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Review Article

Review: BioIntelligent Dentistry - Modeling the Biological Mechanisms of Phytocannabinoids in Dental Health and Disease

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Summary

Dental disease is the #1 infectious disease worldwide. The WHO Global Oral Health Status Report [1] estimated that oral diseases affect close to 3.5 billion people worldwide, with 3 out of 4 people affected living in middle-income countries. Globally, an estimated 2 billion people suffer from caries of permanent teeth and 514 million children suffer from caries of primary teeth.

Prevalence of the main oral diseases continues to increase globally with growing urbanization and changes in living conditions. More severe oral conditions include: periodontal diseases affecting 19% (1 billion cases) of adults worldwide; edentulism (total tooth loss) 23% of people 60 years or older; oral cancer 13th most common. With continuing and growing conflicts worldwide Noma, a severe gangrenous disease of mouth and face in children suffering malnutrition from war, extreme poverty, and poor oral hygiene resulted in an estimated 140,000 new cases in 1999 with a death rate of 90% deaths.

The systemic effects of oral pathogens are both a significant comorbidity and a causal factor in multiorgan and neurological systemic diseases. Reliance on traditional treatments, such as antiseptic mouth rinses and broad-spectrum antibiotics before surgical procedures, has led to unintended consequences, including drug-resistant microbes and the inhibition of cells responsible for tissue and bone growth as well as immune function.

Clinical studies focused on systemic effects have produced conflicting and inconclusive results regarding the benefits of phytocannabinoids. The widespread use of terms like the "entourage effect" to explain positive results often serves commercial interests more than patient care. However, preclinical research has successfully explored the effects of cannabinoids on biofilms and bacterial susceptibility, demonstrating potential benefits in dentistry [2]. Most of these studies have focused on cannabidiol (CBD) isolates, with less attention given to cannabinoids such as CBG, CBC, and CBN. Other phytocannabinoid classes, including terpenes and flavonoids, which have similar or complementary properties, have been largely overlooked in dental formulation development.

Additionally, broad-spectrum and full-spectrum cannabis/hemp extracts have been largely ignored in dentistry-likely due to regulatory challenges involving agencies such as the DEA, FDA, FTC, USDA, and State and Federal legislative bodies.

Recognizing that the oral cavity has a limited number of ways to respond to infection, inflammation, trauma, and surgical procedures, we explored the potential of THC-free hemp-derived phytocannabinoid extracts to address these conditions. The development of phytocannabinoid formulations tailored to specific oral health challenges is a promising avenue of research. This led to the creation of PAIR DenticDSTM, a broad-spectrum phytocannabinoid-based anti-inflammatory rinse and other DenticDSTM products.

This paper aims to examine the molecular mechanisms underlying new treatment approaches for dental care using the direct biological activities of hemp-derived phytocannabinoids. We believe that BioIntelligent Dentistry - defined here as utilizing natural plant-based therapies to maintain and improve oral health – rather than relying on pharmaceuticals or industrial antiseptic chemicals will be a welcome and disruptive advancement in modern dentistry for both dental professionals and patients alike. Modeling the Biological Mechanisms of Phytocannabinoids in Dental Health and Disease is the first step in the paradigm shift towards the practice of BioIntelligent Dentistry.

Abbreviations

QCAs: Quaternary Ammonium Compounds; CBD: Cannabidiol; CBG: Cannabigerol; CBS: Endocannabinoid System; NAEs: N-acylethanolamines; MMAPs: Microbe-Associated Molecular Patterns; PTI: Pattern Triggered Immunity; NLRs: Nucleotide-Binding Oligomerization Domain-like Receptors; ETI: Effector Triggered Immunity; BOMB: Blood Oral Mucosal Barrier; MSCs: Mesenchymal Stem C3ells; eCBs: endogenous or Exogenous Cannabinoids; CBR: Cannabinoid Binding Receptor; TJPs: Tight Junction Proteins; PLF: Periodontal Ligament Fibroblasts; AMPs: Anti-Microbial Peptides; HD: Hemidesmosomes; JE: Junctional Epithelium; MRSA: Methicillin Resistant Staphylococcus aureus; QS: Quarum Sensing; CHX: Chlorhexidine; CBDV: Cannabidivarian; CBN: Cannabinol; THC: Tetrahydrocannabinol; THCv: Tetrahydrocannabivarin; RAU: Recurrent Aphthous Stomatitis; CPC: Cetylpridinium Chloride; Tregs: T-regulatory Cells; ECS: Endocannabinoid System; PAMPs: Pathogen-Associated Molecular Patterns; DAMPs: Damage Associated Molecular Patterns.

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The Oral Cavity

Striking technological advances have been made in dentistry over the last 20 years plus. Advancements include 3D imaging of bone and soft tissue; laser directed therapies; and dental transplants ranging from single tooth implants to the highly complex half and full arch implant surgeries such as All on Four.

The mouth is a unique environment, constantly exposed to microbial activity and physical stress. Traditional methods like brushing and flossing have proven inadequate in maintain oral hygiene, often leading to frustration for both patients and clinicians. There is an urgent need for innovative, effective, and safe formulations that support the physical, microbiological, and immune barriers of the oral mucosa [3] - a need that remains unmet.

While therapeutic modalities such as gels, rinses, sprays, and powders have been developed, most mouth rinses—used both professionally and at home are still dominated by antiseptics. These antiseptic chemicals trace their origins to alcohol-based hospital floor cleaners, later introduced into dentistry through marketing that labeled bad breath ("halitosis") as a problem to fear. Modern "antiseptic" dental products now include additional chemical agents, such as Quaternary Ammonium Compounds (QACs), which are essentially biocides-indiscriminate microbial killers [4].

An Organ System in Full View

Unlike internal organ systems of the heart, lungs, kidney, liver, gut, oral tissues are in full view! Unlike systemic medicine, though different diseases do affect the mouth, the pathological response is limited to a smaller number of identifiable processes- inflammation, infection, bone and tissue wound healing. Common multiple procedural etiologies performed in the dental operatory include extraction, scaling and root planning, root canals, temporaries and implants all present significant challenges in managing bleeding, trauma, and infection control. Dentists and specialists must work within a small, dark space, dealing with soft tissue, bone, and a complex oral microbiome consisting of hundreds of microbial species.

Because dental diseases stem from a limited number of biological processes, they present a unique opportunity for targeted therapeutic solutions (Figure 1). This paper makes the case both clinically and scientifically for why phytocannabinoids, with their combined antimicrobial, anti-inflammatory, and tissue-healing properties, offer a comprehensive treatment solution for a wide range of dental diseases.

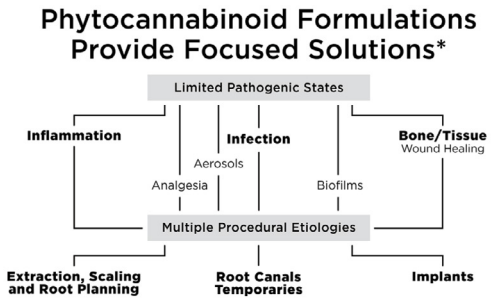

Figure 1: Common pathologies central to dental disease or the response to disease and dental procedures can be managed by phytocannabinoids.

Transforming Dental Care with Phytocannabinoids: A Revolutionary Step for Modern Dentistry

The landscape of dental health is evolving rapidly. Traditional approaches to oral care, reliant on chemical antiseptics and antibiotics, while effective in the short term, can disrupt the delicate microbial ecosystem of the oral cavity. This disruption often results in microbial resistance, delayed tissue healing, and long-term oral health imbalances [5,6].

Phytocannabinoids, a group of naturally occurring plant compounds, offer a groundbreaking shift in modern dental care. These bioactive compounds, including Cannabidiol (CBD) and Cannabigerol (CBG), provide a multi-targeted approach to oral health management. Their anti-inflammatory, antimicrobial, and tissue-regenerative properties align with the body's natural healing mechanisms, making them invaluable tools for both preventive care and post-surgical healing.

What are Phytocannabinoids?

Phytocannabinoids are natural plant-based compounds primarily found in cannabis and hemp. The family of molecules which make up the phytocannabinoids include: the cannabinoids CBD, CBG, CBD. CBN (multiple others), terpenes [7] like myrcene, linalool, caryophyllene and limonene contribute to smell and taste; major flavonoids in cannabis which are antioxidants, colorants and plant protectants include Cannflavins A, B and C [8].

These molecules most often may be delivered individually as isolates or can be prepared as whole plant extracts which are referred to as full spectrum or broad-spectrum extracts which contain the complex mixture of cannabinoids, terpenes and flavonoids we refer to as phytocannabinoids.

While the psychoactive compound THC is widely known, nonpsychoactive cannabinoids such as CBD, CBG, CBC, CBN and others including their varians such as CBDv, many with similar or improved activities are gaining attention for their therapeutic applications, particularly in dentistry [9]. Like flavonoids, most terpenes don't attach to the body's cannabinoid receptors. However, some terpenes, like beta-caryophyllene and alpha-humulene, are also considered cannabinoids, as they influence cannabinoid receptors. Both phytochemicals terpenes and flavonoids may enhance the potency of cannabinoids through synergy and have their own potential health effects [10].

How Phytocannabinoids Interact with Human Biology

These bioactive molecules interact with the human biology on multiple levels including the systemic endocannabinoid system (ECS), a complex cell-signaling network involved in regulating inflammation, immune response, and cellular repair processes [11]. The ECS plays a vital role in maintaining homeostasis throughout the body. When activated by phytocannabinoids, the major ECS receptors (CB1 and CB2) can regulate inflammation, pain, and cellular repair. World-wide research with application across multiple disciplines of systemic medicine [12] indicate that phytocannabinoids can reduce inflammation, control microbial overgrowth, and stimulate tissue healing without disrupting natural bacterial balance [13], making them highly suitable for dental health.

The complex interaction of these molecules, the increasing

number of potential receptors and their anatomic locations are being advanced continually and is beyond the scope of this manuscript. However, we do take the position put forth originally by others [14] that discussion of these complex molecules, their receptors and each other should be discussed scientifically and most accurately explained by traditional pharmacological terms pertaining to other plant-based medicinal products and polypharmacy in general (e.g., synergistic interactions and bioenhancement).

Beyond Cannabis: Natural Sources of Phytocannabinoids

Phytocannabinoids in nature extend beyond cannabis and hemp, making them also potentially available for future dental applications. Many from plants are recognizable common foods or additives. Examples include: Sunflowers: CBG-like compounds, Black Truffles: Anandamide, Black Pepper: Beta-Caryophyllene, Cacao: N-Acylethanolamines (NAEs), Echinacea: Cannabimimetic compounds.

Additionally, other plants have been used as natural plant extracts to treat oral and dental disease., This includes plants such as *Mentha piperita* L. (peppermint), *Melaleuca alternifolia* (Maiden and Betche) Cheel (tea tree oil), *Calendula officinalis* L., *Aloe vera* L., *Citrus limon* (L.) Osbeck, *Camomilla matriciana, Rosmarinus officinalis* L. (rosemary), *Thymus vulgaris* L. (thyme), and Eugenol (a compound produced by multiple medicinal plants) [15].

Chemical *vs.* Biologic Approaches in Dentistry

Advancement in dental care regimens fall along two approaches. First, the historical chemical and pharmaceutical approach of traditional antiseptics and antibiotics which we know disrupts the oral microbiome, result in a number of side effects like mucositis, stomatitis, and dry mouth and is an important contributor to growing worldwide antibiotic resistance.

The alternative is a natural and biological approach. While some plant-based dental products exist, none have been specifically developed using a scientific framework that takes into account: known biological activities; validated mechanisms of action; and critically, the ability to address dental specialties and daily oral hygiene needs.

Phytocannabinoids provide the superior, natural alternative, effectively targeting harmful bacteria while preserving beneficial ones, supporting systemic health, and reducing the risk of adverse effects.

Why Do Plant Phytocannabinoids Work in Man?

The environmental challenge to survival is identical!

All living things, including plants and humans face the same threats- pathogens of all types (bacteria, viruses, fungi, parasites), environmental challenges whether it be fire, or man-made chemical, or biologic toxins and trauma (Table 1). Perhaps it shouldn't really be a surprise that plants, man's first Medicinals, produce molecules with broad therapeutic functions (antimicrobial, anti-inflammatory, wound healing). Through centuries of cultivation and selective breeding, plants like cannabis and hemp have been naturally optimized for medicinal applications, with genetic compositions and phytochemical profiles that can be tailored for specific therapeutic uses.

Table 1: The response to environmental and biological challenges is a highly conserved across evolution.

Why do plant products work? Plants and Man Evolutionarily far apart!
LUCA - Last Universal Common Ancestor ⟶ LCA - Last Common Ancestor of Animals
But at least some of the basics are still present!

Shared Pathogens	
Plant	Man
Virus	Virus
Nodaviridae- replicate in plants, animals, insects! - Phytoviruses(?) - Providence Virus (Insects)	
Bacteria	Bacteria
Pseudomonas aeruginosa (Hu)/P. syringae (tomato)	
Fungi	Fungi
Aspergillosis, Candida auris*, Invasive candidiasis, Pneumocystis pneumonia (PCP)	
Protozoa	Protozoa
Toxoplasma gondii, Trypanosoma, Cruzi, Plasmodium, Giardia lamblia, and Phytomonas	

Response to Pathogens	
Plant	Man
Epidermis	Epidermis
Innate Immunity	Innate Immunity
MMAPs - microbe associate molecular patterns PTI response, NLRs, ETI (and trauma damage!)*	
Phytocannabinoids	Endocannabinoids
	Adaptive Immunity

*note: Shared pathological responses to disease and procedures

Plants and Humans: An Evolutionary Connection of 100 million Years

In that ultimate history book and clock- DNA, the genetic blueprint of plants and man has preserved many of the same basic fundamental mechanisms to survive! Various pathogens can infect and threaten both plants and man including viruses, bacteria, fungi and protozoa.

Composition of the human oral microbiota totals 400 to 1000 members 94% of oral microbiome are bacteria of three broad classes: commensal (beneficial) bacteria, opportunistic bacteria, and pathogenic bacteria parenthesis. The remaining 6% of the microbiota consists of potential additional disease threats posed by viruses, archaea, protozoa and fungi.

Multiple shared genetic responses to pathogens have been conserved throughout evolution. Notably, plants and humans share innate immunity mechanisms, including: MMAPs (microbe-associated molecular patterns); PTI (Pattern-triggered immunity) response; NLRs (Nucleotide-binding oligomerization domain-like receptors); and ETI (Effector-triggered immunity) including responses to trauma and damage.

As we design new dental formulations, we can leverage these shared genetic responses. The cross-activity between plant-derived phytocannabinoids and the human endocannabinoid system highlights an evolutionary link that enables these compounds to influence cellular and microbial responses in both plants and humans.

Phytocannabinoids and endocannabinoids share the same evolutionary purpose: they help organisms adapt to trauma (includes surgical interventions), and pathogenic threats by modulating immune function and cellular signaling. Given their conserved biological roles, these molecules present a compelling scientific basis for ameliorating dental and systemic diseases.

Phytocannabinoid Properties Align with Oral Treatment

Phytocannabinoids offer a unique multi-faceted approach to dental care, addressing several key challenges faced by dental professionals today to treat disease and maintain oral health.

- **Regulating the oral microbiome**

Phytocannabinoids support microbial balance, promoting a

healthy equilibrium of bacteria similar to their systemic homeostatic role.

- **Anti-inflammatory properties**

Chronic inflammation is central to many dental issues, including gingivitis, periodontitis, and peri-implant mucositis. Phytocannabinoids reduce pro-inflammatory cytokines such as TNF-α and IL- 6, helping to manage inflammation without compromising the immune response. Inflammatory pathways, when left unchecked, can lead to tissue degradation, bone loss, periodontal disease and systemic health complications. Phytocannabinoids aid in mucosal repair, preventing the entry of oral microbes into the bloodstream by crossing a leaky blood-oral mucosal barrier (BOMB).

- **Antimicrobial effects**

Many dental pathologies arise from bacterial and fungal infections. Phytocannabinoids, particularly CBD and CBG, have demonstrated selective antimicrobial properties against pathogens like Porphyromonas gingivalis, Candida albicans and drug-resistant Staphylococcus aureus (DRSA) reducing infection without promoting drug resistance. This makes them especially valuable in controlling biofilm formation, a key contributor to persistent infections in root canals, peri-implantitis, and chronic periodontitis. Their dual action as an antimicrobial and immune modulator enhances the overall resilience of the oral environment.

- **Tissue regeneration**

Phytocannabinoids stimulate fibroblast activity and collagen production, two critical components of tissue repair. This property is particularly beneficial in post-surgical care, helping with faster recovery after procedures like tooth extractions and implant placement. By enhancing cellular proliferation and collagen matrix formation, phytocannabinoids provide structural integrity to healing tissues, reducing the risk of infection and complications during the recovery phase. Bone marrow cell culture data suggests that cannabinoids may stimulate the recruitment of mesenchymal stem cells (MSCs) from the bone marrow indirectly via an accessory cell and mediated via the CB2 receptor [16]. This recruitment may be one mechanism responsible for the increased bone formation seen after cannabinoid treatment *in vivo*.

- **Biofilm control**

Dental biofilms, a leading cause of plaque buildup and caries, are resistant to many conventional treatments. Phytocannabinoids disrupt the formation and adhesion of these biofilms, reducing cavity formation and protecting against periodontal disease [2]. They inhibit quorum sensing [17] a bacterial communication process essential for biofilm development, which further prevents the spread of harmful bacteria within the oral cavity.

Understanding the Phytocannabinoids' Biological Mechanisms of Action

Phytocannabinoids interact with the body's biological pathways to promote health by working to balance the oral microbiome to limit the spread of infection, reduce inflammatory processes and speed wound healing.

Phytocannabinoids as anti-microbials *in vivo*

Phytocannabinoids work directly on commensal bacteria offering a natural way to manage bacterial and fungal infections without contributing to drug resistance. They inhibit pathogens while allowing commensal bacteria to thrive, making them a more balanced solution than conventional antibiotics. By supporting the microbiome's beneficial bacteria and inhibiting pathogenic species the commensal bacteria's populations lining the oral mucosal surfaces increases the bacterial layer to protect against pathogenic bacterial penetration (Figure 2C) as with p. gingivalis [18]. Additional barrier reinforcement is achieved by the activity of endogenous or exogenous cannabinoids (eCBs, synthetic CBs, and PhytoCBs) through binding to the cannabinoid binding receptor (CBR, Figure 2A/B) activating increased production of a number of evolutionarily conserved proteins. Two such potentially critical proteins, whose activity has been demonstrated in the mucosal linings of the gut, prevent microbial penetration into the mucosal epithelium and adjacent tissues (Figure 2B) are tight junction proteins (TJPs) which help oral mucosal cells strengthen the bonds between each other; and anti-microbial peptides (AMPs) which eliminate pathogens by a process known as pathogen dismissal [13].

CBR2 receptors (Figure 2A) are found throughout the oral cavity. Notably, CBR2 receptors are found in oral mucosal epithelial cells and also in the periodontal tissue [19]. CBR 1 and TRPV1 receptors are also distributed throughout oral and craniofacial tissues including on oral mucosal epithelial cells. The dual expression of both CBR1 and CBR2 and their component synergistic and antagonistic roles is not yet well understood.

Additionally, documented anti-Quarum Sensing activity (Figure 2D) by CBG through inhibition of the bacterial signal-transduction system results in reduction of bacteria in biofilms and alters the biofilm structure [17]. These bacterial focused activities extend throughout the alimentary canal's mucosal linings (and dental surfaces) encompassing the QS system inhibiting autoinducers AI-1, AI-2, and CAI-1 activities in reducing biofilm development to direct stimulation of the antimicrobial products generated upon stimulation of oral commensal bacteria.

Phytocannabinoids have direct anti-microbial activity against bacterial populations as measured by diffusion zone inhibition assays where CBD/CBG cannabinoids exhibited in vitro anti-microbial inhibition activity against plaque equivalent to chlorhexidine [21]. CBG has previously been found to display anti-bacterial properties toward clinical isolates of methicillin-resistant Staphylococcus aureus (MRSA) [22].

Phytocannabinoids directly inhibit the Quarum Sensing (QS) bacterial signal transduction system

Medicinal plants have received recognition as a new source for effective QS inhibitory substances. Several phytochemicals and plant by-products have been acknowledged as QS quenching agents including curcumin, flavonoids and components of cranberry [23]. The interference of CBG with the bacterial signal-transduction system provides an additional novel innovative way phytocannabinoids may be used to combat bacterial biofilm formation and subsequent development of bacterial virulence factors.

These biological mechanisms (pathways) are utilized by cannabinoids to mediate pathogen driven microbiome dysbiosis and may function to replace or act as potential adjuvants to prescription antibiotics [24]. Good oral products will moderate the balance of these populations, assisting the good bacteria to thrive and control the bad and opportunistic. They are never, or rarely to be wiped

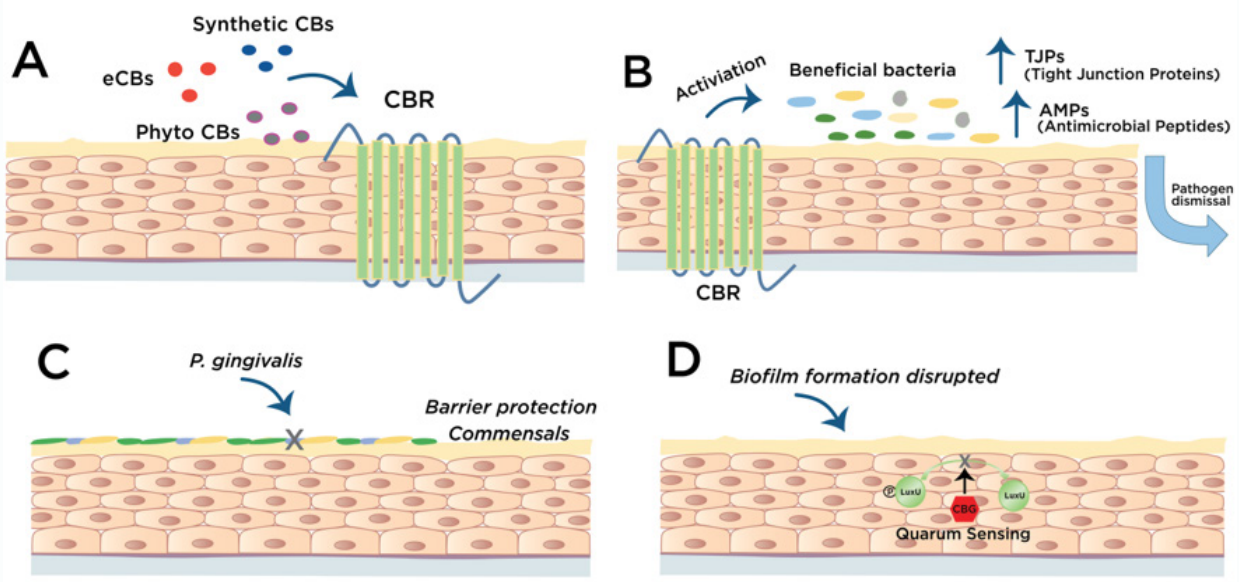

Figure 2: (A-D): Phytocannabinoids have multiple natural anti-microbial, anti-inflammatory and wound healing effects on oral microbiome and oral commensals.
(A) Phytocannabinoids (exogenous, synthetic and endocannabinoids) all interact with multiple CBR1, CBR2 and TRPV1 receptors in the oral tissues.
(B) Phytomediated microbiome modulation leads to stimulation of beneficial commensal bacteria to produce;
a) AMPs (anti-microbial peptides) eliminate pathogens (both gram- and +), enveloped viruses and fungi through a process known as barrier integrity pathogen dismissal, and
b) TJPs (tight junction proteins) improve the oral mucosal barrier integrity to help your mouth's mucosal cells strengthen their bonds (HD, hemidesmosomes) to each other to resist bacteria from entering between cells. This physical barrier limits potential spreading of an infection though oral epithelial spaces which are much larger than the gut and may not be as substantial a factor as in the gut. However, between cell-to-cell junctions' leakage in the oral mucosa does occur through HD between the basal layer of the junctional epithelium (JE) and the hard service of the tooth [20]. These sites are constantly under physical, mechanical and biological challenge, which provides ongoing opportunities for oral to systemic disease transmission resulting in the potential of multi-organ disease.
(C) Increased beneficial commensal bacterial populations, secondary to phytocannabinoid stimulation and pathogen removal, line the mucosal epithelium and present an additional physical barrier [18] to potential invasion by pathogens such as P. gingivalis.
(D) Though not directly an anti-microbial activity, cannabinoids like CBG inhibit QS through antagonizing autoinducers of biofilm formation in members of the oral microbiome responsible for biofilm development and growth. Resultant lack of stimulation of these bacteria in oral biofilms results in significant decreased and incomplete biofilm coverage of dental surfaces [17].

out completely. However, the phytocannabinoids are not on their own sufficient to replace pharmaceutical antibiotics in cases of overwhelming infection. They are important in renewing the natural oral microbiomes constituents and function thereby assisting in preventing such infective states in the future.

Phytocannabinoids anti-inflammatory and immunemodulatory activity in the oral environment

Pre-clinical and placebo-controlled clinical studies monitored the effect of phytocannabinoids in subjects.

- Evaluation of the in vitro properties of the immune modulatory activity of CBD and CBG on oral bacteria and PLF found [25];
  - Production of the anti-inflammatory IL-10 cytokine was stimulated by CBD and CBG, and;
  - TGFβ and IL-4, two anti-inflammatory and regulatory cytokines, were increased by CBG.
- Response was postulated to be due to presence of CB1 receptors throughout periodontal tissue, including gingival fibroblasts.
- The anti-inflammatory effects of CBD on primary human gingival fibroblast cultures exhibited [26]:
  - Decreased production of pro-inflammatory markers IL-6 and IL-8 following lipopolysaccharide induction and;
  - Clear inhibition of growth was observed in the anaerobic G-negative P. gingivalis, primarily after CBD application. MIC values for CBD were comparable to the chlorhexidine (CHX) positive control with S. mutans.
  - Result of the clinical study showed a statistically significant improvement in multiple empiric measurements after 56 days of CBD application in patients with diagnosed chronic periodontitis.
  - Multiple articles in this special edition confirm the clinical reduction of inflammation illustrative of the immunemodulatory activity of the DenticDSTM PAIR rinse micellar phytocannabinoid formulation across multiple presentations.

Statistically significant systemic anti-inflammatory reductions of the pro-inflammatory markers TNFα and IL-6 indicate a potential role for Full Spectrum Hemp Oil micellized by PurzorbR technology as a potential adjuvant or natural plant product alternative treatment for chronic and acute systemic inflammatory diseases including patients with COVID-19 [27].

Phytocannabinoids in tissue regeneration and wound healing

Phytocannabinoids stimulate fibroblast activity and collagen production, two critical components of tissue repair. This property is particularly beneficial in post-surgical care, helping with faster recovery after procedures like tooth extractions and implant placement as well as to stabilize tooth attachment to the periodontal ligament via CB2R. By enhancing cellular proliferation and collagen matrix formation, phytocannabinoids provide structural integrity to healing tissues, reducing the risk of infection and complications during the recovery phase.

A variety of natural occurring cannabinoids have been shown in vitro to directly stimulate collagen production. Cannabidivarian (CBDV), CBG Cannabinol (CBN), CBD, Tetrahydrocannabinol (THC), and Tetrahydrocannabivarin (THCv) all exhibit the ability to stimulate colony formation and collagen production in bone marrow stem cell cultures in vitro via CBR2 receptors [16].

Natural plant phytocannabinoids vs. chemical antiseptics and pharmaceutical antibiotics

Commercial antiseptics like chlorhexidine have long been used in dental care. Other commonly found "actives" found in your mouthwash bottles are chemicals like alcohol, cetylpyridinium chloride, QACs [4] and combinations of "natural" plant oils whose purified molecular actives include eucalyptol, menthol, and thymol all molecules which are antiseptic alcohols. Increased risk for oral cancer has been associated with a high frequency of use over an extended period of time of antiseptic/chemical mouthwashes hinting at a dose-response relationship [28] and should be viewed as cautionary.

Problematic as well are the "inactive ingredients" commonly found in common over the counter commercial mouthwashes which may be responsible for a number of side effects which include: lauryl sulfate's mucosal irritation and increased incidence of recurrent aphthous stomatitis (RAU); combine to produce a lower pH than saliva resulting in higher risk of cavities and demineralization; may cause tooth staining; increased blood pressure; and allergic and hypersensitivity reactions.

Comparing phytocannabinoids to traditional antiseptics

Chemical antiseptics like chlorhexidine have long been used in dental care. More recently molecules defined as QACs have also become prevalent in commercially available mouth rinses. Both come with significant drawbacks [4]:

- **Non-selective bacterial elimination:** Chlorhexidine (CHX), cetylpridinium chloride (CPC) and other antiseptics are biocides which eliminate both harmful and beneficial bacteria, disrupting the natural oral microbiome's balance [29] with any chance of natural self-correction.

- **Delayed healing:** Chemical antiseptics can kill fibroblasts activity [30], which make the collagen essential for tooth or implant attachment and slow down tissue repair essential for wound healing thereby increasing postprocedural complications [31,32].

- **Microbial resistance:** Prolonged use of antiseptics, QACs and antibiotics promote antimicrobial resistance, making infections harder to manage [4,30,31].

- **Oral microbiome metabolism**: In addition to microbial resistance CHX promotes dysbiosis of the natural microflora by decreasing health promoting commensal species responsible for nitrate (NO3-) concentration in salivary glands where it is reduced to nitrite (NO2-), swallowed and reduced to nitric oxide (NO) in the stomach and other tissues. NO induces multiple health benefits improving oral and heart health and improved blood pressure control [33].

- Natural Immunity: is not supported.

- Stains teeth: with bad after taste effects.

As discussed earlier, unlike antiseptics that are formulated at concentrations designed to kill 99% or more of the oral microbiome, the PAIR Phytocannabinoid Rinse (Table 2) is based on a scientific understanding of:

- How phytocannabinoids interact with beneficial oral bacteria to support antimicrobial and anti-inflammatory functions.

- The role of fibroblast cells in collagen production, which is essential for gum attachment to teeth (wound healing), as well as T-regulatory cells (Tregs), which mediate anti-inflammatory and antimicrobial responses.

- The synergy between phytocannabinoids and the body's natural ECS. Phytocannabinoids work with the body's

- Own cannabinoid molecules (endocannabinoids) and their cellular targets to promote mucosal wound healing, reduce inflammation, and support antimicrobial defense.

Table 2: Comparative properties of DenticDSTM PAIR to leading commercial classes of oral mouthwashes.

Product	DenticDS™ PAIR Rinse	Chlorhexidine Rinses Peridex	Listerine Cool Mint	Cetylpyridinium Cl Crest Pro / loRinse
Molecular class	Phytocannabinoids with silver nanoparticles	Antiseptic	Antiseptic, with Eucalyptol, Menthol, Methyl Salicylate, Thymol	Antiseptic
Effect on periodontal ligament fibroblasts	Stimulates Collagen in periodontal ligament	Kills fibroblasts	Inhibits osteogenic activity induces osteopenia	Minimal concentration to eradicate E. coli and P. aeruginosa cytotoxic keratinocytes/fibroblasts
Anti-microbial	Protects commensals, Reduces pathogens, Inhibits p gingivalis entry	Kills 99% everything including protective commensal bacteria	Kills 999% of all bacteria, increases opportunistic organisms	99% germ kill, reduces adhesion yeasts
Drug resistance	None	Crosss-resistance to antibiotics	Rebound drug resistance	Repeated use drug resistance
Wound healing	Stimulates mucosal fibroblasts and osteogenesis	Potential to cause chronic wounds	None	May delay due to killing of fibroblasts and keratinocytes
Taste	Pleasant lemon mint	Not pleasant	Strong and stringent	Taste alteration
Anti-inflammatory	Directly reduces pro-inflammatory markers	Long term treatment may lead to biofilm immune response resistance	Minimal to No effect	Fights plaque and gingivitis
Tooth staining	No	Yes	No	Yes
Allergic reaction	None reported	Severe allergic reaction potential	None	Yes, gastrointestinal issues, increase BP
Fungal infection	Active against thrush and canker sores	No effect	No effect	Effective, Potential cross-resistance fluconazole
Biofilm, plaque	Active against biofilm formation	Active against	Does not destroy, may slow growth	Combined with brushing reduces plaque

Ref: Int. J. Mol. 2022.23.808(Chlorhexidine) Antimicro. Agent and Chemo. 2020,64,8: J med Microbial, 2015 Ar;64(pt4):407-414; http//www.healthline.com/health/ethyl-alcohol-vs-isopropyl-alcohol; Antimicrobial Agents and Chemotherapy, Feb. 2005, p. 843-845; Journal of Medical Microbiology, Volume 73, Issue 6;https//doi.org/10.1099/jmm.0.001830.

Advantages of phytocannabinoids over antiseptic mouth rinses

Unlike traditional antiseptics, which indiscriminately kill both harmful and beneficial bacteria, phytocannabinoids offer a superior alternative to antiseptic mouth rinses by targeting pathogenic bacteria while preserving beneficial microbiome components. Furthermore, they actively support tissue healing rather than hindering it, making them ideal for both preventive and post-surgical applications. Their ability to selectively modulate cellular immune responses adds another layer of therapeutic benefit, minimizing unnecessary immune suppression while controlling pathogenic activity.

Why we care

"As our understanding of the oral-systemic disease connection

deepens, it's essential for dentists and physicians to collaborate closely to manage every patient's health more effectively." Carl W. Magyar, DDS and David L Cooper, PhD, MD.

Protect the link between oral and systemic health

Protecting the overall total health of the patient begins with managing the oral to systemic disease transmission pathway through the BOMB [34]. By incorporating DenticDSTM PAIR, a phytocannabinoid-based rinse, into both daily oral hygiene routines and dental procedures, patients and dental professionals can take proactive steps to reduce the constant risk of transitory oral bacteremia increasing the risk of systemic multiorgan disease transmission [35] (Figure 3).

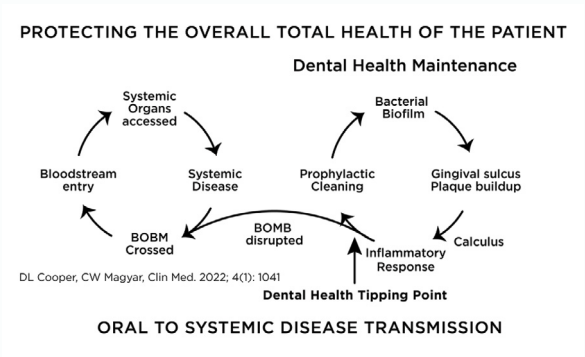

Figure 3: Oral health to systemic disease ecosystem.
Illustration of interrelationship of good oral health with overall systemic health. The breakdown of oral mucosa avails direct access to the systemic blood supply with potential multi-organ consequences. (Figure 3 Modified from Clin. Med. 2022; 4(1): 1041.)

Oral systemic health ecosystem

Oral health is critically important to overall well-being. Most often the dental health threatening cascade begins with (i) poorly controlled bacterial biofilm development which leads to (ii) gingival sulcus plaque buildup and with further lack of intervention (ii) calculus formation generating the (iv) pathological response seen by the dental professional as an inflammatory response (i.e. gingivitis) of the gingiva which can ultimately lead to significant periodontal disease complicated by bone and soft tissue loss.

An early warning sign of this process is bleeding gums, which indicate gingival breakdown and potential bacterial entry into the bloodstream. Preventing biofilm formation and strengthening the oral barrier reduces the risk of oral pathogens spreading systemically-potentially affecting vital organs like the brain, heart, lungs, and digestive system.

More than 70 years ago, research demonstrated that common dental procedures-including mastication (17%) and periodontal cleaning (40%)-could directly introduce oral bacteria into the bloodstream [35]. Even routine brushing can trigger transient bacteremia in 24% of cases, posing a constant risk of acute and chronic systemic inflammation that may lead to life-threatening complications.

Mouth-Gut axis

The oral and gut microbiomes populate the connected and continuous gastrointestinal tract They are affected bidirectionally by mechanical, nutritional and other influences which may lead to varied states of dysbiosis. There are major differences in their mucosal surface's function and structure which determine the porosity of these barriers to a wide variety of molecular molecules and microbes. An example is the phenomena of tolerance to microbial agents which allows microbial populations to exist within varied anatomical sites distinct along the whole of the digestive tract. An example is the phenomena of tolerance to microbial agents which allows microbial populations to exist within varied anatomical sites distinct along the whole of the digestive tract [36]. However, both rely on shared host immune pathways as barriers and whose response, is thought to be a critical determining factor in the development of systemic inflammatory disease. Therefore, the translocation of inflammatory oral microbiota, as in periodontal disease, to the GI tract resulting in the potential etiology of numerous systemic diseases sharpens our scrutiny of: (1) what microbial species are responsible, (2) the shared innate host immune pathways and (3) the differences in cellular response to the insults of inflammatory generated dysbiosis as additional potential biological targets for therapy.

Continued reliance on antiseptics and antibiotics

There is growing concern over the effects of antibiotics on gut microbiota as well as the contribution of antiseptics on development of drug and antiseptic resistance by the oral microbiome. In the gut there are 100 trillion microbes from 1000 species and 7000 strains. These bacteria have important and varied roles throughout the gut: digestion, energy, synthesizing vitamins and amino acids, supports development and strength of the immune system. Maintaining the oral commensal population's dominance over the mucosal barrier, protects against enterogenous pathogens [18].

Over generations of constant use by dentists and physicians alike, antibiotic/antiseptic administration has led to not only the increasing world-wide threat of antibiotic treatments becoming less and less useful but also:

- Microbial dysbiosis limiting our oral microbiome's natural ability to moderate and control pathogenic microbiota*;
- Contributed to poorly regulated and increased rates of diabetes, obesity, IBD, asthma, RA, depression, and superinfections;
- Resistance to QACs in antiseptics contributing to both antimicrobial resistance but also human health including dermal and respiratory effects, developmental and reproductive toxicity, and disruption of metabolic functions [4]; and;
- Gut bacterial commensal microbiome population losses contribute to alteration in metabolites like bile salts. This includes disruptions in host-microbe interactions impact immune regulation, as conserved receptors like PRRs, TLRs, and NOD-like receptors recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).

Oral microbiome recovery and homeostasis

Understanding the microbial content of an individual's oral microbiome is important. Dysbiosis occurs not so much by disappearance of healthy commensal bacterial strains with the interjection of new pathogenic strains but by a change in the relative proportions of each. Various microbes have their own characteristic survival and growth characteristics which may be exploited to a) moderate potential bad actors and b) stimulate the good ones. Examples include family members from probiotic strains of both

Streptococcus salivarius and Lactobacillus salivarius which may reduce mucosal inflammation, improve immunity, kill pathogenic bacteria and limit invasion and growth of bacterial species such as P. gingivalis. Genetically conserved responses to pathogens by these probiotic bacterial strains consist of various antimicrobial expressed proteins, peptides, TJPs and transporter proteins, all utilized to increase survivability and delay antibiotic resistance development [37].

Prescriptive CareTM: clinical innovation for proactive continuous care

Despite receiving professional care, many patients struggle to maintain their oral health, which can lead to severe systemic health problems, including cardiovascular disease [38] leaky gut syndromes [39], high blood pressure [40] ventilator [41,42] and non-ventilator pneumonias [42], and low birthweight babies [44] to name just a few. Dental health maintenance through routine scheduled prophylactic cleanings and daily hygiene forestalls the initiating cascade event biofilm development but does not totally remove it. Development of improved dental treatment formulations devoid of the risks associated with antiseptics and over used pharmaceuticals has not kept pace with the technological advances made in the mechanics and engineering of dental restorations and implantology.

Developing a formulary of products which will maintain and at the least lessen significantly a patient's oral hygiene declining presentation between visits is the promise of developing additional natural plant phytocannabinoid products. This is also of continued and increasing importance in patients with dentures, as well as in the increasing numbers of patients undergoing half and full arch implant procedures whose biofilm development may also lead to multiple untoward systemic complications such as pneumonia and cardiovascular disease [45].

The introduction of PAIR Rinse, as the first mainline phytocannabinoid dental treatment formulation is a critical tool for maintaining oral health between visits. The oral mucosa's epithelial cell lining is a physical and immunological barrier protecting not just the mouth but the body from environmental exposures, physical and chemical damage, microbes and toxins [3]. Understanding the mechanisms by which the oral mucosa deals with the challenges of inflammation, infection, and wound healing is essential for developing dental treatment formulations and the incorporation of biomarker advancements such as PCR enabled point of care diagnostics, multiplex proteomic determinations and now metagenomic profiles of dental disease, all developed previously in the parallel systemic medicine field of Precision Medicine crafting individualized, personalized therapies to the patient.

Discussion

The articles in this Special Issue describe how dentists, physicians, chemists and engineers have incorporated the scientific basis responsible for how the oral mucosa deals with these health threatening challenges to produce products based on intrinsic biological pathways which is shown here to be superior to chemicals and pharmaceutical products for many oral disease indications. In particular this issue focuses on the utilization of PAIR which allows dental professionals and patients to be proactive about oral hygiene. Understanding support for the mouth's mucosal barrier is interconnected with overall health and the risk of multiorgan systemic disease emphasizes that Dental Health is Well Health.

Understanding the multiple biological mechanisms of action of phytocannabinoids in dental disease

As clinical studies and investigation have shown in the following articles of this special issue phytocannabinoids are effective and safe across a broad range of oral disease. Clinical evidence of efficacy and safety is visually, empirically and patient confirmed. How to explain the striking positive results of these natural product preparations vs. the conflicting results found systemically? In large part this may because the Oral Cavity is a unique window by which the biological activities of the phytocannabinoids can be directly observed and in a time accelerated fashion. Compared to systemic clinical pharmaceutical studies for conditions, such as cancer or neuropsychiatric disease, which take years, oral clinical studies may be performed at a fraction of the expense and time.

This article has attempted to bring together the findings of investigators from around the world to develop a sound scientific basis for the mechanisms underlying phytocannabinoid activity in the oral cavity. Through understanding the direct and indirect biological pathways phytocannabinoids involve in their modification of dental health and disease allows continued development of improved formulations for both personal hygiene and care in the operatory spanning pre-operatory to post-operatory care- thus developing the much-needed Continuum of CareTM with the core elements of Precision Dentistry.

Finally, the systemic mechanisms of the phytocannabinoid family [46] of molecules pleiomorphic and allosteric interactions with host receptors are not covered here in detail [47,48]. The activities of the phytocannabinoids from broad spectrum cannabis and hemp extracts are better understood and described by relying on traditional pharmacological terms used for other plant-based medicinal products and polypharmacy in general (e.g., synergistic interactions and bioenhancement) [14]. This manuscript is in addition, importantly, an attempt to present an improved mechanistic understanding of the biological role of phytocannabinoids in the oral cavity with hopes improved modeling of both oral and systemic mechanisms will move others away from terms (i.e. entourage effect) utilized primarily for marketing in the Cannabis industry Scientific and commercial parties should rely on the evidence-based science behind this remarkable natural plant activities hemp which we believe to have shown in this special issue of Clinics In Medicine as potentially disruptive to both the chemical and pharmaceutical suppliers of dental treatments.

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