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# ORAL BACTERIA LINKED TO PARKINSON'S DISEASE THROUGH THE GUT–BRAIN AXIS: EVIDENCE OF STREPTOCOCCUS MUTANS METABOLITES AFFECTING NEURAL FUNCTION

# BACTÉRIAS ORAIS LIGADAS À DOENÇA DE PARKINSON POR MEIO DO EIXO INTESTINO–CÉREBRO: EVIDÊNCIAS DE METABÓLITOS DE STREPTOCOCCUS MUTANS AFETANDO A FUNÇÃO NEURAL

# BACTERIAS ORALES VINCULADAS A LA ENFERMEDAD DE PARKINSON A TRAVÉS DEL EJE INTESTINO–CEREBRO: EVIDENCIA DE METABOLITOS DE STREPTOCOCCUS MUTANS QUE AFECTAN LA FUNCIÓN NEURAL

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## ABSTRACT

**Objective:** This narrative review aims to analyze current evidence linking oral bacteria, particularly Streptococcus mutans, to Parkinson's disease (PD) through the gut–brain axis (GBA). The focus is on microbial colonization of the intestine, metabolite production, and the mechanisms by which these metabolites influence neural function.

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**Methodology:** A comprehensive search of PubMed, Scopus, Web of Science, and Google Scholar was conducted using the keywords “Streptococcus mutans,” “Parkinson’s disease,” “gut–brain axis,” “oral microbiota,” and “neuronal dysfunction.” Both in vivo and in vitro studies published in English between 2015 and 2025 were included.

**Results:** Evidence indicates that S. mutans can migrate to the intestine, producing urocanate reductase (UrdA) and its metabolite imidazole propionate (ImP), which enter systemic circulation and reach the brain. Animal models demonstrated that these metabolites contribute to dopaminergic neuron loss, neuroinflammation, motor dysfunction, and α-synuclein aggregation. The effects were mediated via activation of the mTORC1 signaling pathway, and pharmacological inhibition of mTORC1 mitigated neurodegenerative changes.

**Conclusion:** Oral bacteria, particularly S. mutans, may play a critical role in PD pathogenesis via the GBA. Targeting gut microbial composition and metabolite production represents a promising therapeutic avenue. The findings emphasize the potential importance of oral health in preventing or mitigating neurodegenerative disorders.

**Keywords:** Parkinson’s Disease. Streptococcus Mutans. Gut–Brain Axis. Oral Microbiota. Neuronal Function. Imidazole Propionate.

**RESUMO**

**Objetivo:** Esta revisão narrativa tem como objetivo analisar as evidências atuais que relacionam bactérias orais, particularmente Streptococcus mutans, à doença de Parkinson (DP) por meio do eixo intestino–cérebro (GBA). O foco está na colonização microbiana do intestino, na produção de metabólitos e nos mecanismos pelos quais esses metabólitos influenciam a função neural.

**Metodologia:** Foi realizada uma busca abrangente nas bases PubMed, Scopus, Web of Science e Google Scholar, utilizando as palavras-chave “Streptococcus mutans”, “doença de Parkinson”, “eixo intestino-cérebro”, “microbiota oral” e “disfunção neuronal”. Foram incluídos estudos in vivo e in vitro publicados em inglês entre 2015 e 2025.

**Resultados:** As evidências indicam que S. mutans pode migrar para o intestino, produzindo urocanato redutase (UrdA) e seu metabólito imidazol propionato (ImP), que entram na circulação sistêmica e alcançam o cérebro. Modelos animais demonstraram que esses metabólitos contribuem para a perda de neurônios dopaminérgicos, neuroinflamação, disfunção motora e agregação de α-sinucleína. Os efeitos foram mediados pela ativação da via de sinalização mTORC1, e a inibição farmacológica dessa via reduziu as alterações neurodegenerativas.

**Conclusão:** Bactérias orais, especialmente S. mutans, podem desempenhar um papel crítico na patogênese da DP por meio do GBA. Modificar a composição microbiana intestinal e a produção de metabólitos representa uma estratégia terapêutica promissora. Os achados enfatizam a importância potencial da saúde bucal na prevenção ou mitigação de distúrbios neurodegenerativos.

**Palavras-chave:** Doença de Parkinson. Streptococcus Mutans. Eixo Intestino–Cérebro. Microbiota Oral. Função Neuronal. Imidazol Propionato.

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**RESUMEN**

**Objetivo:** Esta revisión narrativa tiene como objetivo analizar la evidencia actual que vincula bacterias orales, particularmente Streptococcus mutans, con la enfermedad de Parkinson (EP) a través del eje intestino–cerebro (GBA). El enfoque está en la colonización microbiana del intestino, la producción de metabolitos y los mecanismos mediante los cuales estos metabolitos influyen en la función neuronal.

**Metodología:** Se realizó una búsqueda exhaustiva en PubMed, Scopus, Web of Science y Google Scholar utilizando las palabras clave “Streptococcus mutans”, “Parkinson’s disease”, “gut–brain axis”, “oral microbiota” y “neuronal dysfunction”. Se incluyeron estudios in vivo e in vitro publicados en inglés entre 2015 y 2025.

**Resultados:** La evidencia indica que S. mutans puede migrar al intestino, produciendo urocanato reductasa (UrdA) y su metabolito imidazol propionato (ImP), los cuales ingresan a la circulación sistémica y alcanzan el cerebro. Modelos animales demostraron que estos metabolitos contribuyen a la pérdida de neuronas dopaminérgicas, neuroinflamación, disfunción motora y agregación de α-sinucleína. Los efectos fueron mediados por la activación de la vía de señalización mTORC1, y la inhibición farmacológica de mTORC1 mitigó los cambios neurodegenerativos.

**Conclusión:** Las bacterias orales, especialmente S. mutans, pueden desempeñar un papel crítico en la patogénesis de la EP a través del GBA. Manipular la composición microbiana intestinal y la producción de metabolitos representa una vía terapéutica prometedora. Los hallazgos resaltan la posible importancia de la salud bucal en la prevención o mitigación de trastornos neurodegenerativos.

**Palabras clave:** Enfermedad de Parkinson. Streptococcus Mutans. Eje Intestino–Cerebro. Microbiota Oral. Función Neuronal. Imidazol Propionato.

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## 1 INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily characterized by tremor, rigidity, bradykinesia, and postural instability, affecting approximately 1–2% of individuals over 65 years old, and representing one of the most prevalent age-related neurological disorders worldwide (Kalia & Lang, 2015). The disease is pathologically defined by the selective loss of dopaminergic neurons in the substantia nigra pars compacta, leading to a significant reduction in striatal dopamine levels, and by the presence of intracellular aggregates of misfolded α-synuclein, known as Lewy bodies (Dauer & Przedborski, 2003). While the etiology of PD is multifactorial, encompassing genetic susceptibilities and environmental exposures, the precise mechanisms triggering neuronal degeneration remain incompletely understood (Klein & Westenberger, 2012).

Historically, PD research focused on central nervous system (CNS) pathology; however, emerging evidence highlights the critical role of peripheral systems in disease initiation and progression. In particular, the gastrointestinal tract has gained attention as a potential site of early PD pathology. The gut–brain axis (GBA) describes a bidirectional communication network between the gastrointestinal system and the CNS, mediated by neural, immune, endocrine, and metabolic pathways (Carabotti et al., 2015). Within this framework, intestinal microbiota have been implicated in modulating neuroinflammation, α-synuclein aggregation, and dopaminergic neuron vulnerability. Several studies have reported that PD patients exhibit significant alterations in gut microbial composition compared to healthy controls, including reduced abundance of short-chain fatty acid–producing bacteria and increased pro-inflammatory species (Scheperjans et al., 2015; Heintz-Buschart et al., 2018). However, the precise microbial taxa and metabolites responsible for these effects have remained largely undefined.

Recent research has expanded this concept to consider oral bacteria as contributors to PD pathogenesis via the GBA. Streptococcus mutans, a Gram-positive oral bacterium well known for its cariogenic potential, has been detected in increased abundance within the intestinal microbiome of PD patients (Koh et al., 2025). Mechanistically, S. mutans produce urocanate reductase (UrdA) and its metabolite imidazole propionate (ImP), which can translocate into the systemic circulation, cross the blood–brain barrier, and accumulate in neural tissue. In murine models, intestinal colonization with S. mutans or with genetically engineered Escherichia coli expressing UrdA resulted in elevated ImP levels in blood and brain, dopaminergic neuron loss, heightened neuroinflammation, α-synuclein aggregation,

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and impaired motor function. These neurodegenerative effects were mediated through activation of the mTORC1 signaling pathway, and pharmacological inhibition of mTORC1 significantly attenuated neuronal loss, neuroinflammation, α-synuclein pathology, and motor deficits (Koh et al., 2025).

These findings suggest a novel mechanistic link between oral health, intestinal microbiota, and neurodegeneration, highlighting the importance of oral hygiene not only for dental health but also for potentially mitigating neurodegenerative processes. The identification of microbial metabolites, such as ImP, as modulators of CNS pathology also presents new opportunities for targeted therapeutic interventions, including modulation of gut microbiota composition, inhibition of specific microbial enzymes, or pharmacological targeting of downstream signaling pathways like mTORC1. Despite these insights, several critical questions remain. The temporal dynamics of oral bacterial colonization in the gut, the factors influencing systemic metabolite levels, the interactions with host genetics, and the translatability of findings from animal models to humans are not fully elucidated. Additionally, the relative contribution of other oral and gut microbial taxa to PD pathogenesis is still under investigation.

Given these gaps, this review aims to comprehensively synthesize current evidence linking oral bacteria, particularly S. mutans, to PD via the gut–brain axis, to elucidate the underlying molecular mechanisms, and to discuss potential preventive and therapeutic implications, emphasizing the broader relevance of oral health in neurodegenerative disease.

## 2 METHODOLOGY

This review synthesizes current evidence on the role of oral bacteria, particularly Streptococcus mutans, in Parkinson's disease (PD) pathogenesis via the gut–brain axis (GBA). The methodology was designed to provide a comprehensive assessment of both clinical and preclinical studies, including microbiome analyses, mechanistic investigations, and experimental models.

### 2.1 LITERATURE SEARCH STRATEGY

A systematic literature search was conducted in PubMed, Scopus, Web of Science, and Google Scholar databases. The following keywords and Boolean operators were used: "Streptococcus mutans" AND "Parkinson's disease" "Oral microbiota" AND "gut–brain axis"

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"Imidazole propionate" AND "neurodegeneration" "Urocanate reductase" AND "dopaminergic neurons"

**Inclusion criteria were:**

1. Studies published in English between 2015 and 2025.
2. Original research articles, including in vitro, in vivo, and clinical studies.
3. Studies investigating the role of oral bacteria in PD pathogenesis, intestinal colonization, metabolite production, or neurodegenerative mechanisms.

**Exclusion criteria were:**

1. Reviews, editorials, or conference abstracts without original data.
2. Studies lacking mechanistic or functional evidence linking oral bacteria to neuronal outcomes.

## 3 RESULTS

### 3.1 ALTERATIONS IN GUT MICROBIOTA AND ORAL BACTERIAL COLONIZATION

Metagenomic analyses of fecal samples from Parkinson's disease (PD) patients revealed a significant increase in intestinal colonization by Streptococcus mutans compared to healthy controls (Koh et al., 2025). The abundance of the urdA gene, which encodes urocanate reductase (UrdA), was also elevated, suggesting enhanced metabolic activity of S. mutans in the gut. This finding establishes a direct link between oral microbial colonization and intestinal microbial dysbiosis in PD patients.

### 3.2 PRODUCTION AND SYSTEMIC DISTRIBUTION OF IMIDAZOLE PROPIONATE

The enzyme UrdA converts urocanate into imidazole propionate (ImP), a metabolite detected at elevated levels in both the serum and brain tissue of PD patients and murine models colonized with S. mutans or UrdA-expressing E. coli (Koh et al., 2025). ImP was shown to cross the blood–brain barrier, indicating that microbial metabolites originating from oral bacteria can exert systemic and central nervous system effects.

### 3.3 NEUROPATHOLOGICAL CHANGES IN ANIMAL MODELS

Murine models demonstrated multiple PD-like neuropathological features after intestinal colonization with S. mutans or engineered E. coli expressing UrdA:

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1. Dopaminergic neuron loss: Immunohistochemistry revealed significant reduction of tyrosine hydroxylase-positive neurons in the substantia nigra.
2. Neuroinflammation: Increased activation of microglia (Iba1+) and astrocytes (GFAP+) indicated enhanced neuroinflammatory responses.
3. α-Synuclein aggregation: Immunostaining showed enhanced formation of Lewy body–like α-synuclein inclusions.
4. Motor dysfunction: Behavioral assays, including rotarod and pole tests, revealed deficits in motor coordination and bradykinesia.

These effects were dose-dependent and correlated with ImP concentrations in the brain, confirming a causal link between microbial metabolites and PD pathology.

### 3.4 MTORC1 SIGNALING PATHWAY ACTIVATION

Activation of the mTORC1 signaling pathway was observed in dopaminergic neurons exposed to elevated ImP levels, suggesting that this pathway mediates the neurotoxic effects of microbial metabolites. Pharmacological inhibition of mTORC1 significantly reduced neuronal loss, neuroinflammation, α-synuclein aggregation, and motor deficits, highlighting mTORC1 as a potential therapeutic target (Koh et al., 2025).

### 3.5 TRANSLATIONAL RELEVANCE

Human studies corroborated these findings: PD patients exhibited elevated levels of ImP in serum and cerebrospinal fluid, and increased abundance of S. mutans in gut microbiota correlated with disease severity and motor symptoms. These observations indicate that oral bacteria and their metabolites may serve as biomarkers for early detection and potential intervention targets in PD.

## 4 DISCUSSION

The findings from preclinical and clinical studies provide compelling evidence that oral bacteria, specifically Streptococcus mutans, contribute to Parkinson's disease pathogenesis via the gut–brain axis. The mechanism involves translocation of oral bacteria to the gut, production of neuroactive metabolites such as imidazole propionate, and activation of neurodegenerative signaling pathways, particularly mTORC1. This study underscores the importance of the oral-gut-brain continuum in neurodegeneration, suggesting that

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interventions targeting oral microbial composition could have systemic effects on neural health. The detection of elevated ImP in both serum and brain tissue strengthens the concept that microbial metabolites act as mediators between peripheral colonization and central pathology.

From a clinical perspective, these results highlight potential preventive strategies, such as rigorous oral hygiene, modulation of gut microbiota through diet or probiotics, and pharmacological targeting of mTORC1. The dose-dependent relationship between ImP levels and neurodegenerative features also opens avenues for biomarker development for early PD detection. Additionally, this research suggests that the pathological processes in PD may initiate outside the CNS, challenging the traditional paradigm that neurodegeneration is exclusively brain-centered. The gut microbiota and oral pathogens emerge as modifiable risk factors, offering novel opportunities for intervention before irreversible neuronal loss occurs.

Finally, the study emphasizes the interconnectedness of systemic health, oral microbiology, and neurodegenerative diseases, advocating for a multidisciplinary approach in both research and clinical management of Parkinson's disease.

## 5 CONCLUSION

Oral bacteria, particularly S. mutans, may play a critical role in PD pathogenesis via the GBA. Targeting gut microbial composition and metabolite production represents a promising therapeutic avenue. The findings emphasize the potential importance of oral health in preventing or mitigating neurodegenerative disorders.

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