

Pelargonium sidoides: A possible preventive role in the development of endodontic flare-up

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Purpose: In the presence of acute or chronic inflammation in the periapical tissues caused by various anaerobic and facultative bacteria, it is aimed to create suitable healing conditions by performing successful root canal treatment. However, endodontic flare-ups may occur between appointments, and this may cause discomfort for the patient and damage the patient-clinician relationship. Therefore, in this brief review, it is aimed to describe the possible preventive effects of the natural medicine Pelargonium sidoides extract (EPs® 7630), which has broad anti-infective and anti-inflammatory properties.

Methods: PubMed and Google Scholar databases were searched and reviewed related to P. sidoides. The anti-inflammatory and antimicrobial effects of P. sidoides extract and its chemical constituents in periodontitis and other systemic infections are discussed.

Results: Clinical and in vitro studies have confirmed that P. sidoides extract and some of its fractions may be involved in inflammatory tissue responses by showing immunomodulatory effects in mild infections of periapical tissues. This implies that the natural remedy, EPs® 7630, could be a potential therapeutic and prophylactic medicine for root canal treatments.

Conclusion: This review provides basic information about the immunomodulatory, anti-infective, and anti-inflammatory effects of EPs® 7630 and outlines its possible functions in periradicular tissues as a promising therapeutic medicine.

Keywords: Endodontic treatment; flare-up; immunomodulation; inflammation; pelargonium sidoides.

Introduction

The dental pulp consists of mesenchymal connective tissue that extends from a pulp chamber within the crown to one or multiple canals in the roots. The hard dentin tissue forms a structural integrity surrounding the pulp tissue in the crown and root parts. In teeth damaged by periodontal disease, trauma, or caries, microorganisms can lead to infection and inflammation in the pulp tissue (1). Although

pulp tissue has various defense mechanisms against microorganisms and their toxins, necrosis of the pulp tissue may occur (2). In untreated cases, microorganisms and toxins can occupy the root canal system, migrate out of the canal via the apical foramen, and invade the peri-radicular tissues (3). This invasion in the peri-radicular region causes apical periodontitis, an oral inflammatory disease, and is characterized by the formation of granulation tissues

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with bone resorption. Apical periodontitis includes complex molecular and cellular mechanisms in which various bioactive molecules, such as lytic enzymes and cytokines, contribute to tissue destruction (4). If apical periodontitis is not correctly diagnosed and treated, it could not only cause tooth loss in the future but could also be a source of other inflammatory diseases associated with systemic diseases, such as cardiovascular disorders and diabetes (5). In addition, the number of people around the world with at least one tooth with apical periodontitis has been reported to range from 16% to 86% according to their age, education level, and access to dental care (6). Although symptomatic apical periodontitis associated with irreversible pulpitis or necrotic pulp is commonly seen clinically, it may appear as an acute abscess when virulent bacteria reach the periapical area in sufficient numbers. A previous study reported that acute apical abscesses that are characterized by localized swelling and lymphadenopathy resulted in 61,439 hospitalizations and were the cause of death for 66 hospitalized patients over a 9-year period (7). Therefore, endodontic treatment aims to retain teeth with pulpal and periapical diseases by maintaining the health of periapical tissues by preventing and treating the infection (8). However, acute exacerbation of a pulpal or peri-radicular pathosis may occur after the initiation or continuation of endodontic treatment procedures, which is also known as an endodontic flare-up. Even if a flare-up occurrence between appointments does not have a significant effect on the success of the endodontic treatment, it is distressing and undesirable for patients due to the development of pain and swelling, thus requiring additional and unscheduled interappointment visits. Systemic antibiotics are indicated in flare-up cases if there are any signs of systemic involvement. The patient's lifestyle and satisfaction with treatment are also affected by this condition (9). For this reason, clinicians should take appropriate precautions to avoid flare-ups (10). Several approaches have been recommended for this purpose, including the preoperative and postoperative intake of some medicines, such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and antibiotics. However, there is a lack of sufficient evidence regarding these prevention strategies to support their effectiveness (11).

Systemic antibiotics are commonly administered as an adjunct to the non-surgical endodontic treatment of acute apical abscesses with systemic involvement or in cases of progressive infections such as cellulitis and spreading infections (12). Antibiotics should also be considered in cases of acute apical abscess in systemically compromised patients that cause impaired immunologic function (13). However, the antibiotic prescription should be limited, as

the overuse of antibiotics could provoke the emergence of antibiotic-resistant bacterial strains. Several recent reports from different countries have shown inappropriate antibiotic administration in endodontic infections, and this has become an international concern (14,15). In this regard, the intensive use of antibiotics in dentistry makes bacteria unsusceptible to prescribed antibiotics and causes them to gain resistance (16). Thus, the emergence of antibiotic resistance is inevitably becoming an important global health problem as it is making infection treatments more difficult. Furthermore, antibacterial chemicals in antibiotic drugs not only kill pathogenic bacteria but also destroy common strains of the human microbiota. Therefore, treatments with herbal antibacterial drugs can be a promising new therapeutic method for eliminating the risk of bacterial resistance development (17).

Pelargonium sidoides, mostly known as African geranium, is a medicinal plant indigenous to South Africa, and its root extract is thought to be effective in the treatment of various acute infections (18). Following the identification of many compounds of *P. sidoides* roots, such as methoxycoumarin and proanthocyanidins, liquid herbal medicine branded EPs® 7630 (active ingredient of Umckaloabo® product, ISO-Arzneimittel, Ettlingen, Germany) began to be produced. This medicine, which is prepared by dissolving the root extract of *P. sidoides* in 11% ethanol, has been approved for use in the treatment of acute respiratory tract infections in various countries across the world, including European countries (19). Since EPs® 7630 has been shown to have antimicrobial and immune modulatory activities in some studies, it has been reported that it can be used in other pathological diseases related to inflammation (20). Hence, in light of the information given in this brief review, we question whether the use of *P. sidoides* extract before and/or after endodontic treatment of pulpal or periapical infections could be an adjunct therapy option that may help to decrease the incidence of flare-ups by alleviating the severity of post-treatment inflammation. Thus, it may minimize the need for systemic antibiotic administration for endodontic infections following root canal therapy. In order to find solutions to endodontic symptoms experienced by patients, we proposed a consistent hypothesis with respect to the evidence collected in this paper. We hypothesized that the prophylactic administration of EPs® 7630 as a natural remedy may reduce the possibility of flare-ups occurring after endodontic treatment or between appointments for nonvital teeth, thereby reducing inappropriate antibiotic use in endodontics.

Evaluation of Hypothesis, Anti-Inflammatory, and Anti-Infective Effects of *P. Sidoides*

An overview of the EPs® 7630: Cytokine–Apical periodontitis relationship

Pathogenic bacteria and their products in infected root canals stimulate periodontal ligament (PDL) cells to release inflammatory mediators that allow inflammatory cells to migrate into the inflammation site. When lipopolysaccharide (LPS) antigens on the surface of pathogenic bacteria stimulate PDL fibroblasts, Toll-like receptors (TLRs) such as TLR2 and TLR4 are expressed, and CD4+ T cells (Helper T Lymphocytes) are activated (21). However, in the early stages of the periapical lesion, interleukin 1 α and tumor necrosis factor- α (TNF- α) cytokines were found to be expressed in the absence of T cells in the inflammation site, and then the effect of T-lymphocytes in the pathogenesis of periapical lesions was questioned (22). Interestingly, some studies have revealed that Pelargonium extract induces TNF- α and IL-1 production by acting on murine-derived macrophages (23,24). Furthermore, in their study on human peripheral blood mononuclear cells, Witte et al. (25) determined that EPs® 7630 targeted CD14+ monocytes and led to the production of high amounts of TNF- α and interleukin 6 (IL-6) pro-inflammatory cytokines. On the other hand, EPs® 7630 pre-treatment inhibited TLR3- and TLR4-mediated TNF- α and interleukin 10 (IL-10) production while increasing IL-6 secretion depending on its concentration. According to these findings, it has been suggested that EPs® 7630 activates the innate immune defense by stimulating an immune response before any infection, thereby promoting the body's ability to quickly and efficiently eliminate potentially incoming microorganisms. Thus, it is thought that it may have a protective effect against microorganisms in the periapical tissue.

Indeed, the ingredients of EPs® 7630 are responsible for the pharmacological activity, and some studies have been performed to identify which ingredients have therapeutic effects, such as anti-inflammatory or antimicrobial (25,26). The ethanol in EPs® 7630 dissolves the roots of *P. sidoides*, leading to the formation of a range of six main components: proanthocyanidins, carbohydrates, minerals, peptides, purine derivatives, and benzopyranones (27). The proanthocyanidin fraction of *P. sidoides* root extract, condensed tannins formed from flavan-3-ol units, leads to antibacterial and anti-inflammatory biological activities (28). Proanthocyanidin can suppress inflammation owing to its potent antioxidant and metalloproteinase inhibitory properties (29). The production of nitric oxide (NO), a potent antioxidant agent, enables macrophages to exert cytotoxic effects against microorganisms (30). EPs® 7630

has been shown to strongly induce inducible NO synthases (iNOS) gene expressions in *Leishmania*-infected raw cells (24). iNOS expression in activated macrophages as an immunological response to pathogenic stimuli induces the release of larger amounts of NO. However, it should be noted that while NO species may usefully function as antimicrobial effector molecules in immune system protection against pathogenic microorganisms, the relatively high level of NO produced during the immune response can be harmful (23). The increase in iNOS gene expression leads to reactive nitrogen species-mediated apoptosis of gingival fibroblasts and tissue loss in periodontitis (31). Therefore, regulation of NO production is important for both periodontal tissues and human health. Jekabsone et al. (29) illustrated that the proanthocyanidin fraction of *P. sidoides* root extract reduced iNOS synthesis in murine bone marrow-derived macrophages, protecting periodontal tissues from damage caused by reactive nitrogen species.

Cyclooxygenase-2 (COX-2) is involved in the production of prostaglandins and thromboxanes that promote inflammatory reactions and is not found in most normal tissues (32). Thus, NSAIDs target a reduction in the synthesis of prostaglandins and thromboxanes by inhibiting the COX-2 pathway, thereby controlling the formation of pain and inflammation (33). Interestingly, the proanthocyanidin fraction of *P. sidoides* root extract was also found to inhibit IL-1 β and COX-2 pro-inflammatory gene expression, which is associated with bone tissue loss in periodontitis, in macrophages treated with LPS and IFN- γ (29).

Mitogen-activated protein kinase (MAPK) is a signal transduction pathway that establishes an important link between the cell surface and the nucleus to regulate cellular programs such as proliferation, differentiation, development, and death. Since this pathway can cross-talk with all molecular pathways, it plays an important role in bone formation (34,35). Some pro-inflammatory cytokines (TNF- α , IL-1 β , etc.) activate MAPK, and EPs® 7630 has also been shown to induce MAPK-dependent pro-inflammatory cytokines in human monocytes (25). In view of these above-mentioned data, an intervention with EPs® 7630 in the treatment of apical periodontitis may be advantageous as it pre-strengthens the innate immune system and induces bone formation via the MAPK pathway. Besides the fact that EPs® 7630 activates human monocytes and induces MAPK-dependent pro-inflammatory cytokines in these cells, it specifically modulates the production of mediators known to lead to the generation of adaptive T helper 17 (Th17) and T helper 22 (Th22) cells in the bone marrow (36). Th17 and Th22 cells, subtypes of CD4+ T cells, are important members of the adaptive immune system and have been found to exist in periapical lesions. IL-23, IL-

6, and transforming growth factor beta activate Th17 cells and cause the secretion of interleukin 17 (IL-17). While the presence of Th17 and IL-17 has been demonstrated in severe chronic apical periodontitis, the roles of Th17 and IL-17 in periapical inflammation are still not fully understood (37). Interleukin 22 (IL-22), secreted by Th22 cells, is a cytokine belonging to the IL-10 superfamily, which is the effector cytokine of the Th17 lineage (38). According to the results of a study on a mouse model, knockout of IL-22 led to an increase in the size of the periapical lesion, suggesting that IL-22 is involved in the host's immune system in periapical inflammation (39). In light of this information, it is thought that EPs® 7630 may have a preventive effect on the development of periapical inflammation through the adaptation of Th17 and Th22.

An Overview of the Apical Periodontitis-Bacteria-EPs® 7630 Relationship

Apical periodontitis is a microbiological problem that causes infection in peri-radicular tissues before or after endodontic treatment. If the entry of microorganisms into the root canal system is not successfully controlled during the initial endodontic treatment, it may lead to the development and persistence of periapical infections. Although microorganisms may not be present in the canal before the treatment, the root canal system may be infected secondarily as a result of the entry of bacteria into the root canal system due to the violation of aseptic conditions during the endodontic treatment (8). These microorganisms in the root canal system might also extrude into the periapical tissues when performing canal instrumentation and could cause an endodontic flare-up, which is characterized by pain and/or swelling. Considering bacteria as a causative factor of endodontic flare-up and persistent periapical infection following endodontic treatment, it is anticipated that antibiotics will assist in the prevention or management of inflammation of the periapical tissues (40). In some studies, it has been reported that antibiotic intervention before or after endodontic treatment of teeth, especially non-vital teeth, may be beneficial to prevent or decrease the incidence of acute infection in periapical tissues (41,42). However, the intensive prescription of antibiotics for endodontic infections renders bacteria unsusceptible to prescribed antibiotics while also exposing patients to a wide range of side effects. Therefore, microbial culture and antibiotic susceptibility testing are considered essential for prescribing a targeted antibiotic, although they increase the cost and delay the commencement of endodontic treatment (43). In a survey study, it was reported that 66% of dentists did not recommend antibiotic susceptibility and culture tests to their patients, and 51.3% reported that their

patients did not respond to prescribed antibiotics (44). These results highlight that dentists should focus on antibiotic susceptibility and culture tests to determine the appropriate antibiotic that should be prescribed for a particular type of bacteria isolated from the canal (45). Apart from bacterial insusceptibility, inappropriate use of antibiotics might cause side effects such as fatal anaphylactic reactions and gastrointestinal disorders (12). These facts may suggest that herbal medicines such as EPs® 7630, which have very few side effects, might be considered natural antibiotics and could be an alternative to prophylactic antibiotic therapy in attempts to prevent odontogenic polymicrobial infections such as apical periodontitis or flare-ups (Fig. 1).

The microflora of endodontic infections involves a combination of Gram-positive and Gram-negative facultative anaerobic bacteria (strictly anaerobic). Anaerobic microorganisms isolated from teeth with untreated apical periodontitis were found in one study as follows: *Peptostreptococcus micros*, *Fusobacterium necrophorum*, *Fusobacterium nucleatum*, *Prevotella intermedia/nigrescens*, *Porphyromonas gingivalis*, and *Porphyromonas endodontalis*. Additionally, *Enterococcus faecalis* is frequently associated with unsuccessful endodontically treated teeth (46). Among them, *E. faecalis* and *P. gingivalis* are important pathogenic bacteria that cause the destruction of periapical tissues (47). It was clearly determined that endophytes isolated from the root of *P. sidoides* endowed a significant antibacterial effect against *E. faecalis* and proanthocyanidins against *P. gingivalis* (26,29). These findings suggest

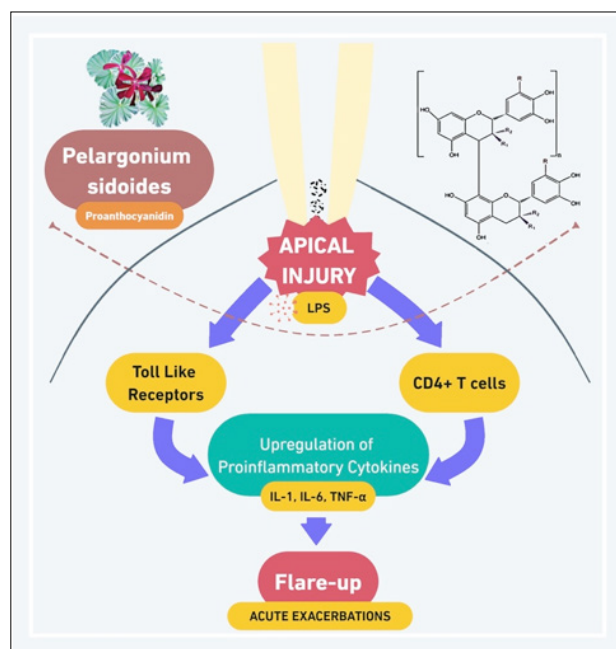


Fig. 1. Possible anti-inflammatory effect of *Pelargonium sidoides* to prevent endodontic flare-up occurrence.

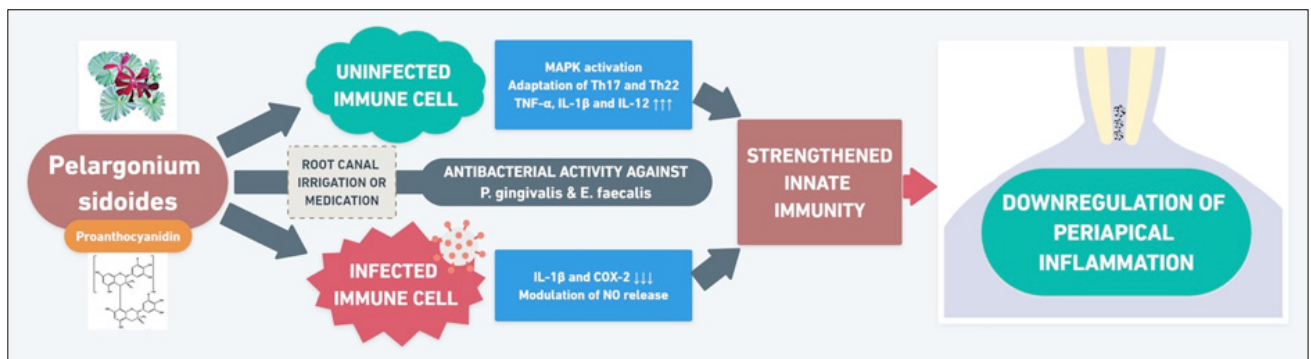


Fig. 2. Schematic depiction of strengthening the innate immunity through *Pelargonium sidoides*.

that *P. sidoides* root extract may be a potential candidate for a harmless prophylactic treatment option for acute exacerbation of periapical pathologies, before or during endodontic intervention, due to its noteworthy antibacterial and anti-inflammatory effects. It can be hypothesized that these effects are mainly induced by an immune modulation mechanism mediated by the activation of macrophages and a consequent increase in NO production, which was discussed thoroughly above. The direct antibacterial effects of *P. sidoides* root extract against endodontic pathogens may be expected if it is used as a root canal irrigant or intracanal medicament where direct contact between the agent and bacteria may occur. Since herbal medicine has experienced rapid growth in recent years due to its beneficial properties, the use of herbal alternatives for endodontic treatment is becoming more popular. Thus, although *P. sidoides* root extract appears promising, preclinical and clinical research are definitively required before it can be used in standard endodontic treatment.

Between the root canal treatment sessions, it is possible to encounter an acute exacerbation of the periapical tissues, which may occur due to these bacteria residing in the root canal system (10). Therefore, the prescription of antibiotics to either prevent endodontic exacerbations or control the periapical infection is considered a reasonable approach, as mentioned above (40). Besides having antibacterial effects, antibiotics possess anti-inflammatory and immunomodulatory effects. For example, the use of amoxicillin, which is one of the most frequently prescribed antibiotics in endodontics, increases the release of TNF- α and IL-1 β , potent pro-inflammatory cytokines, from macrophages (48). In the early stages of infection, TNF secretion occurs with macrophage activation, and excessive systemic TNF secretion may be fatal, while moderate secretion may be beneficial in terms of prognosis (23). In a study, it was determined that *P. sidoides* root extract induced the release of TNF- α , IL-1 β , IL-12, and NO from uninfected macrophages (49). Therefore, EPs® 7630 may be beneficial for

the prognosis of infection by inducing moderate TNF- α , IL-1 β , IL-12, and NO secretion in uninfected cells, which constitutes an important parameter in the evaluation of the anti-inflammatory potential of the herbal medicine (50). The secretion of pro-inflammatory cytokines (TNF- α , IL-1 β , and IL-12) may reduce the burden of infection in the periapical region by playing a role in the early recruitment of immune cells. Accordingly, for immunomodulatory regulation, EPs® 7630 may limit the pro-inflammatory cytokines released from infected immune cells in the acute stage of periapical inflammation while increasing pro-inflammatory cytokines released from uninfected immune cells in the early stage of infection (Fig. 2).

It has been proven that EPs® 7630 has a strong antimicrobial effect against *Staphylococcus aureus*, *Streptococcus pneumoniae*, Beta-hemolytic *Streptococcus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *H. influenzae*, which are microorganisms associated with the respiratory system (51). Numerous clinical studies have provided evidence that EPs® 7630 therapy creates beneficial effects in patients suffering from respiratory tract infections such as sinusitis, tonsillitis, and bronchitis related to these microorganisms (18,36,51). However, it is highly likely that *P. sidoides* root extract creates favorable results in the treatment of respiratory system diseases, as it might stimulate the non-specific immune system rather than its direct antimicrobial effect (23).

Polymorphonuclear neutrophils, which play an important role in defense against pathogens, release soluble peptides with broad-spectrum antimicrobial activity such as defensins, human neutrophil peptides (HNP) 1–3, and the bactericidal/permeability-increasing protein (BPI). Surprisingly, EPs® 7630 was found to increase the release of HNP 1–3 and BPI antimicrobial peptides by up to 150% and 127%, respectively, depending on its concentration. This finding indicates that the immune system can respond more rapidly and effectively to pathogens under EPs® 7630 treatment (52). With regard to this evidence in our review, herbal

Table 1. Summary of selected studies demonstrating the antibacterial and anti-infective potential of *P. sidoides*

References	The aim of studies	Subjects	Important results
(Trun et al. (24), 2006)	to analyse Nitric oxide synthase and cytokines gene expression of <i>P. sidoides</i> root extract	Leishmania-infected RAW 264.7 cells	Shown strongly the gene expressions of iNOS and a series of cytokine mRNAs, providing for immuno-modulatory actions
(Witte et al. (25), 2015)	to evaluate the immunoregulatory effects of EPs® 7630 on human blood immune cells.	Human Monocytes	Induced MAP kinase-dependent pro-inflammatory cytokines and the generation of adaptive Th17 and Th22 cells.
(Jekabsone et al. (29), 2019)	to evaluate the antibacterial and antiinflammatory activity of Proanthocyanidin Fraction of <i>P. sidoides</i> Root extract in bacterial LPS-mediated inflammation	Human Gingival Fibroblasts, Rat Gingival Fibroblast, Bone Marrow-Derived Macrophages of mice, Human Peripheral Blood Mononuclear Cells	Escherichia, LPS-induced death of fibroblasts, decreased LPS-induced release of IL-8 and prostaglandin E2 from fibroblasts and IL-6 from leukocytes, blocked expression of IL-1 β , iNOS, and IL-1 β and COX-2 expression in LPS-treated leukocytes.
(Aboobaker et al. (26), 2019)	to evaluate the antimicrobial activity of endophytes isolated from the root of <i>P. sidoides</i>	Fungal culture isolated from <i>P. sidoides</i> root material	one fungal strain PS8 from <i>P. sidoides</i> showed noteworthy activity against <i>Staphylococcus aureus</i> , <i>Enterococcus faecalis</i> and <i>Escherichia coli</i>
(Thäle et al. (49), 2008)	to provide further insight into the underlying principles of the therapeutic benefits of EPs® 7630	infected bone marrow-derived macrophages	led to modulated release of NO, production of intra- and extracellular IL-1, IL-12 and TNF- α , and changed the expressions of the surface markers CD40 and CD119 at an early time of post infection
(Koch and Wohn (52), 2007)	to evaluate if EPs® 7630 has an effect on the release of antimicrobial peptides from neutrophils	heparinized whole human blood	enhanced release of antimicrobial peptides (BPI and HNP 1–3)
(Savickiene et al. (17), 2018)	to compare the isolated proanthocyanidins from <i>P. sidoides</i> root extract with whole extract in terms of the composition, antioxidant properties and antibacterial activity	<i>P. gingivalis</i> and <i>Streptococcus salivarius</i> culture	proanthocyanidins showed significantly stronger antioxidant capacity and selectively targeted <i>P. gingivalis</i> compared to the root extract

iNOS: inducible nitric oxide synthases, NO: Nitric oxide, MAP: Mitogen-activated protein, Th17: T helper 17, Th22: T helper 22, LPS: Lipopolysaccharide, IL-6: Interleukin 6, COX-2: Cyclooxygenase-2, TNF- α : Tumour necrosis factor- α , BPI: Bactericidal/permeability-increasing, *P. sidoides*: *Pelargonium sidoides*, *P. gingivalis*: *Porphyromonas gingivalis*.

medicines containing natural phytochemicals such as EPs® 7630 may also be deemed an alternative medicine to antibiotics in the prevention and therapeutic management of acute exacerbations of periapical infections (Table 1).

Conclusion

Some natural medicines, such as EPs® 7630, may exhibit anti-infective activities that show promise as adjunctive treatments in the presence of inflammation. Today, more attention is drawn to the necessity of using alternative natural medicines due to resistance to and the side effects of drugs. Some natural products with the ability to act as anti-microbial and anti-inflammatory might precisely target the pathogen as a response to specific stimuli. Therefore, herbal liquid root extracts, EPs® 7630, may be a promising natural medicine to reduce the likelihood of flare-up occurrence after endodontic treatment or between appointments for nonvital teeth. The administration of EPs® 7630 in endodontics as a preventative for unpredictable flare-ups may reduce the possibility of bacterial resistance and systemic side effects due to inappropriate antibiotic prescription. Overall, this review strengthens the idea that in vitro, in vivo, and clinical studies are needed to test our hypothesis and better understand the anti-infective effects of *P. sidoides* root extract in endodontics, both prophylactically and therapeutically.

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