlating with a significant reduction in plasma nitrite levels.[39] Moreover, in 15 subjects treated with antihypertensive medication, daily use of CHX mouthwash for 3 days led to an increase in systolic blood pressure of 2.3 mmHg and a trend for decreased plasma nitrite concentrations compared to the control group using tap water.[40]

The previous evidence has shown that eliminating these oral bacteria with CHX-based mouthwash reduces the conversion of nitrate to nitrite, which is associated with an increase in blood pressure in normotensive individuals. This reduction occurs because the nitrate-to-nitrite conversion by oral bacteria is critical for maintaining adequate NO levels, necessary for vasodilation and blood pressure control. These findings suggest that while CHX mouthwash effectively manages oral pathogens in the short term, its long-term use can disrupt the oral microbiome, leading to negative systemic effects such as increased blood pressure.

It is worth noting that not only do mouthwashes impact the oral microbiome, but other factors such as smoking[41] as well as other extrinsic host factors like diet, lifestyle, oral hygiene practices, environmental conditions, and access to dental care[42] (Table 1).

Chlorhexidine mouthwashes and the risk of Alzheimer's disease

The long-term use of CHX mouthwash has been shown to significantly impact the oral microbiome and systemic health. The previous section established that CHX mouthwashes can increase blood pressure by reducing the population of nitrate-reducing bacteria in the oral cavity, which are essential for the conversion of nitrate to nitrite and the production of NO. This disruption leads to decreased vasodilation and higher blood pressure. Given that hypertension is a well-documented major risk factor for AD, CHX mouthwash may indirectly contribute to an increased risk of AD onset.

Cohort studies have shown that midlife hypertension is strongly associated with an increased risk of late-life dementia. For instance, in the Framingham Offspring cohort study of 1,440 individuals, elevated systolic blood pressure (≥140 mm Hg) in midlife was associated with a 1.6-fold increased risk of developing dementia over an 18-year follow-up period. This risk increased further if hypertension persisted into later life (HR 2.0).[43] Similarly, a UK cohort study involving 8,639 civil servants found that a single measure of systolic blood pressure of 130 mm Hg or higher at age 50, but not at 60 or 70 years, was associated with a 1.4-fold increased risk of dementia.[44] These studies underscore the critical role of blood pressure management in reducing the risk of

neurodegenerative diseases. Hypertension contributes to vascular damage, which can impair blood flow to the brain and may contribute to amyloid deposition, promoting neuroinflammation and neurodegeneration, all of which are key processes in the development of AD.[45] As hypertension is a modifiable risk factor for AD, any agent that contributes to elevated blood pressure could potentially increase the risk of developing this neurodegenerative disease. Therefore, the use of CHX mouthwashes, by promoting higher blood pressure, may indirectly facilitate conditions that lead to AD.

Despite these associations, it is crucial to note that the link between CHX mouthwashes and AD remains indirect. Current evidence suggests that CHX mouthwash can elevate blood pressure, which is a known risk factor for AD. However, direct studies linking CHX use to the onset of AD are lacking. This gap in research highlights the urgent need for longitudinal and cohort studies to explore whether a direct causal relationship exists between CHX mouthwash use and the development of AD. Longitudinal studies following individuals over time and cohort studies comparing different populations with varying levels of CHX mouthwash use could provide the necessary data to determine if there is a direct link. Such studies would help clarify the potential risks associated with long-term CHX mouthwash use and guide recommendations for its use in oral hygiene practices, particularly among populations at risk for hypertension and AD.

Conclusion and call for future research

While indirect evidence suggests a potential link between mouthwash use, oral microbiome disruption, and increased risk of AD, there are no direct studies conclusively proving this connection. The body of available research highlights the importance of oral health and its impact on systemic health, including cardiovascular health and cognitive function. However, to establish a direct causal relationship, there is an urgent need for longitudinal and cohort studies that can provide more definitive evidence. Future research should focus on long-term studies that track the use of mouthwashes, changes in the oral microbiome, blood pressure regulation, and cognitive health-related outcomes over time.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

All authors contributed to the present manuscript's conceptualization, design, methodology and final version.

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