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Research Article

# Dose Escalation Study: DenticDS™ Pair vs Placebo in Adult Patients with Gingivitis

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## Abstract

**Background:** Mild and moderate gingivitis is a common patient presentation to the dental office. However, bleeding gums are not an innocent finding, representing instead a direct pathway to oral-systemic pathogen transmission with potential multi-organ disease effects.

**Materials and methods:** A three-dose escalation Pilot study was performed on patients with mild to moderate gingivitis with Phytocannabinoid Anti-Inflammatory (PAIR) Rinses. Patients were followed by bleeding on probing (BOP) and periodontal pocket depth (PPD) to empirically measure effectiveness of PAIR treatment.

**Results:** In patients with moderate to severe inflammatory gum disease, all three test doses exhibited decreases bleeding points of 43%, 51% and 72%, all above placebo's 26%. Combining all three dosing results compared to placebo resulted in a significant two-tailed *p*-value of 0.024.

**Conclusion:** PAIR treatment significantly reduced empiric measures of inflammatory gum disease utilized in this study. Phytocannabinoid Anti-Inflammatory Rinses (PAIR) was shown to be an effective anti-inflammatory treatment at all three doses, superior to any placebo effect.

**Keywords: Phytocannabinoids; Cannabinoids; Gingivitis; Periodontal disease; Phytocannabinoid anti-inflammatory rinse; Periodontal disease; Institutional review board; Perio-Charting**

## Abbreviations & Acronyms

PAIR: Phytocannabinoid Anti-Inflammatory Rinse; BOP: Bleeding on Probing; IRB: Institutional Review Board; PPD: Periodontal Pocket Depth

## Introduction

Gingivitis is an inflammatory condition of the gingival tissue caused by microbial plaque deposits located in or close to the gingival sulcus. There are in addition many systemic etiologic factors which can stimulate additional plaque buildup or reduce the soft-tissue area of the gingival epithelium and connective tissue defense against microbial attack [1]. Recent studies have shown the efficacy of cannabinoids on reducing bacterial content from dental plaque [2] and cannabinoid infused mouthwash products as effective as chlorhexidine on inhibiting culturable bacterial content from dental plaque samples [3]. These studies describing activity against plaque's microbial content illustrate the ability of phytocannabinoids to have significant antimicrobial effects.

## Materials and Methods

### Patient population

A random series of patients presenting for dental care from the active two-site general dentistry offices of Maygar Dental were selected conforming to general inclusion criteria: carrier the diagnosis of gingivitis, 18 years an older, stable on current medications for at least 2 months, 20 or more natural teeth, minimal total of 10 bleeding points and no prosthetic dental treatments. Exclusion criteria included tobacco or vaping users, users of CBD or marijuana, pregnant or nursing patients, use of anti-inflammatories in last two months. Informed consents were obtained according to standard IRB tenets under FDA advisory authority. An overriding IRB approved clinical study, "PhytoEnhanced Oral Anti-Inflammatory Rinse (PAIR) vs Placebo in Adult Patients with Gingivitis" approved November 20, 2019 governed specific patient cases within this study.

### Formulation

PAIR™ (Phytocannabinoid Anti-Inflammatory Rinse) Oral Rinse combines two advanced nanoformulation chemistries consisting of a broad-spectrum micellar phytocannabinoid formulation from hemp and a nano-silver nanoparticle [4]. The PAIR™ micellization process involves a decarboxylated full spectrum hemp oil including cannabidiol (CBD), cannabidivarin (CBDV) and tetrahydrocannabivarin (THCV) in a mixture suitable for oral ingestion. The oil is extracted from industrial hemp with column chromatography to remove THCΔ9. The silver nanoparticle (NP) contains elemental (zero-valent) metallic silver coated with silver oxide. The technology achieves unique tetrahedral molecular arrangement of silver and oxygen.

### Protocol

Baseline evaluations were done on all Patients from Maygar Dental practice pool who have been evaluated and diagnosed with gingivitis after an empiric measurement by probing of gums and bleeding points. After being consented, subjects were to be randomized into 4 groups (3 active and a placebo rinse). Bleeding on probing (BOP), often referred to as the bleeding point assay, is an indicator of tissue inflammatory response to bacterial pathogens. This assay is used routinely in dental practice as a clinical indicator of periodontal disease progression [5].

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The presence of gingivitis over an extended period of time is a leading predictor of future periodontal deterioration. BOP values are also highly associated with periodontal pocket depth (PPD) illustrative of periodontal breakdown greater than or equal to 6 mm [6]. All BOP assays were performed by a licensed dental hygienist who performed all probings on an individual patient during the study period.

Arms 1, 2 and 3 received increasing doses of the active rinse throughout the study. Arm 4 received the placebo control (Figure 1). All groups were given unmarked 500 ml opaque bottles containing the randomly assigned dental rinse. Study Subjects were asked to fill out a medical history, and emergency contact information. They were instructed to pull the rinse for one minute (provided with a one-minute sand timer) and expectorate two times per day (morning and night) at least 30 minutes after eating and no fluids for 30 minutes following treatment. Patients then were returned to the office and repeat BOP performed 8 weeks later. At the end of the study the change in the number of bleeding points and a reduction in inflammation were evaluated to determine the efficacy of the test oral rinse. No adverse event information was reported for duration of study.

## Results

Percent reduction in Bleeding on Probing (BOP) Comparison of four data sets. Doses 1, 2 and 3 when analyzed individuals did not reach statistical significance due to small sample sizes (Table 1). However, by combining all three dosing results then comparing to the placebo a two-tailed *p*-value of 0.024 was found to be significant (Figure 2).

It is important to note this study was designed for a larger consented patient study. Halfway through this Pilot Study, COVID shut down many Florida dental offices including the two committed to this study. Therefore, the study closed early. Understanding no new patients could be consented and a long interim delay was in progress the data was opened for review. Unblinding the patients who had been accrued resulted in the findings as presented.

Periodontal pocket depths were measured across all patients. Notable, but again difficult to substantially claim statistical significance was that in individual patients up to 10% of PD pockets showed a decrease from one to 3 mm's in select but not all patients. This is not surprising since the PAIR Rinse was not designed specifically for this outcome. However, in an accompanying paper [7] detailing selected and representative Case Studies the combination of our PAIGel and the PAIR Rinse reduced a peri-implantitis patient's pocket depth from 7 mm to 2 mm**!** Our understanding of the pathobiology of periodontitis that the PAIR Rinse is an effective anti-inflammatory thereby shrinking the pocket depth through reducing dilated blood vessels secondary to the inflammatory process. The phytocannabinoid gel and rinse give equivalent, often superior continuous benefit compared to placement of an antibiotic or Arestin.

## Discussion

Other treatment options to reduce dental plaque and subsequent gingival inflammation may include improved personal oral home care including flossing, brushing, irrigation, automated toothbrushing and more frequent in-office professional oral preventative maintenance. A range of chemical or plant based oral rinses are commercially available with varying degrees of therapeutic anti-inflammatory results.

An interesting observation is the size of the placebo effect in the study population. Variables here which we believe contribute is the older age of both practices and the enthusiasm of patients to participate with two dental practices for which they have decades of experience and trust in the professionals. FDA requirements for claiming anti-gingivitis efficacy in FDA drafts require a decrease of 15% or more [8]. In this pilot study we utilized BOP, a secondary measure. In future studies we will also utilize the accepted primary endpoint of Gingival Index and utilize Plaque Index as either a co-primary index or as a secondary index along with BOP accordingly.

One major factor contributing to ongoing oral health issues is the reliance on traditional mouth rinses that use strong antiseptics to kill bacteria. While effective at reducing bacteria overall, these products can disrupt the delicate balance of the oral microbiome, leading to the overgrowth of harmful pathogens. Long-term use has been linked to antibiotic resistance [9-11], inhibition of gingival fibroblasts necessary for collagen formation and mucosal wound healing [12].

Contrast this to the phytocannabinoids in DenticDS™ PAIR which stimulates the commensal bacteria to eliminate the pathogenic bacteria through production of antimicrobial peptides (AMPs), helps the mucosal cell linings resist infection through production of tight membrane junctions (TMJs), works naturally on cellular receptors to limit inflammation and swelling from TNFα and IL-1,6; and works with your tissue and mucosal fibroblasts stimulate bone growth and wound healing [13].

## Conclusion

PAIR treatment significantly reduced empiric measures of inflammatory gum disease utilized in this study. Phytocannabinoid Anti-Inflammatory Rinses (PAIR) was shown to be an effective anti-inflammatory treatment at all three doses, superior to any placebo effect. Combining all three study doses compared to Placebo a statistically significant p-value=0.024 was obtained.

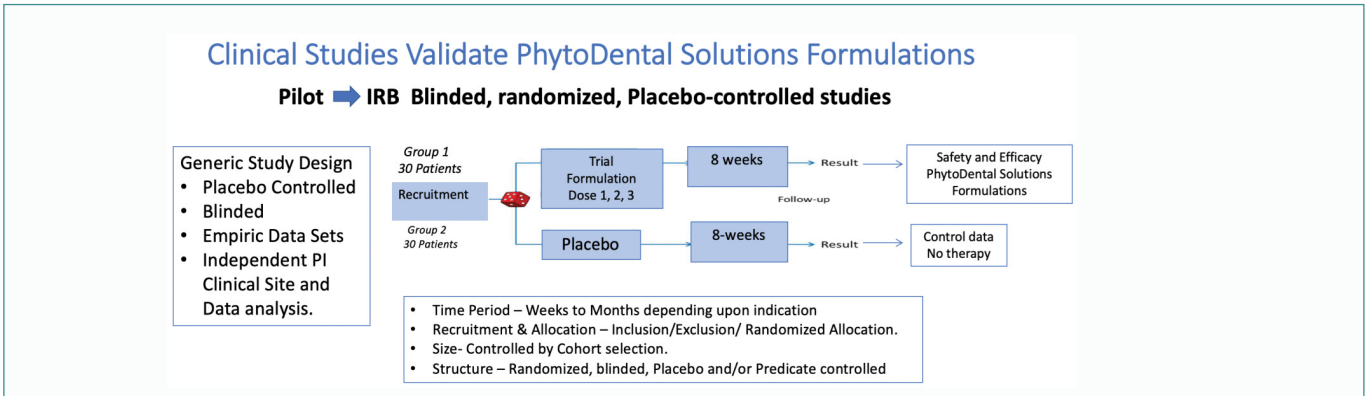


**Figure 1**: Clinical Study Outline and Protocol

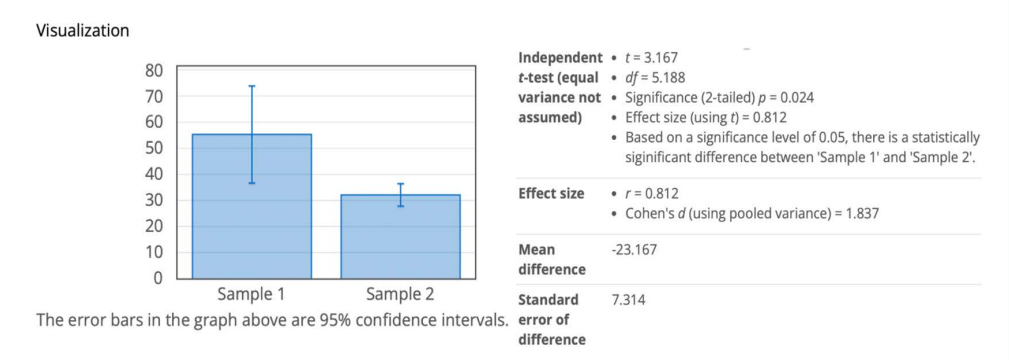


**Figure 2**: Statistical Analysis Combined PAIR Dose Escalation Data Sets (sample 1) versus Placebo Control (sample 2).

**Table 1:** Dose Escalation Study DenticDS™ PAIR, Change in Bleeding on Probing..

| | Average | Median | Observed Range | p- value |
|---|---|---|---|---|
| Dose 1 | -43% | -43% | -41 to -45% | N.S. |
| Dose 2 | -51% | -51% | -38 to -64% | N.S. |
| Dose 3 | -72% | -72% | -58 to -85% | N.S. |
| All Doses | -55% | -55% | -38 to -85% | $p = 0.024$ |
| Placebo | -26% | -33% | - 9 to -33% | control |

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