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Campus de Araçatuba

Bharbara de Moura Pereira

EFEITOS DO CONSUMO DE VINHO TINTO DESALCOOLIZADO NO REPARO ALVEOLAR APÓS A EXODONTIA DE DENTES COM PERIODONTITE APICAL INDUZIDA

Araçatuba - SP
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Tese apresentada à Universidade Estadual Paulista (UNESP), Faculdade de Odontologia de Araçatuba, para obtenção do título de Doutora.
Área de Concentração: Endodontia

Orientador: Prof. Dr. João Eduardo Gomes Filho

Coorientador: Prof. Dr. Edilson Ervolino

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Ana Claudia M. Grieger Manzatti CRB-8/6315

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O caminho está na minha frente porque é o que eu escolhi."

Kevin Parker

RESUMO

PEREIRA, B. M. **Efeitos do consumo de vinho tinto desalcoolizado no reparo alveolar após a exodontia de dentes com periodontite apical induzida**. 2026. Tese (Doutorado) – Faculdade de Odontologia, Universidade Estadual Paulista (UNESP), Araçatuba, 2026.

A periodontite apical (PA) influência negativamente a cicatrização após a extração dentária. Fatores locais e sistêmicos, como o estado nutricional, influenciam a inflamação e o reparo ósseo. O vinho tinto desalcoolizado (VTD), rico em polifenóis e sem etanol, pode modular a inflamação e favorecer a cicatrização óssea. Este estudo avaliou os efeitos locais e sistêmicos da PA induzida e do consumo preventivo de vinho tinto (VT), VTD e álcool (AL) no reparo alveolar após a extração dentária. Foram utilizados 35 ratos machos *Wistar* distribuídos em 5 grupos (n=7): Controle Positivo (CP) – extração de dentes saudáveis; Controle Negativo (CN) – extração de dentes com PA; VT – VT + extração de entes com PA; VTD- VTD + extração de dentes com PA; AL – solução alcóolica de 12,5% + extração de dentes com PA. A administração das dietas ocorreu diariamente via gavagem durante 75 dias na dose de 4,28ml/kg de cada solução, os grupos controle receberam água destilada. A PA foi induzida no 15º dia, nos primeiros molares inferiores e superiores de todos os grupos, exceto CP. No 45º dia, os dentes foram extraídos e após 30 dias de reparo (ao final dos 75 dias), os animais foram eutanasiados, e amostras de sangue, maxilas e mandíbulas foram coletadas para análises hematológicas, imunoenzimáticas (ELISA), microtomográficas, imunohistoquímicas e histológicas, incluindo a quantificação de fibras colágenas por meio da coloração por Picrosirius Red. A análise estatística foi realizada com nível de significância de 5%. A suplementação com VTD manteve os parâmetros hematológicos dentro dos valores de referência e reduziu os níveis de TNF-α, enquanto o álcool aumentou os níveis de IL-1β ($p < 0,05$). Na análise histológica, CP e VTD apresentaram menor infiltrado inflamatório em tecido conjuntivo e ósseo que AL ($p<0,05$). CP e VTD mostraram melhor reparação epitelial e conjuntiva que CN, VT e AL ($p<0,05$). VTD apresentou maior imunomarcação para BMP-2, BMP-7 e OCN, menor para TRAP e RANKL, maiores valores de BS, BV, BV/TV, BS/BV e Tb.Th, menor Tb.Sp e predominância de fibras maduras ($p<0,05$). Conclui-se que a suplementação com VTD favoreceu o reparo do osso alveolar após a extração dentária em dentes com PA de forma local e sistêmica.

Palavras-chave: vinho; etanol; periodontite periapical; polifenóis; inflamação; extração dentária.

ABSTRACT

PEREIRA, B. M. **Effects of dealcoholized red wine consumption on alveolar repair after extraction of teeth with induced apical periodontitis**. 2026. 2026. Tese (Doutorado) – Faculdade de Odontologia, Universidade Estadual Paulista (UNESP), Araçatuba, 2026.

Apical periodontitis (AP) negatively influences healing after tooth extraction. Local and systemic factors, such as nutritional status, influence inflammation and bone repair. Dealcoholized red wine (DRV), rich in polyphenols and ethanol-free, can modulate inflammation and promote bone healing. This study evaluated the local and systemic effects of induced AP and preventive consumption of red wine (RV), DRV, and alcohol (AL) on alveolar repair after tooth extraction. Thirty-five male Wistar rats were used, distributed into 5 groups (n=7): Positive Control (PC) – extraction of healthy teeth; Negative Control (NC) – extraction of teeth with AP; RV – RV + extraction of teeth with AP; DRV – DRV + extraction of teeth with AP; AL – 12.5% alcoholic solution + extraction of teeth with AP. The diets were administered daily via gavage for 75 days at a dose of 4.28 ml/kg of each solution; the control groups received distilled water. PA was induced on day 15 in the first lower and upper molars of all groups except CP. On day 45, the teeth were extracted, and after 30 days of repair (at the end of the 75 days), the animals were euthanized, and blood, maxillary, and mandibular samples were collected for hematological, enzyme-linked immunosorbent assay (ELISA), microtomographic, immunohistochemical, and histological analyses, including the quantification of collagen fibers using Picrosirius Red staining. Statistical analysis was performed with a significance level of 5%. Supplementation with VTD maintained hematological parameters within reference values and reduced TNF-α levels, while alcohol increased IL-1β levels ($p < 0.05$). In histological analysis, CP and VTD showed less inflammatory infiltrate in connective and bone tissue than AL ($p<0.05$). CP and VTD showed better epithelial and connective tissue repair than CN, VT, and AL ($p<0.05$). VTD showed higher immunostaining for BMP-2, BMP-7, and OCN, lower for TRAP and RANKL, higher values of BS, BV, BV/TV, BS/BV, and Tb.Th, lower Tb.Sp, and a predominance of mature fibers ($p<0.05$). It is concluded that VTD supplementation favored alveolar bone repair after tooth extraction in teeth with PA, both locally and systemically.

Keywords: wine; ethanol; periapical periodontitis; polyphenols; inflammation; tooth extraction.

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Chapter 1

LISTA DE ABREVIATURAS E SIGLAS

AL	Alcohol
ANOVA	Analysis of variance
AP	Apical periodontitis
ARRIVE	Animal Research: Reporting of In Vivo Experiments
BMP-2	Bone morphogenetic protein-2
BMP-7	Bone morphogenetic protein-7
BS	Bone surface
BS/BV	Bone surface-to-volume ratio
BV	Bone volume
BV/TV	Bone volume fraction
CAPES	Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
CEUA	Comissão de Ética no Uso de Animais
CNPq	Conselho Nacional de Desenvolvimento Científico e Tecnológico
DMEN	Dulbecco's Modified Eagle's Medium
DRW	Dealcoholized red wine
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
FAPESP	Fundação de Amparo à Pesquisa do Estado de São Paulo
FOA	Faculdade de Odontologia de Araçatuba
IL-10	Interleukin 10
IL-17	Interleukin 17
IL-17A	Interleukin 17A
IL-1β	Interleukin 1 beta
NC	Negative control
OCN	Osteocalcin
OPG	Osteoprotegerin
PC	Positive Control
PVPI	Povidone-iodine
RANK	Receptor activator of nuclear factor kappa B
RANKL	Receptor activator of nuclear factor kappa-B ligand
ROI	Region of interest
RW	Red wine

Tb.N	Trabecular number
Tb.Sp	Trabecular separation
Tb.Th	Trabecular thickness
TNF-α	Tumor necrosis factor alpha
TRAP	Tartrate-resistant acid phosphatase
UNESP	Universidade Estadual Paulista

SUMÁRIO

1 GENERAL INTRODUCTION*

Alcohol consumption is present in various cultures and regions of the world (WHO, 2018). This practice is influenced by a variety of factors, including social, psychological, behavioral, economic, legal, and environmental aspects (Petticrew *et al*., 2017). Globally, alcohol consumption is associated with three million deaths (Shield *et al*., 2020). Furthermore, it is widely recognized that alcohol consumption contributes to more than 200 diseases, accounting for a considerable portion of the global burden of disease (Macdonald *et al.*, 2005; Rehm *et al*., 2010), which results in public health challenges, as it increases healthcare system expenditures (WHO, 2014).

Alcohol consumption can negatively affect the bone repair process and is associated with decreased bone density and mineral content (Elmali *et al.,* 2002). Alcohol inhibits osteoblast proliferation, resulting in decreased bone volume, while the rate of bone resorption is accelerated due to increased osteoclastic activity (Koo *et al.,* 2004). Mice exposed to alcohol exhibit decreased osteopontin expression levels and reduced biomechanical stiffness (Natoli *et al.,* 2018).

At higher concentrations, alcohol appears to potentiate inflammatory responses and increase susceptibility to bacterial infections due to its broad immunosuppressive effects, which may result in tissue damage (Szabo; Saha, 2015). Alcohol also impairs the migration of white blood cells to sites of injury and infection, causing functional abnormalities in T and B lymphocytes, natural killer cells, and monocytes/macrophages, in addition to altering cytokine production (Bautista, 2001; Deaciuc, 1997; Mandrekar; Catalano; Szabo, 1999). Chronic alcohol consumption in mice with alcohol-induced osteoporosis leads to a significant decrease in bone mineral density, accompanied by upregulation of nuclear factor of activated T cells 1 and receptor activator of nuclear factor kappa B ligand (RANKL) expression. Alcohol also suppresses the activity of antigen-presenting cells and natural killer T-like cells, resulting in decreased interleukin-4 (IL-4) secretion (Naruo *et al*., 2021).

Studies have shown that alcohol consumption may also be associated with the worsening of periodontitis and increased bone resorption in endodontics. In periodontics, alcohol has been shown to reduce cortical bone area, bone formation rates, and mineral apposition rates in rats at concentrations starting from 8.1% v/v (Hogan *et al*., 1997). A more recent study conducted in rats with induced periodontitis and chronic consumption of alcohol

* Lista de referências no Apêndice A

at concentrations of 14%, 25%, and 36% demonstrated worsening of periodontitis, with increased local inflammatory responses and bone resorption (Almeida *et al*., 2020). In endodontics, the evaluation of daily alcohol consumption at different concentrations led to alterations in the inflammatory pattern and increased bone resorption in induced apical periodontitis (AP) in Wistar rats. Even at lower concentrations (5% and 10%), alcohol consumption resulted in a moderate to severe inflammatory response, without exerting beneficial effects on immune system regulation when compared to the control group (Dal-Fabbro *et al*., 2019a).

One of the most widely consumed alcoholic beverages is red wine (RW), which has been associated with several health benefits, including the prevention and management of chronic diseases such as cardiovascular disease, metabolic syndrome, cognitive decline, depression, and cancer (Pavlidou *et al.,* 2018). In general, the beneficial effects of RW are observed with regular and moderate consumption, approximately 150 mL/day for women and 300 mL/day for men (Rotondo; Di Castelnuovo; Gaetano, 2001; Walzem, 2008). RW contains water, ethanol, glycerol, polysaccharides, various acids, and polyphenols (Snopek *et al.*, 2018). It is believed that the beneficial effects of RW are primarily due to its phenolic compounds (Haseeb; Alexander; Baranchuk*,* 2017). RW produced from Merlot grapes presents a complex composition with more than 41 individual compounds, including anthocyanins and condensed tannins, also known as proanthocyanidins. The biological effects of these compounds are associated with their ability to scavenge or inhibit reactive oxygen and nitrogen species, transfer electrons to free radicals, activate antioxidant enzymes, and modulate oxidative stress and inflammation (Majkić *et al*., 2019; Araújo *et al.,* 2021).

The phenolic compounds in RW can be divided into flavonoids and non-flavonoids. Flavonoids represent more than 85% of the phenolic components in RW and include different molecular families such as flavonols (quercetin), flavones, and anthocyanidins. Non-flavonoid compounds include hydroxycinnamic acids, hydroxybenzoic acids, stilbenes, and their derivative, resveratrol (Stockley *et al.,* 2012).

Our research group evaluated the moderate prophylactic administration of RW in rats with induced AP, which showed a decrease in inflammatory intensity and tartrate-resistant acid phosphatase (TRAP) staining; however, these results were not superior to those observed in the control group (Dal-Fabbro *et al.,* 2021). When alcohol was administered at the same dose and concentration as observed in RW, a negative effect was identified, namely increased bone resorption and greater severity of the inflammatory profile (Dal Fabbro *et al*., 2019b, 2021). In contrast, the isolated administration of two polyphenols present in RW (resveratrol

and quercetin) produced significantly better outcomes, including a less intense inflammatory process, reduced lesion size (microtomographic analysis), and increased OPG expression (Dal Fabbro *et al.,* 2021).

These data collectively support the hypothesis that the beneficial effects of RW are primarily due to its polyphenols, whereas alcohol exerts an antagonistic effect on the prevention of bone resorption and inflammation during the development of periapical lesions. Moreover, although isolated polyphenols from RW have been explored in the literature, there are no studies evaluating the combined effects of these phenolic compounds in the absence of alcohol on apical periodontitis repair.

Thus, the possibility arises of investigating dealcoholized red wine (DRW), produced similarly to conventional RW (maceration, fermentation, and bottling), differing only by undergoing a dealcoholization process prior to bottling. This process has minimal impact on the phenolic content of wine and may even increase its concentration in the final product (Belisario-Sánchez *et al*., 2009; Corona *et al*., 2019; Pham *et al*., 2019). In wines produced from Merlot grapes, dealcoholization has been shown to cause minimal alterations in phenolic compounds, including flavonols, tartaric esters, stilbenes (trans- and cis-resveratrol), flavonols (rutin, quercetin, and myricetin), flavan-3-ols ((+)-catechin and (−)-epicatechin), anthocyanins (particularly malvidin-3-glucoside), and non-flavonoids (gallic, caffeic, and p-coumaric acids) (Belisario-Sánchez *et al*., 2009).

DRW may contribute to the treatment of AP, as this condition is characterized by inflammation of periapical tissues resulting from infection of necrotic pulp tissue (Nair, 2004). The severity of inflammation and the extent of bone loss are influenced by systemic and local conditions, involving cells, inflammatory mediators, metabolites, effector molecules, and antibodies (Holland *et al.,* 2017; Nair, 2004; Kajiya *et al.,* 2010). Inflammatory cytokines play a critical role in the immune response by initiating and coordinating cellular events and regulating the host response to endotoxins.

Bone resorption in these pathologies is a key factor in lesion progression, initiated by the proliferation of immature osteoclast precursor cells and their differentiation into mature osteoclasts responsible for the degradation of organic and inorganic bone components. RANKL (receptor activator of nuclear factor kappa B ligand) is a key molecule in osteoclast activation, while OPG (osteoprotegerin) acts as a decoy receptor for RANKL. An increased RANKL/OPG ratio favors bone resorption through osteoclastogenesis and osteoclast activation (Austah *et al.,* 2016; Becconsall-Ryan; Tong; Love*,* 2010; Boyce; Xing, 2008; Britton *et al*., 2014; Dal-Fabbro *et al*., 2019a; Eriksen, 2010; Gomes Filho *et al.,* 2015;

Hofbauer; Kuhne; Viereck, 2004; Holland *et al.,* 2017; Kajiya *et al.,* 2010; Kawashima *et al.,* 1996; Martins *et al.,* 2016).

Treatment of AP is performed through endodontic and/or surgical procedures (tooth extraction), aiming to eliminate antigens primarily located within the root canal system (Karamifar; Tondari; Saghiri, 2020). Once the endodontic infection is effectively controlled, inflammation gradually decreases, bone resorption is halted, and the repair process begins, allowing tissue healing (Ricucci *et al.,* 2014), as the interaction between microbial factors and the host immune response leads to inflammation and bone resorption in the apical region as a defense mechanism against infection (Cintra *et al*., 2018; Nair, 2004; Subramanian; Mickel, 2009).

However, persistent endodontic infection may impair bone formation and remodeling during alveolar healing following tooth extraction (Kim *et al*., 2017). Bone repair, as a fibroproliferative response mediated by growth factors and cytokines, begins with a vascular and cellular inflammatory phase leading to granulation tissue formation (Poleti *et al*., 2022). This is followed by connective tissue maturation and osteoblast differentiation for bone formation, ultimately restoring homeostasis (Devlin; Sloan, 2002). This repair process can be influenced by both local and systemic factors (Georgiou *et al*., 2020; Ozcan-Kucuk *et al.,* 2018).

Due to the limitations of clinical and in vitro studies in assessing the resolution of endodontic infections in humans, and the requirement of bone healing to visualize repair, animal models involving pulp exposure followed by extraction represent a viable alternative for evaluating inflammatory responses and periapical tissue repair (Georgiou *et al*., 2020; Goldman *et al*., 2019). Furthermore, tooth extraction in rats offers advantages in terms of cost-effectiveness and simplicity compared to studies in humans or dogs (Li *et al*., 2022), which require considerably longer durations, especially for evaluating AP repair.

Thus, the aim of this study was to analyze and compare the modulatory effects of different diets—comprising RW, DRW, alcohol, and water—administered via gavage on the repair of AP induced in Wistar rats following tooth extraction.

4 GENERAL CONCLUSION

Dealcoholized red wine is capable of systemically and locally modulating bone repair in the alveoli of teeth with induced apical periodontitis.

APÊNDICES

APÊNDICE A – Lista de Referências da Introdução Geral

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