Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v30i18.3260

EXPLORING NATURAL COMPOUNDS TO PREVENT ORAL INFECTIONS RELATED TO THE EAR, NOSE, AND THROAT

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Abstract
Oral health plays a crucial role in preserving overall welfare. It involves conserving the delicate balance in the oral bacterial community, where beneficial microbes defend against external pathogens. However, when this balance is disrupted, the body becomes susceptible to a extensive range of infections. To combat fungal, bacterial, or viral threats, synthetic medications are commonly used. Nevertheless, these drugs can lead to undesirable outcomes, including toxicity, side effects, and drug resistance. As a result, research has shifted its focus towards seeking safer and more effective alternatives. Specifically, there is growing interest in developing new designs based on natural compounds. This article provides an extensive overview of plant-based, and bee product-based solutions that have been explored for their anti-microbial characteristics. Its goal is to comprehensively present the latest advancements in preventing oral infections within the ear, nose, and throat (ENT) field.

Keywords: oral infections; oral health; alternative treatments; ENT infections; natural antimicrobials; natural compounds

Introduction

The microbiome of the mouth is an integral constituent of the human microbial environment and fulfills a pivotal function in protecting against the invasion of exogenous microorganisms, thereby exerting an influence on overall health. Moreover, the oral microbiome exhibits associations with systemic diseases, given that the oral cavity functions as a gateway to the digestive and respiratory systems, both of which possess a rich vascular network [1].

The occurrence of imbalances within the delicate balance of microbes in a well-functioning oral cavity is intricately linked to the onset and progression of diverse systemic and oral illnesses. Certain pathogens have the ability to undergo rapid proliferation within the oral mucosae, subsequently disseminating to adjacent tissues. If left untreated, these infections can progress to affect the entire body, giving rise to systemic infections. As a result, the prevention of oral infections has emerged as a noteworthy area of scientific investigation. The field of preventive medicine primarily centers on the mitigation of oral infections and their related complications by means of implementing appropriate oral hygiene practices [2]. Mouth rinses and toothpaste frequently incorporate active constituents such as chlorhexidine, hyaluronic acid (HA), and fluoride ions which, although efficacious, may present clinical limitations (e.g., alterations in taste perception, xerostomia, dental staining, accumulation of calculus, development of mucosal lesions) [3]. Furthermore, the utilization of artificial chemical

antibiotics has been observed to engender drug-resistant microorganisms that exhibit diminished susceptibility to established therapeutic interventions, thereby compelling the exploration and creation of innovative therapeutic modalities [4].

In order to mitigate the difficulties inherent in chemical products, there has been a growing focus on the utilization of natural compounds for the purpose of avoiding and managing oral infections [5]. Numerous natural products have been investigated for their pharmacological attributes as prospective remedies for oral infections caused by bacteria, fungi, and viruses.

This review provides a comprehensive overview of the composition of the microbiome in the mouth, potential problems, and conventional treatments for prevalent oral infections. The focus of this study lies primarily on natural antimicrobial compounds, with a specific emphasis on providing comprehensive and methodical descriptions of their origins and potential applications.

Oral Microbiome Composition

The human oral cavity hosts a diverse community of microorganisms, including bacteria, fungi, and viruses. Among these, bacteria are the most prevalent, with over 500 different species inhabiting the oral cavity. Research indicates that approximately 95% of the oral bacterial population falls into six major phyla: *Proteobacteria, Firmicutes, Actinobacteria, Spirochaetes, Fusobacteria,* and *Bacteroidetes*. The residual 5% encompasses microbes from phyla like *Synergistetes, Saccharibacteria, Gracilibacteria, SR1, Chlamydia*, *Chlorobi, Tenericutes*, and *Chloroflexi* [6]. Some genera, such as *Gemella, Streptococcus, Granulicatella, Fusobacterium*, and *Veillonella* are found throughout various oral niches, while others like *Bacteroides, Prevotella, Corynebacterium, Neisseria*, and *Pasteurella* are limited to specific sites [7].

In addition to bacteria and fungi, the oral cavity can harbor various viruses that may contribute to conditions such as oral tumors, oral ulcers, periodontitis, and oral infections. However, unlike bacteria and fungi, most viruses in the mouth are transient and primarily affect other parts of the body. These oral viruses, including cytomegalovirus, herpes simplex virus (HSV), human immunodeficiency virus (HIV), mumps, and human papillomavirus (HPV), are associated with lesions in and around the mouth, gingivostomatitis, salivary gland infections, papillomas, focal epithelial hyperplasia, condylomas, and other health issues.

Oral Infections: Causative Pathogens and Aggravating Potential

Oral health involves maintaining a delicate balance of microorganisms, and fluctuations in oxygen, nutrients, and saliva's pH-regulating effects can lead to the growth of certain microorganisms, potentially causing opportunistic infections. These changes can occur in individuals with compromised immune systems, those undergoing treatments like radiotherapy, chemotherapy, extended antimicrobial therapy, or steroid use, as well as people dealing with conditions such as xerostomia, diabetes, or cancer [8]. Nevertheless, even individuals who are otherwise in a state of good health may experience the onset of oral infections as a consequence of various risk factors, such as tobacco use, excessive alcohol consumption, inadequate dietary intake, improperly fitted dental prosthetics, infancy, advanced age, or pregnancy.

Chronic pathogens residing within the oral cavity have the potential to give rise to localized infection sites, thereby giving rise to subsequent health complications such as the development of biofilms, impaired mastication and deglutition, distorted gustatory perception, unpleasant breath odor, systemic malnourishment, and reduction in body mass.

Oral candidiasis, also referred to as "thrush," is a frequently encountered oral infection, particularly observed in individuals with HIV infection and the geriatric population [9]. The condition at hand pertains to the excessive proliferation of *Candida* spp., with a particular emphasis on *Candida albicans*, infiltrating the outermost layers of tissue and inflicting harm upon the surface of the oral mucosa. This frequently results in the manifestation of intense odynophagia and challenges with the act of swallowing. Prophylactic treatment against *Candida* may be provided to at-risk patients to prevent systemic infections.

Aspergillosis represents the subsequent most prevalent opportunistic fungal infection, following candidiasis. The etiology of this condition can be attributed to various species of Aspergillus, with a predominant presence of *Aspergillus flavus*, *Aspergillus fumigatus*, *Aspergillus terreus*, and *Aspergillus niger* [9]. The primary mode of exposure to this organism involves the inhalation of spores that typically inhabit both the lower and upper respiratory tracts. Despite the existence of antifungal therapies and advancements in managing the illness, invasive aspergillosis continues to exhibit a high fatality rate.

Herpes simplex viruses type 1 (HSV-1) and type 2 (HSV-2) are extremely common infectious viruses with DNA that establish a persistent infection within the host, with periodic reactivation occurring in response to stressful circumstances or immunosuppression. The clinical presentation involves the manifestation of painful ulcerations, commonly observed in the oral cavity, hard palate, gingiva, labial mucosa, and perioral region, occasionally merging to form substantial herpetic lesions [10].

Common oral bacterial pathologies arise due to the excessive proliferation of microorganisms, including but not limited to *Streptococcus salivarius, Streptococcus mutans, Streptococcus sanguinis, Porfiromonas gingivalis, Streptococcus aureus, Prevotella intermedia, Enterococcus faecalis, Actinobacilus actinomycetemcomitans, Escherichia coli, Klebsiella* spp., *Enterobacter* spp., *Pseudomonas* spp., and various others. *Streptococcus mitis*, a bacterium frequently encountered in the oropharynx and nasopharynx, has the potential to induce infections in individuals with compromised immune systems and concurrent moderate to severe clinical presentations [11]. Chemotherapeutic agents have the potential to heighten the susceptibility to oral infections through the modulation of receptor interactions, augmentation of bacterial adhesion, diminishment of salivary secretion, and alteration of oral pH. The potential involvement of local factors, such as dentures, piercings, implants, wounds, xerostomia, and mucositis in the development of bacterial infections has been reported.

Synthetic Antimicrobial Drugs for the Treatment of Oral Infections

Treatment options for various types of oral infections depend on factors such as the infection type, its location, and the patient's condition. To manage oral candidiasis, which is a fungal infection, the most commonly used antifungal drugs include polyenes like amphotericin B and nystatin, azoles such as clotrimazole, miconazole, fluconazole, voriconazole, itraconazole, ketoconazole, and posaconazole, as well as echinocandins like caspofungin, micafungin, and anidulafungin. These antifungals can be administered either topically or systemically. However, their use is limited by issues like toxicity, adverse effects, and the development of drug resistance [12].

Various antifungal agents, such as itraconazole, amphotericin B, echinocandins, and voriconazole, are commonly employed in the management of aspergillosis among individuals with uncompromised immune systems. The efficacy of these interventions in individuals with compromised immune systems remains uncertain. Surgical debridement may additionally constitute an integral component of the therapeutic modality [13].

In the case of herpes simplex virus (HSV) infections, which are viral in nature, the primary treatment involves using antiviral drugs that inhibit viral DNA replication. Acyclovir is the preferred drug for this purpose, although valaciclovir offers advantages like higher oral bioavailability, increased plasma levels of the parent compound, improved efficacy, and reduced dosing frequency [14].

For bacterial infections, antibiotics are the conventional choice for microbial control. However, their effectiveness can be compromised by bacterial biofilm resistance. Alternative strategies to combat bacterial biofilms include the use of bacteriophages and quorum-sensing inhibitors [15].

Natural Sources of Antimicrobial Compounds

The demand for innovative solutions has arisen due to therapeutic difficulties such as unwanted side effects, limited effectiveness, and the emergence of drug resistance observed in conventional therapies, as documented in various studies. Natural antimicrobial agents, as a substitute for synthetic drugs, have garnered growing interest. These compounds sourced from nature have become

increasingly significant, whether employed to address symptoms, subsequent complications, or the infection itself, in managing oral infections, as indicated in numerous research articles.

Plant-Derived Natural Compounds

Cinnamon (*Cinnamomum zeylanicum*), commonly used in cooking, has also found applications in the field of medicine. It has been studied for its potential benefits during pregnancy, its role in diabetes management, and its use in addressing gynecological issues. Moreover, its properties relevant to oral infections, including antioxidative, antimicrobial, and anti-inflammatory characteristics, have been the subject of investigation [16].

Turmeric (*Curcuma longa*), a perennial herbaceous plant, exhibits diverse pharmacological characteristics that are relevant to treatments for oral infections. The chloroform extract of the substance comprises turpentine, fatty acids, and sesquiterpenes, thereby contributing to its comprehensive antibiofilm efficacy. Sesquiterpenes possess the notable ability to perturb the integrity of bacterial cell membranes owing to their lipophilic nature, thereby exerting a profound impact on bacterial proliferation and metabolic processes.

Green tea, scientifically known as *Camellia sinensis*, is a highly esteemed botanical reservoir of multifunctional antimicrobial phytochemicals. The efficacy of the aqueous extract derived from green tea in diminishing the quantity of viable fungal cells present within biofilms developed on acrylic resin has been demonstrated. Moreover, green tea exhibits a high content of polyphenols, thereby conferring potent antioxidant and antiviral attributes. The polyphenols exhibit inhibitory effects on enzymes that inflict damage upon cellular membranes, thereby impeding the binding and entry of viruses into host cells [17].

Citrus fruits are recognized as a bountiful reservoir of phytochemical compounds that exhibit a diverse array of health-promoting effects. These effects encompass but are not limited to their potential as anticancer agents, antiviral agents, antitumor agents, antioxidants, and anti-inflammatory agents. The potential of these agents in the prevention and treatment of oral infections has attracted considerable attention.

Peppermint (*Mentha piperita*) is a botanical intervention that has garnered recognition for its therapeutic potential in managing a diverse array of symptoms and medical conditions. The substance exhibits antiseptic, antibacterial, and antifungal characteristics. The inhibitory effects of peppermint essential oil on the development of biofilms by *Candida albicans* and *Candida dubliniensis* have been observed in a dose-dependent manner, whereby the maximum concentration tested was 2 μL/mL [18].

The antibacterial activity of Garlic (*Allium sativum*) extract has been observed, wherein its active constituent, allicin, exhibits the ability to permeate bacterial membranes, perturb cellular structures, modulate the gene expression of microbes, and elicit oxidative stress.

Coconut oil has emerged as a viable therapeutic alternative, specifically for individuals diagnosed with head and neck cancer who are undergoing radiation therapy. The substance has the ability to establish a defensive barrier within the oral cavity, thereby preserving the moisture of the mucosal lining. The utilization of this cost-effective and secure methodology serves to effectively address xerostomia, a prevalent complication that detrimentally affects the overall well-being of individuals.

Honey and Beehive Products

The therapeutic potential of honey and bee-derived substances has generated interest in their applications within the field of otorhinolaryngology. Furthermore, the immune-modulating and antimicrobial attributes of propolis, honey, bee pollen, and royal jelly, have proven valuable for a wide range of uses.

Honey possesses anti-bacterial, anti-viral, and anti-inflammatory properties, with a favorable safety profile and the ability to enhance wound healing. Its mechanisms of action involve factors like hyper-osmolarity, low pH, the generation of H_2O_2, and a distinctive composition rich in antioxidant compounds. Additionally, honey has been investigated for its antiviral effectiveness against herpes lesions, with comparative studies demonstrating its superiority to synthetic drugs in terms of healing time, pain relief, symptom resolution, and duration of acute attacks [19].

Propolis, a non-toxic natural product, exhibits anticancer, antimicrobial, antifungal, anti-inflammatory, and antiviral properties. The aforementioned attributes have garnered considerable attention due to their notable role in impeding the formation of biofilms and managing the condition known as denture stomatitis. The utilization of propolis extracts in the formulation of mouthwashes, medicinal products, dental varnishes, and toothpaste, has been observed to exhibit potential in the management of *Candida* spp. proliferation.

Royal jelly, a substance secreted by the diligent honeybee workers to provide sustenance to the esteemed queen bee, is renowned for its remarkable composition abundant in essential minerals, vitamins, beneficial fatty acids, carbohydrates, proteins, and an array of free amino acids. The substance has exhibited wound-healing, immunomodulatory, bacteriostatic, antimicrobial, and antioxidant properties against a range of microorganisms [20]. Bee pollen, a product derived from bees, exhibits significant pharmacological properties, encompassing antimicrobial, antifungal, antiviral, immune-stimulatory and anti-inflammatory effects. The ethanol extract has demonstrated efficacy against various pathogens, thereby presenting an intriguing possibility for the prevention and management of oral infections [21].

Hybrid Treatment Options

Some oral pathogens have developed resistance to single-plant extracts, necessitating the development of hybrid treatments. One approach involves creating innovative formulations that blend multiple plants. For instance, a mixture consisting of *Mangifera indica* L., *Azadirachta indica, Hemidesmus indicus* (L.) R.Br., *Cinnamomum zeylanicum* Blume, *Caryophyllus aromaticus* L., *Quercus infectoria* Oliv., *Terminalia belerica* Roxb., *Terminalia chebula* Retz, and *Emblica officinalis* Gaertn was formulated into chewable poly-herbal tablets, exhibiting strong antimicrobial activity against dental bacteria [22].

An additional approach involves the development of antimicrobial pharmaceutical agents that leverage the benefits inherent in both naturally occurring compounds and nanotechnology. An exemplary instance entails the fabrication of nanostructures comprising of composite films composed of polylactic acid, wherein magnetite nanoparticles are embedded and conjugate with Eucalyptus essential oil. The aforementioned coatings, although devoid of any detrimental impact on the viability of eukaryotic cells, exert a substantial disruptive influence on the process of bacterial biofilm development and maturation. Consequently, these coatings exhibit considerable potential as therapeutic nanosystems with anti-infective properties.

Moreover, it has been observed that hydrogels incorporating silver nanoparticles modified with tannic acid exhibit notable efficacy in combating herpes virus infection. These hydrogels exert their antiviral effects by impeding viral connection, entry, and subsequent spread following infection [23].

Moreover, the concomitant effect of naturally occurring compounds and conventional pharmaceutical agents introduces an alternative therapeutic modality. The co-administration of curcumin and antibiotics has been shown to exhibit a synergistic effect, leading to the restoration of bacterial susceptibility to synthetic drugs. This combined therapeutic approach effectively mitigates bacterial toxicity while facilitating the enhanced penetration of antibiotics into bacterial cells. In the realm of viral infections, the coadministration of acyclovir with honey demonstrated enhanced therapeutic efficacy in comparison to the singular utilization of the antifungal medication for the management of oral lesions. This combined approach facilitated expedited recuperation and ameliorated the concomitant discomfort experienced by afflicted individuals [24].

Conclusions and Future Perspectives

In conclusion, research on oral infections is currently a prominent area of study, primarily due to the rising resistance of pathogens to traditional drugs, the risk of contamination and invasion, and the psychological consequences of such infections. The limitations of synthetic drugs, including toxicity, adverse effects, and reduced effectiveness, have prompted an investigation of natural replacements. Various compounds and substances sourced from plants, fungi, algae, and other natural reservoirs have been extensively examined for their anti-microbial potentials, demonstrating encouraging

outcomes in combatting oral pathogens. Furthermore, the precise mechanisms underlying the action of some of these natural anti-microbial agents remain incompletely understood, necessitating further research. It is crucial to assess the specific targeting capabilities of these natural treatments towards pathogens rather than beneficial microorganisms. Ultimately, a tailored approach matching treatment to the causative pathogen and the individualized requirements of each patient is essential for the development of personalized anti-infective therapies.

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