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The Effect of N-acetylcysteine on Periodontitis: A mini-review of literature

Efeitos da N-acetilcisteína sobre a Periodontite: Uma mini-revisão da literatura

Los efectos de la N-acetilcisteína en la periodontitis: Una mini-revisión de la literatura

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André dos Santos Carvalho
ORCID: https://orcid.org/0000-0001-5259-6481
Federal University of the Parnaiba Delta, Brazil
E-mail: fko.andre@gmail.com
Even Herlany Pereira Alves
ORCID: https://orcid.org/0000-0001-7566-1282
Federal University of the Parnaiba Delta, Brazil
E-mail: even.herlany@gmail.com
Mateus Cardoso do Amaral
ORCID: https://orcid.org/0000-0003-2735-9892
Federal University of the Parnaiba Delta, Brazil
E-mail: mateuscamaral@gmail.com
Hélio Mateus Silva Nascimento
ORCID: https://orcid.org/0000-0003-1551-8139
Federal University of the Parnaiba Delta, Brazil
E-mail: helio_mateus_@hotmail.com
Ayane Araújo Rodrigues
ORCID: https://orcid.org/0000-0001-7792-6993
Federal University of the Parnaiba Delta, Brazil
E-mail: ayanerodrigues2012@hotmail.com
Vinicius da Silva Caetano
ORCID: https://orcid.org/0000-0002-6310-8495
Federal University of the Parnaiba Delta, Brazil
E-mail: vsvinicius3@gmail.com
Ana Clara Silva Sales
ORCID: https://orcid.org/0000-0003-4978-235X
Federal University of the Parnaiba Delta, Brazil
E-mail: clarasales02@gmail.com
Thais Amanda de Lima Nunes
ORCID: https://orcid.org/0000-0002-1924-4828
Federal University of the Parnaiba Delta, Brazil
E-mail: amandalima-@hotmail.com.br
Wesley Rodrigues da Silva
ORCID: https://orcid.org/0000-0002-2241-5843
Federal University of the Parnaiba Delta, Brazil
E-mail: mr.wesleyrodrigues@gmail.com
John Arlley Sousa Pinho de Lira
ORCID: https://orcid.org/0000-0001-6565-6260
Federal University of the Parnaiba Delta, Brazil
E-mail: arlley_pinho@hotmail.com
Paulo Roberto Carneiro Gomes
ORCID: https://orcid.org/0000-0002-2911-7785
Federal University of the Parnaiba Delta, Brazil
E-mail: paulo.c.gomes1@outlook.com
Francisco Alex da Rocha Coelho
ORCID: https://orcid.org/0000-0002-3308-375X
Federal University of the Parnaiba Delta, Brazil
E-mail: alex123rocha@hotmail.com
João Paulo Araujo de Sousa
ORCID: https://orcid.org/0000-0002-9255-8735
Federal University of the Parnaiba Delta, Brazil
E-mail: cigajp@hotmail.com
Jacks Renan Neves Fernandes
ORCID: https://orcid.org/0000-0001-7868-0673
Federal University of the Parnaiba Delta, Brazil
E-mail: jacks.renan@ifpi.edu.br
Daniel Fernando Pereira Vasconcelos
ORCID: https://orcid.org/0000-0002-3331-452X
Federal University of the Parnaiba Delta, Brazil
E-mail: prof.dr.daniel.vasconcelos@gmail.com

Abstract
Recently, there is strong evidence for the beneficial role of antioxidants in the treatment of periodontal diseases. A drug that is gaining more and more focus in new research is N-acetylcysteine, an antioxidant that contributes to the increase in glutathione (GSH), used as a mucolytic agent, however, recent studies have shown its significant role in decreasing levels of reactive oxygen species and in the bone resorption process in experimental periodontitis, therefore, this review sought to elucidate whether N-acetylcysteine is effective in the treatment of periodontitis and also in the involved mechanisms already mentioned in the literature. The present study is a mini-review, in which a search was performed on Google Scholar, PubMed and Web of Science and databases for the collection of studies published in the last 10 years (2009-2020). The mini-review included studies that addressed a direct or indirect link between the effects of N-acetylcysteine on periodontitis, studies published in recent years, and in vitro and in vivo studies (animal and / or human models). Seven articles were selected from the following databases: PubMed (03) and Google Scholar (04) were subsequently analyzed. As for the language and the journal, all were published in international Journals and in English. It was concluded that N-acetylcysteine was effective in bone resorption in experimental periodontitis, but further studies are suggested in order to elucidate all the mechanisms involved in the observed results.
Keywords: Bone resorption; N-acetylcysteine; Periodontitis**;** Oxygen-reactive species.

Resumo
Recentemente, há fortes evidências do papel benéfico dos antioxidantes no tratamento de doenças periodontais. Uma droga que está ganhando cada vez mais foco em novas pesquisas é a N-acetilcisteína, um fármaco antioxidante que contribui para o aumento de glutationa (GSH), usada como agente mucolítico, no entanto, estudos recentes demonstraram seu papel significativo na diminuição dos níveis de espécies reativas de oxigênio e no processo de reabsorção óssea na periodontite experimental, portanto, esta revisão procurou elucidar se a N-acetilcisteína é eficaz no tratamento da periodontite e também nos mecanismos envolvidos já mencionados na literatura. O presente estudo trata-se de uma mini-revisão, em que uma busca foi realizada no Google Acadêmico, PubMed e Web of Science e bancos de dados para a coleta de estudos publicados nos últimos 10 anos (2009-2020). A mini-revisão incluiu estudos que abordaram uma ligação direta ou indireta entre os efeitos da N-acetilcisteína na periodontite, estudos publicados nos últimos anos e estudos *in vitro* e *in vivo* (modelos animais e / ou humanos). Sete artigos foram selecionados nas seguintes bases de dados: PubMed (03) e Google Acadêmico (04) posteriormente foram analisados. Quanto ao idioma e ao periódico, todos foram publicados em jornais internacionais e em idioma inglês. Concluiu-se que a N-acetilcisteína foi eficaz na reabsorção óssea na periodontite experimental, mas sugerem-se novos estudos a fim de elucidar todos os mecanismos envolvidos nos resultados observados.
Palavras-chave: Reabsorção óssea; N-acetilcisteína; Periodontite; Espécies reativas de oxigênio.

Resumen
Recientemente, existe una fuerte evidencia del papel beneficioso de los antioxidantes en el tratamiento de las enfermedades periodontales. Un fármaco que está ganando cada vez más atención en las nuevas investigaciones es la N-acetilcisteína, un antioxidante que contribuye al aumento de glutatión (GSH), utilizado como agente mucolítico; sin embargo, estudios recientes han demostrado su importante papel en la disminución de los niveles de reactivos especies de oxígeno y en el proceso de resorción ósea en periodontitis experimental, por lo que esta revisión buscó dilucidar si la N-acetilcisteína es efectiva en el tratamiento de la periodontitis y también en los mecanismos involucrados ya mencionados en la literatura El presente estudio es una mini-revisión, en la que se realizó una búsqueda en Google Scholar, PubMed y Web of Science y bases de datos para la colección de estudios publicados en los últimos 10 años (2009-2020). La mini revisión incluyó estudios que abordaron un vínculo directo o indirecto entre los efectos de la N-acetilcisteína en la periodontitis, estudios publicados en los últimos años y estudios in vitro e in vivo (modelos animales y / o humanos) posteriormente se analizaron. Se seleccionaron siete artículos de las siguientes bases de datos: PubMed (03) y Google Scholar (04). En cuanto al idioma y la revista, todos fueron publicados en periódicos internacionales y en inglés. Se concluyó que la N-acetilcisteína fue eficaz en la resorción ósea en la periodontitis experimental, pero se sugieren más estudios para dilucidar todos los mecanismos involucrados en los resultados observados.
Palabras clave: Reabsorción ósea; N-acetilcisteína; Periodontitis; Especies de oxigenio reactivas.

1. Introduction

N-acetylcysteine (NAC) is obtained from the amino acid L-cysteine, a source of sulfhydryl (SH) groups. In the body, it is converted to metabolites, promoting detoxification and acting directly as a free radical sequestrant, being able to stimulate the synthesis of glutathione (GSH) (Schmidt al., 1996). NAC is used as a mucolytic agent in some respiratory diseases, where the intake is made orally and the metabolism occurs in the liver. However, it also appears to have beneficial effects in

conditions characterized by decreased GSH or oxidative stress, such as smoking, heart disease, HIV infection and cancer (Sima et al., 2014; Zhang et al., 2014; El-Shinnawi & Soory, 2015).

The use of N-acetylcysteine in inflammatory diseases such as periodontitis has also been reported, both *in vivo* and *in vitro* (Moon et al., 2009; Ohnish et al., 2015). Periodontitis is a chronic inflammatory disease with the destruction of the supporting tissues and dental protection, as well as alveolar bone resorption (Garcia et al., 2016), such condition is mainly caused by the colonization of Gram-negative and Gram-positive results in the subgingival sulcus that lead to response of the organism and periodontal pockets (Ismail et al., 2013).

A large part of the focus of periodontitis-related research has been on the management of inflammation. Nonetheless, advances in the understanding of bone metabolism are opening new pathways to the studies on bone loss pathology in periodontitis. This knowledge, along with the development of new drugs that may inhibit the loss/destruction of the bone, provides us with opportunities to target not only inflammation of soft tissue, but also bone loss in destructive periodontitis (Bartold & Cantley, 2010).

Therefore, it is of fundamental importance to improve the knowledge of this drug on the periodontium, evaluating its anti-inflammatory and anti-oxidant potential in periodontitis.

In this topic, the role of antioxidant substances in models of experimental periodontitis, revealing new results on the use of substances, may thus fill or show some gaps on the role of N-acetylcysteine in periodontitis. The use of substances with antioxidant properties in periodontitis models is increasing.

Both micro and macro-nutrients have been proven to control the molecular mechanisms that generate the reactive oxygen species (Jayakumar et al., 2010). Chapple and Matthews (2007) evidence the capacity of antioxidants in the inhibition of the formation of reactive oxygen species being effective in their removal and repair of the biological damage in the tissue. Sima & Glogauer (2014) have demonstrated that the overproduction of ROS by oral polymorphonuclear cells (neutrophils) in chronic periodontitis is associated with the severe destruction of the periodontium. In this context, one of the major concerns for both the professional and the patient is related to alveolar bone loss, and the treatment attempts to focus more on the minimization or regression of this bone loss (Ohnish et al., 2009).

The results of Akman et al. (2013) demonstrated that the administration of alpha lipoid acid (ALA) and Vitamin decreased bone resorption and periodontal destruction in rats. However, the authors suggest that the studies may be human-directed. Corrêa et al., (2017) demonstrated that the combined use of resveratrol and curcumin (plant-derived substances) with biological properties caused a reduction of alveolar bone loss in periodontitis in rats.

2. Methodology

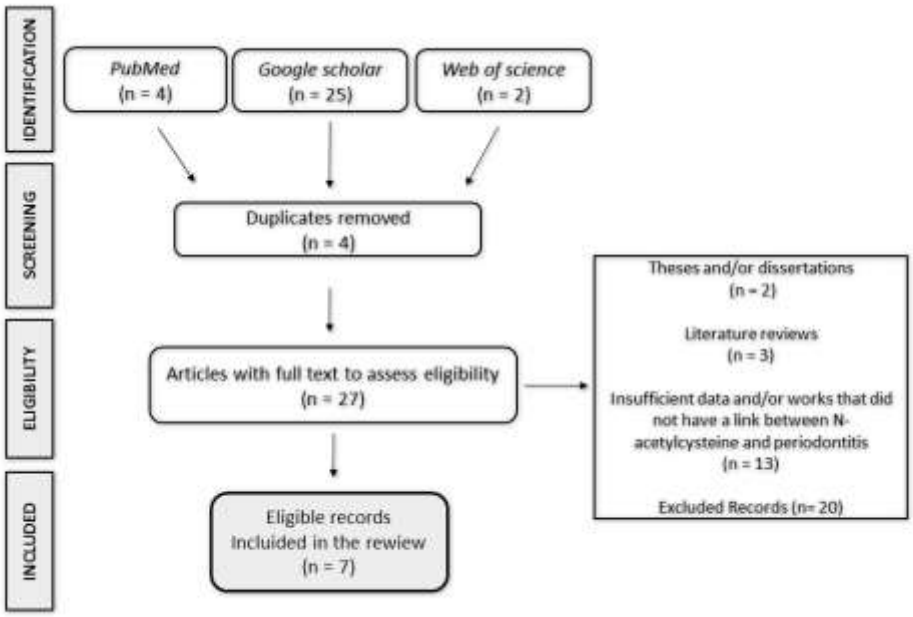
2.1 Search strategy

As a type of research, the one proposed by Koche (2011) was used, in order to survey the existing literature on the proposed theme. The search process was made in the Google Scholar and PubMed and web of Science databases for the collection of studies published over the last 11 years (2009-2020), in order to answer the following question: does N-acetylcysteine have any positive effect upon the alveolar bone metabolism in periodontitis? We used the combination of the specific descriptors: periodontitis, N-acetylcysteine, alveolar bone loss and periodontitis, N-acetylcysteine, alveolar bone loss, using boolean operators between the terms. Two independent investigators reviewed all titles, abstracts and references of the papers to identify relevant studies. There was no language restriction in the collection of the studies.

2.2 Inclusion criteria

The articles were selected using the method proposed by Mohan et al. (2009), with the stages divided into: identification, screening, eligibility and inclusion. Studies that addressed a direct or indirect link between the effects of N-acetylcysteine and improvements in the clinical parameters of periodontitis, studies published in recent years, and in vitro and in vivo studies (animal and / or human models) were included in the systematic review. Studies that did not contain enough data, that did not have any link between N-acetylcysteine and periodontitis, as well as literature reviews, theses and dissertations, were excluded from the analysis. The process of identifying and selecting the articles included in this review are outlined in the flowchart of the research phases, using the PRISMA method, Figure 1.

Figure 1. Flowchart of the Research phases.



Source: Authors.

2.3 Data extraction

Two calibrated researchers performed the data collection and discussion following a standardized form: title, authors, year of publication and of studies.

3. Results and Discussion

Seven articles that were found in the PubMed (03), Google Scholar (04), databases were analysed in this study. Regarding the language and periodical, they were all were published in international magazines and in the English language.

The papers that used acetylcysteine in experimental periodontitis models, both *in vivo* and *in vitro*, were selected. The results revealed a lack of studies involving the use of N-acetylcysteine in models of periodontal diseases, especially periodontitis. Works such as Toker et al. (2009) Ohnishi et al. (2009); Toker et al. (2012) and Alam et al. (2014) evidenced a decrease in alveolar bone loss, an important evaluation score of progressive periodontitis.

The results of human studies have shown that Alkadasi et al. (2017) carried out a study in patients with moderate chronic periodontitis, by means of the analysis of the crevicular fluid after the treatment with N-acetylcysteine. The authors managed to observe that the treatment was able to reduce the index of depth of the bag and the levels and RANKL. These results are available in Table 1.

Table 1. Among Findings in the systematic journal.

Author	Title	Model	Results
1. Toker et al. (2009)	N-Acetylcysteine, a thiol antioxidant, decreases alveolar bone loss in experimental periodontitis in rats.	*In vivo*: Animal	In 11 days, greater alveolar bone loss was observed in the LO group, compared to the other groups: NAC7, NAC35, NAC70 (P <0.5). There was no statistically significant difference in the number of osteoclasts (P> 0.5). The effect of NAC was dose dependent.
2. Ohnish et al. (2009)	Oxidative stress causes alveolar bone loss in metabolic syndrome model mice with type 2 diabetes	*In vivo*: Animal	N-acetylcysteine restored endothelial expression of nitric oxide synthase in gingival keratinocytes, suppressed alveolar bone loss, and decreased plasma concentrations of hydrogen peroxide without improving obesity or diabetes.
3. Toker et al. (2012)	N-acetylcysteine decreases alveolar bone loss on experimental periodontitis in streptozotocin-induced diabetic rats	*In vivo*: Animal	At the end of the 30-d study period, alveolar bone loss was significantly higher in the STZ + L group compared with the other groups (p <0.05). Also, alveolar bone loss in all NAC groups was significantly lower than in the STZ + L and L groups (p <0.05). The osteoblastic activity in the NAC100 group was significantly higher than in the other groups (p <0.05).
4. Alam et al. (2014)	N-acetylcysteine and the human serum components that inhibit bacterial invasion of gingival epithelial cells prevent experimental periodontitis in mice.	*In vitro*: Cell culture	N-acetylcysteine decreased oxygen species and invaded F. nucleatum cells in HOK-16B cells. N-acetylcysteine also reduced alveolar bone loss in experimental periodontitis induced by P. gingivalis and T. denticola.
5. Moon et al. (2015)	In vitro effects of N-acetyl cysteine alone and in combination with antibiotics on Prevotella intermedia.	*In vitro*: Cell culture	N-Acetylcysteine presented antibacterial activity against Pl. Intermedia P. with MIC value of 3 mg / ml and significantly reducing biofilm formation. N-Acetylcysteine did not affect the antibiotic susceptibility of planktonic P.
6. Orihuela et al. (2015)	Biologycal impacts of resveratrol, quercetin and N-acetylcysteine on oxidative stress in human gingival fibroblast	*In vivo:* Human	N-Acetylcysteine treatment consumes less oxygen and enhances more non-mitochondrial respiration. the resveratrol is the most effective antioxidant in terms of real-time cytotoxicity analysis, reduction of ROS production and enhancement of type I collagen synthesis and mitochondrial respiration in HGFs.
7. Alkadasi et al. (2017)	Effect of adjunctive use of systemic antioxidant therapy (N-acetylcysteine) on soluble receptor activator nuclear factor KB ligand levels in gingival crevicular fluid following surgical periodontal treatment for chronic periodontitis	Human	The use of adjuvant acetylcysteine resulted in a significant decrease in depth of probing, clinical insertion levels and sRANKL levels in the gingival crevicular fluid between the surgical treatment groups at the end of 7 months.

Source: Authors.

Our searches in the databases cited demonstrate that the use of NAC in experimental periodontitis models is ground breaking and has recently risen in the literature. In light of that, it is the first literature review that shows such results, demonstrating the main benefits of the *in vitro* and *in vivo* administrations of NAC on Periodontitis. Orihuela et al. (2015) carried out a study to evaluate human gingival fibroblasts (HGFs) under oxidative stress induced by hydrogen peroxide. The authors reached the conclusion that the use of N-acetylcysteine was able to reduce oxygen consumption and increase non-mitochondrial respiration, but when compared to another drug, N-acetylcysteine was proven to be less effective in terms of real-time cytotoxicity analysis, reduced production of ROS, increased type I collagen synthesis and mitochondrial respiration in HGFs.

Several *in vitro* studies have demonstrated that N-acetylcysteine is effective in inhibiting biofilm formation and decreasing bacterial variability in biofilms (Hashem et al., 2015). The presence of local factors such as bacterial plaque may cause an imbalance with the exacerbated migration of neutrophils to the gingiva and the gingival fluid and can trigger a deregulation in the distribution of ROS (Battino et al., 1999).

Tribble and Lamont. (2010) have demonstrated the mechanisms involved in the invasion of epithelial tissues by bacteria and their dissemination to the gingival tissues. Kim et al. (2012) reported later in an *in vitro* study that human serum significantly reduces the invasion of oral bacteria into the epithelial cells of the gingival tissue.

Alam et al. (2014) characterized the components present in human serum responsible for the inhibition of bacterial invasion to epithelial cells. These components were (human serum albumin) HSA and combined human IgG (PIgG), both combined with the use of N-acetylcysteine, reduced bacterial involution and alveolar bone loss in experimental periodontitis. Toker et al. (2009) showed that the administration of N-acetylcysteine through feed inhibited the formation of osteoclasts, being effective in ligature-induced periodontitis. In Toker et al. (2012) the effects of N-acetylcysteine on experimental periodontitis induced by streptozotocin in diabetic rats were evaluated, where all groups treated with the drug had a significant reduction of alveolar bone loss when compared to the other groups.

According to Wang et al. (2014) the increase in oxidative stress can raise the release of cytokines through the activation of inflammatory cells. With the activation of neutrophils, the generation of ROS can occur. In the same study, pre-treatment with N-acetylcysteine decreased the generation of ROS, cytokine release and autophagy in the liver in a model of ischemia and reperfusion. These facts corroborate the evidence the action of the N-acetylcysteine in pathophysiological processes associated with some disorders, particularly oxidative stress, apoptosis and mitochondrial dysfunction (Toker et al., 2012).

Oxidative stress is associated with the pathogenesis of several inflammatory diseases, including periodontitis, culminating with the destruction of the periodontium. These events cause an imbalance between oxidant and antioxidant enzymatic and non-enzymatic system, generating reactive oxygen species (ROS) through the nuclear polymorphs, being considered highly destructive (wang et al., 2014).

These findings are in agreement with most of the studies included in this review, which showed that N-acetylcysteine acted to inhibit bacterial migration to the gingival tissues, reducing ROS levels, consequently decreasing the process of alveolar bone resorption in experimental periodontitis.

4. Final Considerations

In view of the findings of this review, N-acetylcysteine was effective in all studies, preventing bacterial migration to oral epithelial tissues, reducing the reactive oxygen species (ROS), consequently reducing alveolar bone loss in experimental

periodontitis. Additional studies that may elucidate mechanisms that are still unknown in relation to the role of N-acetylcysteine in periodontitis, which may make it an effective adjunct in the treatment of oral diseases.

Future studies are suggested, with the focus of evaluating not only the effect of NAC on periodontitis, but also on the comorbidities caused by this disease, such as non-alcoholic fatty liver disease, covering even more its antioxidant capacity on the imbalance in the production of EROS in the face of inflammatory pathologies

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