Archives of Oral Biology 87 (2018) 196–203

Contents lists available at ScienceDirect

Archives of Oral Biology

journal homepage: www.elsevier.com/locate/archoralbio

Review

The alveolar bone protective effects of natural products: A systematic review

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ARTICLE INFO

Keywords:
Periodontitis
Bone loss
Natural products
Animal studies
Alveolar bone

ABSTRACT

Objectives: This systematic review was carried out to identify which naturally-occurring agents and constituents isolated therefrom have effects in preventing bone loss in a ligature-induced periodontitis model.
Materials and methods: Eight databases were systematically searched for studies of experimental periodontitis. The data were extracted, analyzed, and the treatment outcomes were given scores based on the level of bone destruction as compared to their untreated induced-periodontitis control.
Results: 294 articles were found, of which 15 met the inclusion criteria. The selected studies tested a multi-herbal formulation; extracts (leaves, barks or fruit) of different plant species; and propolis. The most usual dosing protocol consisted of 3-times-a-day, 11-day treatment. The combined gel of *Myracrodruon urundeuva* (5%) and *Lippia sidoides* (0.5%) was the most active treatment, reducing 45–65% bone loss in the region of molars as compared to 73.4% of doxycycline (gold-standard). *Ginkgo biloba* extract (28–56 mg/kg) and propolis (100–200 mg/kg) prevented bone destruction by 50% and 40–44%, respectively. The other tested samples showed intermediate/weak activity in modulating bone resorption.
Conclusions: The gel of *M. urundeuva* and *L. sidoides*, and *G. biloba* and propolis extracts showed strong alveolar bone protective effectiveness in induced-periodontitis in rats. Further translational research should bridge the gap between the rat study outcomes and the clinical efficacy and long-term toxicity of these formulations in humans. The compilation of the vast literature database presented herein may drive further *in vivo* and clinical studies with the selected efficacious formulations to subsidize their pharmaceutical application.

1. Introduction

Periodontitis is an immune-inflammatory disease characterized by clinical attachment loss and destruction of alveolar bone as a result of the host response to the presence of polymicrobial subgingival biofilms (Aral et al., 2015). As one of the most widespread inflammatory conditions affecting the adult population, this disease still remains a major public health burden worldwide (Jin et al., 2016).

The presence of specific gram-negative anaerobes on tooth surfaces in close relationship with the periodontium triggers an inflammatory response involving host immune cell recruitment and release of cytokines (*e.g.*, IL-17, IL-1β, TNF-α), chemokines (*e.g.*, CXCR2) and other signaling molecules, which ultimately lead to activation of osteoclasts and bone destruction (Hajishengallis, 2014; Hajishengallis, Moutsopoulos, Hajishengallis, & Chavakis, 2016). The use of anti-inflammatory drugs can decrease the rate of periodontal bone loss in periodontitis (Aral et al., 2015). Conventional non-steroidal anti-inflammatory drugs and selective inhibitors of cyclooxygenase-2 (COX-2) have shown positive effects in modulating the host immune-inflammatory responses (Bezerra et al., 2000), but their long-term use may also lead to undesirable side-effects, such as gastric disorders, internal bleeding, increased risk of heart attack and stroke, among others. In addition to conventional anti-inflammatory drugs, other therapeutic classes have also been employed to mitigate bone loss due to their secondary anti-inflammatory effects, such as low-dose antimicrobials (*e.g.* doxycycline) (Payne et al., 2007) and selective serotonin reuptake inhibitors (*e.g.* fluoxetine) (Branco-de-Almeida et al., 2012). Despite their extensively studied pharmacological efficacy, some of these drugs may present considerable side effects at a long term, which encourages the development of novel, well-tolerable drugs with anti-inflammatory and antimicrobial properties to ameliorate alveolar bone loss in patients with chronic periodontitis.

Throughout the history of mankind, nature has been the major source of bioactive molecules with therapeutic properties and of

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https://doi.org/10.1016/j.archoralbio.2017.12.019
Received 31 January 2017; Received in revised form 18 December 2017; Accepted 21 December 2017
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pharmaceutical leads. Some of the drugs used in the treatment of chronic periodontitis are of synthetic, semisynthetic or completely natural origin. Thus far, approximately 25% of the anti-inflammatory agents and 73% of the antibacterials come from natural products or their derivatives (Newman & Cragg, 2016). Hence, a large number of plant extracts and compounds can be considered potential candidates for the treatment of infectious and pathogen-associated inflammatory conditions affecting the periodontium (Botelho, Rao et al., 2007; Botelho et al., 2008; Calixto, Campos, Otuki, & Santos, 2004).

In this systematic review, we screened the most promising natural products modulating bone loss in ligature-induced periodontitis in rats and carried out a comparative analysis with the gold-standard doxycycline. The compilation of the vast literature database presented herein may suggest avenues for further *in vivo* and clinical studies with the selected efficacious agents and their isolated constituents.

2. Material and methods

2.1. Study question

This systematic review was carried out to address the specific question: "Based on the current literature, which naturally-occurring agents and isolated constituents therefrom have effects in preventing bone loss in ligature-induced periodontal disease?".

2.2. Search strategy for study selection

The guidelines of the PRISMA statement (*Transparent Reporting of Systematic Reviews and Meta-Analyses*) (Liberati et al., 2009) were followed. The systematic review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) under protocol number CRD42015028002 (http://www.crd.york.ac.uk/PROSPERO). Eight databases were systematically searched for studies of experimental periodontitis up to May 2016 (Table 1).

2.3. Eligibility criteria

A systematic screening of the articles was performed by two independent examiners according to the following inclusion criteria:

(1) **Biological activity:** effects of naturally-occurring agents in preventing alveolar bone loss in ligature-induced periodontitis. Outcome of interest: reduction of bone loss assessed through radiography, photography, and other methods.
(2) **Plant material and chemical elucidation:** chemically characterized natural products and/or their isolated constituents.
(3) **Study design:** experimental studies in animal models. Sample size and study power (at least 80%) should be adequate so that to include the study in this review.
(4) **Methodological quality:** accuracy of methods and outcomes; internal and external validity, compliance with high-quality scientific standards.
(5) **Language:** Articles written in English, Spanish or Portuguese. Examiners agreed that in cases of inconsistence the final verdict on which articles should be included in this review would be reached by consensus.

2.4. Data analysis

The extracted data were analyzed using descriptive statistics. Due to differences in the assessment methods of the included studies, we decided to score the measurements of the induced-periodontitis group into 5 points, where "0" consists in the lowest bone loss value and "5" the highest bone loss value. The results of the other groups were normalized accordingly so that to allow inter-study comparisons.

3. Results

3.1. Data retrieval

According to the previously set strategy, 294 articles were found, of which 15 met the inclusion criteria and were included in the final review after thorough analysis (Aral et al., 2015; Barrella, Suffredini, Ribeiro, Cirano, & Pimentel, 2012; Benatti et al., 2012; Botelho, Rao et al., 2007; Botelho et al., 2008; Carmona et al., 2013; Chang et al., 2014; Cheng et al., 2010; Ozdemir, Kara, Erciyas, Ozer, & Ay, 2012; Paixão et al., 2015; Pimentel et al., 2012; Sağlam, Köseoğlu, Hatipoğlu, Esen, & Köksal, 2015; Sezer et al., 2013; Toker et al., 2008; Yang, Wen, Xue, & Ding, 2014) (Fig. 1). All articles were published in the last 10 years by authors from different countries, as follows: Brazil (46.7%), Turkey (33.3%), Taiwan (13.3%), and China (6.7%). The 15 studies addressed the effects of naturally-occurring agents and their isolated constituents in modulating alveolar bone loss in ligature-induced periodontitis and therefore will be further discussed herein.

Table 1
Search strategy and bibliographic databases used to retrieve the articles for this systematic review.

Primary bibliographic sources	Search strategy (descriptors and combinations with Boolean operators)
SciVerse Scopus (Since 1995)	• ("naturally-occurring agents" OR "natural compounds" OR "natural products" OR "herbal medicines") AND ("alveolar" AND "bone loss" OR "bone regeneration" OR "bone resorption") AND ("periodontal disease" OR "periodontitis")
EMBASE (Since 1966)	• ("naturally-occurring agents" OR "natural compounds" OR "natural products" OR "herbal medicines") AND ("alveolar" AND "bone loss" OR "bone regeneration" OR "bone resorption") AND ("periodontal disease" OR "periodontitis")
Web of Science (Since 1990)	• (naturally-occurring agents OR natural compounds OR natural products OR herbal medicines) AND (alveolar AND bone loss OR bone regeneration OR bone resorption) AND (periodontal disease OR periodontitis)
Medline *via* Pubmed (Since 1966)	• (naturally-occurring agents OR natural compounds OR natural products OR herbal medicines) AND (alveolar AND bone loss OR bone regeneration OR bone resorption) AND (periodontal disease OR periodontitis)
SciELO (Scientific Electronic Library Online) (Since 1998), **LILACS (Latin American and Caribbean Health Sciences Literature)** (Since 1982), **and Cochrane Library**	• ("produtos naturais" OR "compostos naturais" OR "plantas medicinais") AND ("alveolar" OR "perda óssea" OR "regeneração óssea" OR "reabsorção óssea") AND ("doença periodontal" OR "periodontite") • ("productos naturales" OR "compuestos naturales" OR "plantas medicinales") ("alveolar" OR "pierda ossea" OR "regeneración ossea" OR "reabsorcion ossea") AND ("enfermidad periodontal" OR "periodontitis") • ("naturally-occurring agents" OR "natural compounds" OR "natural products" OR "herbal medicines") AND ("alveolar" AND "bone loss" OR "bone regeneration" OR "bone resorption") AND ("periodontal disease" OR "periodontitis")
Google Scholar	• Manual searches according to the reference lists of the articles

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