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Different doses of avocado/soybean unsaponifiable influences the progression of induced periodontitis in rats

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Aim: To evaluate the effects of different doses of avocado and soybean unsaponifiable extract (ASU) on the progression of induced periodontitis in rats. **Methods:** Thirty-five rats underwent induction of periodontitis by inserting ligatures around the upper second molar of one hemiarch, while the second molar of the other hemiarch was left without the ligature. The animals were subsequently randomly distributed into 5 groups according to the administered solution: CTR: Saline solution (SS); ASU1: ASU at a concentration of 0.3 g/kg/day; ASU2: ASU at a concentration of 0.6 g/kg/day; ASU3: ASU at a concentration of 1.2 g/kg/day; ASU4: ASU at a concentration of 2.4 g/kg/day. The solutions were administered daily, by gavage, from the day of insertion of the ligatures until the day of euthanasia of the animals, which was performed 15 days after the periodontitis induction. The analysis of the distance from the cemento-enamel junction (CEJ) to the top of the bone crest (BC) and the % bone volume was performed using micro-CT. The inflammatory infiltrate was evaluated by stereometric analysis. One-way ANOVA complemented by Tukey test was used to compare the different groups with the significance level of 5%. **Results:** ASU groups presented smaller JCE-BC distances than the CTR group ($p<0.05$). The CTR group had a lower number of fibroblasts and extracellular matrix and a higher amount of inflammatory cells than the ASU groups ($p<0.05$). **Conclusion:** ASU promoted reduction against bone tissue resorption and in the inflammatory pattern, mainly at concentrations of 0.3 g/kg/day to 1.2 g/kg/day.

Keywords: Animal experimentation. Anti-inflammatory agents. Periodontitis.

Introduction

Periodontitis is an inflammatory disease characterized by the progressive destruction of tooth support structures induced by a dysbiotic biofilm[1]. Despite the role of the bacteria in the onset of periodontitis, the progression of this disease, characterized by the loss of the attachment periodontium, is strongly associated with the host response to the microbial challenge[2].

It has been shown that some risk factors influence the prevalence and progression of periodontitis, especially those that interfere with the bone remodelling process[3]. Indeed, in clinical studies, the association of some diseases recognized to be harmful to bone tissue has been shown to present a consistent relationship with the occurrence of periodontitis[4,5]. Among these pathologies, arthritic diseases such as osteoarthritis and rheumatoid arthritis stand out, since the pathological mechanisms of bone resorption are very similar to what occurs in periodontitis[3,6]. Because the drugs used by these patients aim to reduce osteolytic processes, it is possible that they may benefit the periodontitis treatment[7,8].

Non-surgical periodontal treatment is the most common therapy for periodontitits[9,10]. However, this may not be successful in all patients, and in these cases, it may be necessary to apply adjunctive treatments[10,11]. Among the adjunct treatments used, there is more scientific documentation available for antibiotic therapy, due to the understanding that periodontitis is initiated and supported by the action of the bacterial biofilm[12]. Despite the good clinical outcomes of antibiotic therapy with adjunctive treatment for periodontitis[13], this therapy has limitations such as the occurrence of side effects (e.g., pseudomembranous colitis) and development of bacterial resistance[14].

Since the periodontal destruction occurs through the inflammatory process induced by the bacterial biofilm, the modulation of inflammation has been indicated a possibility in the adjunctive treatment of periodontitis[15]. One alternative is the use of avocado and soybean unsaponifiable extract (ASU). This medication has been used in the treatment of rheumatoid arthritis and osteoarthritis, due to its anti-inflammatory and proliferative effects[7,8]. ASU has also been shown to improve periodontal repair in preclinical experiments in rats with experimental periodontitis[16-18]. However, these studies used dosages indicated for the treatment of osteoarthritis and rheumatoid arthritis[16-18], and the effect of the variation of the dosage of ASU on the inflammation associated with the induced periodontitis was not tested before.

Thus, the objective of the present study was to evaluate the effect of different dosages of ASU on the induced periodontitis severity. The null hypothesis of this study is that ASU does not interfere with the inflammation and bone loss associated with induced periodontal disease.

Material and Methods

This study was approved by the Animal Use Ethics Committee of the Universidade Estadual Paulista - UNESP, Faculty of Dentistry of Araraquara, Brazil (CEUA 14/2014). The animals were kept in the vivarium of the institution, in an environment with controlled temperature, humidity, and light cycles. Additionally, water and specific feed were provided *ad libitum*. This study was conducted in accordance with the ARRIVE preclinical study guidelines.

Groups and study design

Thirty-five animals were randomly allocated into 5 groups with 7 animals each: CTR: Administration of saline solution (SS); ASU1: Administration of ASU (Piascledine 300, Expanscience Lab, France) at a concentration of 0.3 g/kg/day; ASU2: Administration of ASU at a concentration of 0.6 g/kg/day; ASU3: Administration of ASU at a concentration of 1.2 g/kg/day; ASU4: Administration of ASU at a concentration of 2.4 g/kg/day. The solutions were administered daily, by gavage, 15 days before the day of insertion of the ligatures until the day of euthanasia of the animals, which was performed 15 days after insertion of the ligatures.

Sample size calculation

The measurement of bone volume around the upper second molars was considered as the primary variable of this study. Establishing a difference of 20% in bone tissue volume as a significant effect size between groups, with a standard deviation of the method established at 8.96[16], it was verified that at least 6 animals per group were needed to obtain a statistical test power of 80% with a type I error fixed of 0.05.

Periodontitis induction

The animals were anesthetized by a combination of Ketamine (Agener União Ltda, São Paulo, SP, Brazil) at a dosage of 0.08 ml/100g of body mass with Xylazine (Rompum, Bayer S.A., São Paulo, SP, Brazil) at a dosage of 0.04 ml/100g of body mass. Subsequently, the rats were placed in a supine position on the operating table with their mouth retracted to move the mandible and tongue to facilitate mouth opening. Ligatures (cotton threads, No. 24) were inserted through a specific probe and tweezers in the subgingival region around the upper second molars in one of the hemimaxillae, which was randomly selected. The contralateral maxillary second molar, which was left without ligatures, served as the internal control for each animal. After a period of 15 days of periodontitis induction, the animals were euthanized by anesthetic overdose.

Harvest of the samples

After the euthanasia, the hemimaxillae were removed and fixed in 4% paraformaldehyde for a period of 48 hours, before being placed in 70º alcohol until the moment of scanning in the micro-CT scanner. The samples were then decalcified in 7% EDTA for subsequent stereometric analysis.

Micro-CT analysis

The samples were scanned in a micro-CT scanner (Skyscan, Aartselaar, Belgium). The images were then reconstructed, spatially reoriented, and analysed using specific software (NRecon/DataViewer/CTan, Skyscan, Aartselaar, Belgium). The volume of bone tissue (BV/TV%) between the roots of the upper second molar was measured after delimiting the region of interest (ROI), which had a rectangular area measuring 1080x1020 μm2 and a depth of 60 sections, each 18 μm thick, using a threshold of 55-255 in greyscale. Values were given as % bone tissue in the region of interest. The ROI selection was performed by a blinded, trained, and calibrated examiner. In addition, linear analysis of the distance from the cemento-enamel junction (CEJ) to the top of the bone crest (CB) was performed around the tooth at 6 points (mesiobuccal, buccal, distobuccal, mesiopalatal, palatine, and distopalatine).

Stereometry

The stereometric analysis of the inflammatory process was performed using a Leica DMLS light microscope (Leica Microsystems, Wetzlar, Germany) at 200× magnification. Six histological sections were evaluated per tooth. These sections were obtained at 50 μm intervals, resulting in a total analyzed extension of 300 μm, encompassing representative areas of the mesial, middle, and distal portions of the tooth. The selected areas of interest were photographed using a Leica DFC 300 FX digital camera (Leica Microsystems, Wetzlar, Germany). Based on stereometric principles, the following parameters were determined: (1) total area of the area of interest, (2) area corresponding to the inflammatory infiltrate, and (3) % area corresponding to the inflammatory infiltrate.

Statistical analysis

The GraphPad Prism 8 software (San Diego, CA, USA) was used for the statistical analysis of this study. Examiner calibration was performed by repeating the microtomographic analysis for linear and volumetric assessments, as well as the histomorphometric analysis, in 10% of the sample. The intraclass correlation coefficient (ICC) was calculated to evaluate the agreement between examiners during the calibration process. The intraclass correlation coefficient (ICC) was calculated to assess intra-examiner agreement, with the lowest value observed being 0.81. The data from the microtomographic and stereometric analysis were numeric and the Shapiro-Wilk normality test was applied to assess if the data were distributed according to the central distribution theorem. As the data were distributed according to normality, parametric tests were applied for the inferential analysis of the data. The data were evaluated comparing the hemimaxillae with and without ligature of all groups through the one-way ANOVA test complemented by the Tukey test. Comparisons of hemimaxillae with and without ligature within each group were performed using the paired t-test. The significance level of the tests applied in this study was 5% ($p<0.05$).

Results

Micro-CT analysis

CEJ-CB

Comparing the unligated hemimaxillae of all groups, it was verified that the animals submitted to the ASU administration presented smaller distances of CEJ-CB than the animals of the CTR group ($p<0.05$). Furthermore, the animals in the ASU3 group presented smaller CEJ-CB distances than the animals in the ASU1 group ($p<0.05$) (Table 1). In addition, when comparing the CEJ-CB distance in the hemimaxillae with ligature, the animals of the ASU groups had smaller CEJ-CB distances compared to the animals in the CTR group (Table 1). Comparing the unligated and ligated hemimaxillae within each group, it was found that the ligated hemimaxilla always presented greater CEJ-CB distances than the control sides in all groups ($p<0.05$) (Table 1).

Table 1. Mean and standard deviation of the CEJ-CB(µm) in all groups. Different letters represent decrescent different statistical significant levels of CEJ-CB(µm) ($p<0.05$) in unligated and ligated hemimaxillae- one way anova complemented by Tukey test; *$p<0.05$- Higher CEJ-CB(µm) than the unligated hemimaxillae – paired t-test.

Group	Unligated	Ligated
CTR	359.9±54.22^{a}	804.2±301.3^{*a}
ASU1	286.2±36.54^{b}	419.6±75.85^{*b}
ASU2	272.2±32.24^{b,c}	454.1±138.1^{*b}
ASU3	220.0±45.99^{c}	473.7±197.2^{*b}
ASU 4	351.7±42.53^{b,c}	617.9±270.6^{*b}

%BV/TV analysis

Regarding the analysis of bone volume in the unligated hemimaxilla, it was verified that the CTR group had lower values than all the ASU groups, but the difference was only statistically significant for the ASU2 group ($p<0.05$) (Table 2). Regarding the bone volume in the hemimaxillae with ligature, the ASU groups presented higher values of bone volume compared to the CTR group, however this difference was not statistically significant ($p<0.05$) (Table 2). Comparing the hemimaxillae with and without ligature within each group, the hemimaxillae with ligature always presented smaller bone volumes than the hemimaxillae. The representative imagens of the microtomographic analysis are exposed in the figure 1.

Table 2. Mean and standard deviation of the % BV/TV in all groups. Different letters represent decrescent different statistical significant levels of % bone volume ($p<0.05$) in unligated hemimaxillae- one way anova complemented by Tukey test; *$p<0.05$- Higher bone volume than the ligated hemimaxillae – paired t-test.

Group	Unligated	Ligated
CTR	66.00±6.52^{*b}	38.27±18.16
ASU1	69.79±6.53^{*a,b}	42.44±9.48
ASU2	73.98±3.95^{*a}	39.10±14.36
ASU3	67.45±3.50^{*a,b}	46.64±14.61
ASU 4	64.44±4.10^{*a,b}	43.36±19.09

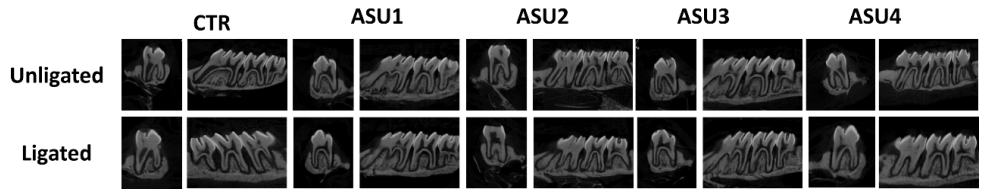

Figure 1. Microtomographic images of the unligated and ligated maxillae in coronal and sagittal planes. It is possible to note that the CTR group presented a subtle decrease in bone level compared to the ASU groups in the unligated maxilla's. Furthermore, it is possible to note that the ASU groups presented a higher amount of bone than the CTR groups.

Stereometry

The area of analysis was not different between the groups evaluated. There were also no differences between the groups regarding the percentage of area of the inflammatory infiltrate in ligated and unligated sides. The ligated sides presented higher inflammatory infiltrate than the unligated sides (Table 3).

Table 3. Mean and standard deviation of the area of analysis and %inflammatory infiltrate assessed by the stereometric analysis in all groups. *$p<0.05$- Higher %inflammatory infiltrate than the unligated hemimaxillae – paired t-test.

Group	Unligated	Ligated
Area of analysis (mm^2)		
CTR	107139 ± 10922	155313 ± 28041
ASU1	147953 ± 20909	148299 ± 31469
ASU2	154820 ± 21913	166426 ± 21446
ASU3	147694 ± 9148	144410 ± 25929
ASU 4	236593 ± 210583	177391 ± 13952
Inflammatory infiltrate (%)		
CTR	5.167 ± 10.01	27.14 ± 13.43*
ASU1	1.539 ± 2.441	28.38 ± 11.35*
ASU2	5.528 ± 10.89	30.65 ± 15.91*
ASU3	0.8905 ± 1.860	28.85 ± 24.20*
ASU 4	2.525 ± 4.942	16.95 ± 11.11*

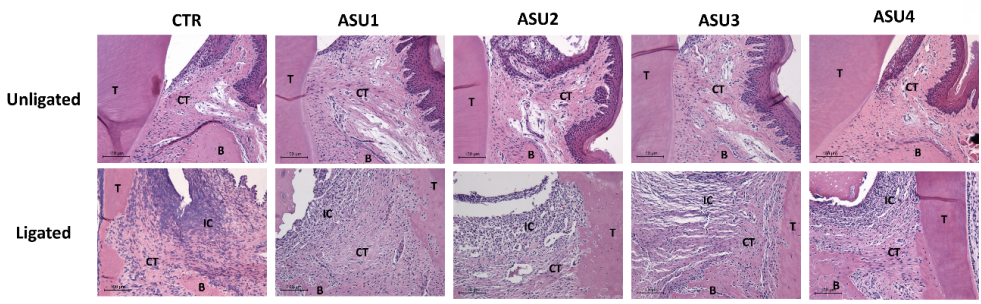

Figure 2. Representative histological images of the marginal gingival region. It is possible to note a lack of perceived differences between the CTR and ASU groups in the inflammatory infiltrate profile in the unligated maxilla's. In addition, it is possible to note that the ASU groups presented less inflammatory cells and a higher amount of connective tissue matrix than the CTR group. T-Tooth, CT- Connective tissue matrix, B- Bone, IC- Inflammatory cells.

Discussion

In general, it was observed in this study that ASU reduced bone loss in jaws submitted or not to the induction of periodontal disease. This effect was not accompanied by a reduction in the inflammatory infiltrate. Thus, it can be established that the null hypothesis of this study was rejected.

Data from the microtomographic analysis showed that the hemimaxillae without induced periodontal disease presented lower bone loss than the hemimaxillae where periodontitis was induced, which confirms the effectiveness of the method of inducing periodontal disease[19]. When comparing the CTR and ASU groups, it was observed that the administration of ASU promoted lower values of CEJ-CB than the CTR group, in both hemimaxillae, whether the disease was induced or not. However, the stereometric analysis showed that ASU administration does not impact the inflammatory infiltrate amount related to the CTR groups.

The beneficial effects on bone tissue demonstrated by the administration of ASU are related to its anti-inflammatory and proliferative property in connective tissues[20,21]. ASU promotes a reduction in the expression of pro-inflammatory biological mediators, such as IL-1β, TNF-α, IL-6, PGE2, and iNOS by inhibiting signalling pathways that stimulate the inflammatory process, such as NF-kβ and MAPK[16,22,23]. As these cytokines interfere with the expression of RANKL, the reduction in their expression promotes suppression of osteoclastogenesis and, consequently, a reduction in the production of MMPs[8].

During the pathogenesis of periodontal disease, cellular inflammatory events precede bone resorption. Thus, to prevent progression and the occurrence of periodontal disease with consequent bone loss, modulation of the inflammatory response may be valid[24,25]. In this way, one can hypothesize that the use of ASU as a preventive medication for the progression of periodontal disease may be possible, since ASU has been shown to reduce the inflammatory process in previous study. However, this finding was not observed in our study. It is important to state that our study

evaluate only the amount of inflammatory infiltrate, and the quality of the inflammatory process was not assessed.

An interesting indication of the ASU can be in previously treated patients, but who are considered at high risk due to the presence of local and systemic modifying factors that change the inflammatory response to a more aggressive version. It is also necessary to consider the side effects of using this medication, which, although rare, can occur. Some patients may experience regurgitation of lipid odor, diarrhea and stomach pains, lymphocytic colitis, hypersensitivity reactions, nausea, and headache[21]. However, there is still a gap in studies regarding these long-term side effects. Bearing in mind that the results obtained in the present study demonstrated that the dosages of 0.3 mg/kg to 1.2 mg/kg present beneficial results in relation to the CTR, without differences between them, it is advisable to use the lowest possible dosage to obtain the benefits with reduced potential to cause side effects.

As limitations of the study, it is not possible to determine the ASU dosage for prevention of periodontal disease, for it is not the aim of this study. Regarding the methodology, there is a limitation of applicability because of the chosen design of using animals to analyse only the prevention of bone loss, but not its repair. This is explained because the ligature was maintained throughout the study, as well as the chosen form of ASU administration and dosage. Further studies are needed to determine clinical protocols for the use of ASU in adjunctive, supportive, and preventive therapy for periodontal disease. An important observation of this study was that there were no statistically significant impacts of ASU on the volume of bone tissue around the evaluated teeth. However, it is noteworthy that bone volume measurements are less sensitive to detect differences than linear measurements. The proliferative effect on connective tissues and blockage of bone reabsorption, such as the synthesis and higher expression of transforming growth factor β1 (TGF- β1) and bone morphogenetic protein 2 (BMP-2) that enhances the extracellular matrix and inhibit pro-inflammatory and pro-catabolic mediators, as well as the regulation of early stages of osteogenesis[7,16,22], were inferences derived from the effects of ASU observed in other studies since the present study did not evaluate the expression of biomarkers of connective tissue proliferation or biomarkers of bone remodelling. This fact does not reduce the importance of the findings, since the clinical parameters normally evaluated in humans are linear in nature. Thus, it can be concluded that ASU promoted a reduction in bone tissue resorption at concentrations of 0.3 g/kg/day to 1.2 g/kg/day, in the sites with inducted periodontitis.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose

Data availability:

Datasets related to this article will be available to the corresponding author upon request.

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Author Contribution

Júlia Siqueira Rodrigues Pavan: Methodology, Formal analysis and investigation, Writing - original draft preparation. **Suzane Cristina Pigossi**: Formal analysis and investigation. **Mauricio Andres Tinajero Aroni**: Methodology, Formal analysis and investigation, Writing - original draft preparation. **Felipe Eduardo Pinotti**: Methodology, Formal analysis and investigation, Writing - original draft preparation. **Rosemary Adriana Chiérici Marcantonio**: Conceptualization, Supervision. **Guilherme José Pimentel Lopes de Oliveira**: Conceptualization, Formal analysis and investigation, Writing - original draft preparation, Funding acquisition, Supervision. All authors critically revised, edited, and approved the final version of the manuscript.

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