



Exploring the Integration of Artepillin C, a Bioactive Constituent of Propolis, in Dental Materials: (A-Review)

S. SOWMYA¹, K.N. RAGHAVENDRA SWAMY¹, RAMA KRISHNA ALLA^{2*}, VIDYA G. DODDADAWAD³, KARTHIKEYA PATIL⁴, C.J. SANJAY⁴ and ANUSHA KONAKANCHI²

¹Department of Prosthodontics, JSS Dental College and Hospital, JSS Academy of Higher Education and Research, Mysore, Karnataka, India.

²Division of Dental Materials, Vishnu Dental College, Bhimavaram, Andhra Pradesh, India.

³Department of Oral Pathology and Microbiology, JSS Dental College and Hospital, JSS Academy of Higher Education and Research, Mysore, Karnataka, India.

⁴Department of Oral Medicine & Radiology, JSS Dental College and Hospital, JSS Academy of Higher Education and Research, Mysore, Karnataka, India.

*Corresponding author E-mail: rkdenalbiomaterials@gmail.com

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ABSTRACT

Honey, often referred to as the "golden elixir," is known for its rich chemical composition. Similarly, Artepillin C (ARC), a key bioactive compound in propolis, a resinous substance collected by bees, has garnered attention for its potent therapeutic properties. This review explores the potential of Artepillin C (ARC), as a transformative element in oral health care. With its broad-spectrum antimicrobial, anti-inflammatory, and immunomodulatory effects, ARC emerges as a promising, low-risk alternative to conventional dental drugs. The successful incorporation of Artepillin C into various dental products, highlighting its multifaceted benefits. This compound emerges as a promising contender for the future of dentistry, offering a comprehensive solution that outshines traditional approaches and introduces a new era in oral health management.

Keywords: Artepillin C, Dental Materials, Oral Health.

INTRODUCTION

Artepillin C (ARC) is a major bioactive compound derived from Propolis, a resinous substance collected by honeybees from various botanical sources. It possesses a broad spectrum of pharmacological benefits, including antioxidant, antimicrobial, anti-inflammatory, anti-diabetic, neuroprotective, gastroprotective, immunomodulatory,

and anti-cancer properties¹. Most studies have focused on its potential in combating oxidative stress, inflammation, diabetes, and cancer using a combination of in vitro and in vivo methodologies^{2,3}. Due to its multiple health benefits-such as antimicrobial activity, antioxidant effects, anti-inflammatory action, inhibition of biofilm formation, and promotion of tissue regeneration, ARC has also attracted growing interest in the field of dental materials^{4,5}.



Artepillin C is a prenylated derivative of p-coumaric acid is found predominantly in Brazilian green propolis (BGP)⁶. This compound is mainly derived from *Baccharis dracunculifolia* plants in Brazil, but has also been identified in Brazilian brown propolis, and various other plant species⁶.

Research has identified p21-activated kinase 1 (PAK1) as a key molecular target of ARC. PAK1 has emerged as a potential target for ARC due its implications in various diseases, including inflammation, diabetes, and cancer⁷. Maruta and He have proposed that inhibiting PAK1 could be a promising antiviral treatment for COVID-19, presenting a novel therapeutic opportunity for Artepillin C7-9. The worldwide recognition of ARC has increased the market value of Propolis, with the concentration of ARC being a benchmark for propolis quality¹⁰. This review aims to summarize the chemical characteristics, pharmacokinetics profile, bioavailability, oral health benefits, and molecular targets of ARC, particularly in the context of dental materials, while outlining future directions for research.

The Chemical Characteristics of ARC:

ARC is a type of phenolic acid with a simpler name (E)-artepillin C. It weighs about 300.4 g/mol and has two prenyl groups attached to its phenyl ring⁶. There are two forms of ARC, E (Fig. 1) and Z (Fig. 2), but the E form is more common and found in Brazilian propolis. It can be sensitive to light and heat, and exposure to sunlight for 5 days turns it into the Z form. If exposed for more than 5 days, it keeps breaking down. Heating it to 50°C also changes it into different forms¹¹. Uto *et al.*,² were the first to make ARC in the lab (synthetic) by prenylating p-halophenols, specifically o,o'-diprenylating p-iodophenol in water and then coupling it with methyl acrylate using Mizoroki-Heck chemistry.

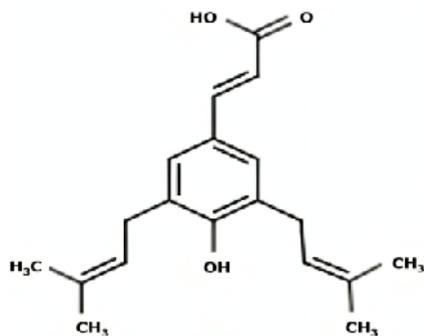


Fig. 1. (E)-artepillin C form⁶

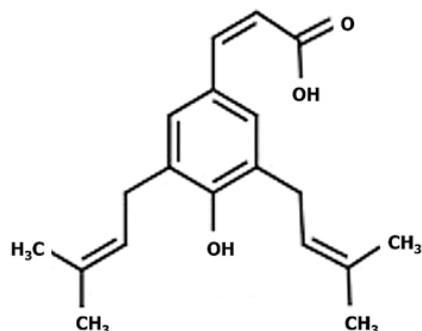


Fig. 2. (Z)-artepillin C form⁶

The Pharmacokinetic Profile of Artipilin C

The concentration of ARC in the blood at different times has been studied, with reports indicating that it peaks approximately one hour after administration, reaching an average of 22 µg/mJL. This suggests that ARC was well-absorbed and bioavailable, contributing to its significant anti-inflammatory effects¹⁰.

ARC has been shown to fight harmful free radicals and act as an effective antioxidant^{12,13}. In one study, ARC at concentrations of 100 and 500 µg/mL reduced lipid peroxidation in red blood cells by 17% and 82%, respectively. Importantly, ARC exhibited low cytotoxicity, with an IC₅₀ value of 588 µM, indicating its safety at effective doses¹³. These findings suggest that ARC has the potential to serve as a powerful dietary antioxidant and can be modified to incorporate as more potent antioxidant in dental materials¹³.

The E form of ARC was found to hinder the growth of various oral bacteria, including *Streptococcus mutans*, *S. mitis*, *S. sobrinus*, *S. sanguinis*, *S. salivarius*, and *Lactobacillus casei*, at concentrations of 200 or 400 µg/mL¹¹. However, the breakdown products of ARC didn't exhibit significant antibacterial effects against most strains. Interestingly, the Z form showed a relatively stronger impact on *S. mitis* and *S. sanguinis*, with MIC values of 50 and 100 µg/mL, respectively¹¹.

The anti-inflammatory effects were attributed to its inhibition of the inducible nitric oxide synthase (iNOS) gene expression by interfering with nuclear factor kappa B (NF-κB) sites in the iNOS promoter. This substance also led to a reduction in the production of prostaglandin E2 (PGE2) during instances of

pain and inflammation¹⁰. The anti-inflammatory responses of this substance were noted through modulation of the NF- κ B signalling pathway¹⁴.

Potential Use in Dental Products

ARC exerts a substantial impact on dental materials (Fig. 3) by targeting key mechanisms, making it a suitable candidate for incorporation into various products such as mouthwashes, toothpaste, gels, and dental restorative materials¹⁵. The specific targets relevant to dental materials are discussed in the following sections.

Antioxidant activity

ARC's potent antioxidant capabilities, derived from its phenolic structure, enable it to effectively neutralize free radicals and reactive oxygen species (ROS), thereby mitigating oxidative stress and protecting cells and tissues from damage¹⁶. These properties highlight its potential in managing oxidative stress-related oral health issues¹⁶. Moreover, ARC has demonstrated significant DPPH radical scavenging activity, further supporting its promise as a therapeutic agent against oxidative stress-associated oral problems¹⁶.

Anti-Inflammatory Effects

ARC demonstrates anti-inflammatory properties by inhibiting pro-inflammatory molecules such as cytokines and prostaglandins¹⁷. Its ability to suppress enzymes like cyclooxygenase (COX) suggests potential in mitigating inflammatory processes in the oral cavity, making it valuable for improving gum health and preventing periodontal diseases¹⁷.

Antimicrobial Properties

ARC, has received increased attention for its ability to inhibit the growth of microorganisms, including those that cause common oral infections¹⁸⁻²⁰. *Streptococcus mutans*, for example, is a primary pathogen responsible for dental caries due to its role in biofilm formation and acid production on tooth surfaces.

*Porphyromonas gingivalis*²⁰, a key pathogen in periodontitis, contributes to the destruction of gum tissue and bone. *Candida albicans* is a fungal species commonly associated with oral candidiasis, a condition prevalent among immunocompromised individuals and denture wearers^{19,20}.

When integrated into dental materials such as composite resins²⁰, adhesives, or cements, ARC can provide a sustained antimicrobial effect. These materials are designed to release antimicrobial agents gradually, ensuring a continuous protection against bacterial colonization and biofilm formation. This proactive inhibition of oral pathogens helps in maintaining oral hygiene, particularly in high-risk areas, such as restorations, crowns, and bridges, which are prone to secondary caries and infection¹⁸⁻²⁰.

The use of ARC in dental treatments is not just limited to reducing infections but also contributes to the longevity of dental restorations. The antibacterial properties help to preserve the underlying tooth structure, potentially reducing the need for frequent replacements of dental work, which can result from recurrent infections. As such, integrating ARC into dental materials represents a significant advancement in preventive dental care.

Immunomodulatory effects, Wound Healing, and Anti-Cancer properties

ARC has been found to influence key immune pathways, potentially enhancing the body's ability to recognize and eliminate pathogens¹⁶. This is particularly important in the oral cavity, where the immune system constantly interacts with a complex microbiome. The modulation of immune responses can help limit chronic inflammation associated with periodontal disease and other oral infections. Through the upregulation of immune cells, such as macrophages and neutrophils, ARC can assist in quicker pathogen clearance, potentially reducing the severity and duration of infections.

In wound healing, ARC has shown promise due to its ability to stimulate the growth of fibroblasts, which are essential for tissue repair and regeneration. Fibroblasts play a crucial role in synthesizing collagen, a structural protein that forms the foundation for new tissue formation^{21,22}. This aspect of ARC makes it particularly valuable in oral surgery and dental procedures, such as tooth extractions, gum surgery, and implant placements, where effective wound healing is critical.

By enhancing fibroblast activity and collagen synthesis, ARC promotes faster and more efficient healing of oral tissues, reducing recovery times and the risk of complications such as infection.

Furthermore, its antimicrobial properties helps in additional protection during the healing process by preventing bacterial colonization and biofilm formation on surgical wounds or dental restorations.

Tissue Regeneration

ARC, plays a significant role in tissue regeneration, particularly in periodontal therapy and guided bone regeneration (GBR). Its anti-inflammatory properties help in reducing cytokine levels, minimizing tissue damage in periodontal disease²³. ARC stimulates fibroblast activity, promoting collagen synthesis and soft tissue repair, essential for reversing gum recession. In GBR, ARC enhances osteoblast proliferation and collagen production, supporting bone regeneration. Additionally, its antimicrobial effects protect against infections, crucial during healing. ARC's combined anti-inflammatory, regenerative, and antimicrobial properties make it highly valuable in dental procedures for rebuilding damaged tissues²³.

Biofilm Disruption

ARC effectively disrupts bacterial biofilms, including dental plaque, making it a valuable agent in enhancing oral hygiene. By inhibiting bacterial adherence, ARC prevents the formation of biofilms on teeth, particularly from *Streptococcus mutans*, a major contributor to dental caries²⁴. ARC also breaks down the protective matrix of established biofilms, making them easier to remove through brushing or professional cleaning. Its antimicrobial properties further reduce bacterial viability, weakening biofilms and limiting their growth. ARC's potential in oral care products such as mouthwashes or toothpastes could help in preventing plaque build-up, reduce the risk of cavities, and support periodontal health²⁴.

Limitations

However, ARC faces challenges related to cell permeability due to its repulsion to negatively charged phospholipid-based plasma membranes²⁵. To address this, researchers have successfully esterized ARC, enhancing its cell permeability without sacrificing water solubility²⁵. Yet additional research is needed in this direction.

Research and Development

While the potential benefits of ARC in dentistry are promising, it's imperative to acknowledge that research in this area is ongoing. Rigorous clinical

trials and further studies are essential to confirm its efficacy and safety when integrated into dental applications. Factors such as ARC concentration, compatibility with other components, and release kinetics must be meticulously examined to ensure the material's effectiveness and safety. Regulatory approval is a critical step before these dental materials can be implemented in clinical practice.

After reviewing several articles, it is evident that there are numerous promising methods for integrating Artepillin C into diverse dental products (Fig. 3)¹⁻²⁰: These include,

1. Formulating Artepillin C-infused toothpaste.
2. Developing Artepillin C-based mouthwashes.
3. Incorporating Artepillin C into dental gels or creams.
4. Creating dental floss or oral strips with Artepillin C.
5. Designing Artepillin C-containing chewing gums for oral health benefits.
6. Designing dental cements with the addition of Artepillin C for enhanced properties and benefits.
7. Creating denture material that's better and more beneficial by adding Artepillin C.

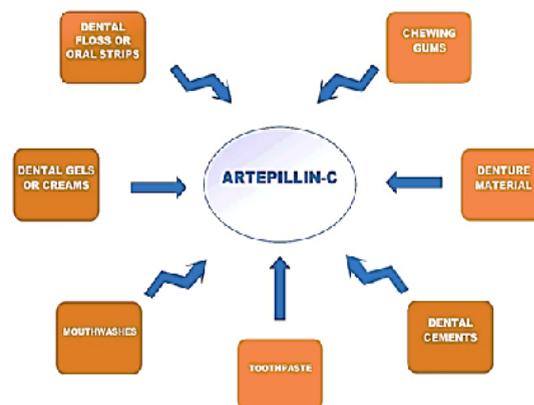


Fig. 3. Integrating Artepillin C into diverse dental products

After thorough research, the integration of Artepillin C into complete denture resin offers potential benefits in terms of antimicrobial, anti-inflammatory, and biocompatible properties.

Approaches for integrating Artepillin C into dental resin encompass

Formulation Development: Research and development to create a resin formula that includes Artepillin C in optimal concentrations.

Material Compatibility: Ensuring compatibility between Artepillin C and the resin matrix to maintain the structural and mechanical integrity of the dental material.

Encapsulation Techniques: Utilizing encapsulation methods to protect the stability and release of Artepillin C within the resin matrix.

Polymerization Considerations: Adapting the curing process to accommodate the presence of Artepillin C and ensuring proper polymerization of the resin.

Testing and Validation: Conducting thorough testing to validate the antimicrobial efficacy, durability, and safety of the Artepillin C-infused resin.

Regulatory Compliance: Ensuring that the final product meets regulatory standards and guidelines for dental materials.

CONCLUSION

Artepillin C from propolis emerges

as a promising addition to dental materials, offering a multifaceted approach to oral health enhancement. Its antimicrobial, anti-inflammatory, and tissue-regenerative properties present exciting possibilities for innovative oral care solutions. However, thorough research and clinical validation are imperative to ascertain its safety and efficacy in dental applications, paving the way for a natural and effective approach to oral health. The ongoing exploration of ARC's mechanisms and potential benefits underscores its significance in advancing healthcare and therapeutic interventions, emphasizing the need for continued research and exploration in this compelling field.

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Conflicts of Interests: None.

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