

Socket!® Oral Pain Gel

Inhibits the Growth of Microorganisms Implicated in Various Oral Infections

Periodontitis

Periodontal diseases are inflammatory, infectious diseases caused by microorganisms and depending on the extent of the inflammation and destruction, periodontal disease can be referred to as either gingivitis or periodontitis. Although it has been suggested that gingivitis may progress to periodontitis, closer examination of the two periodontal diseases reveals more differences than similarities. In periodontitis, the inflammation extends beyond the oral gingiva, where inflammatory compounds degrade connective and bone tissue. Moreover, periodontitis can be divided into two groups: early-onset (juvenile or aggressive) periodontitis and adult (chronic) periodontitis.^[1, 2] There are several anaerobic, Gram-negative bacteria implicated in the development of periodontitis and eight major pathogens have now been clearly identified as the culprits.^[3] While over 400 different species of microorganisms reside in the gingival crevice,^[4, 5] *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythensis*, and *Fusobacterium nucleatum* are the most pathogenic and prevalent isolates implicated in periodontitis.^[6-9]

These pathogenic organisms are not present at birth and studies have revealed that vertical transmission (from parent to offspring through ovum, placenta, blood and saliva) of these organisms is prevalent.^[10] This mode of transmission fits the transfer and acquisition of *A. actinomycetemcomitans*, in which maternal saliva is the source of these Gram-negative bacteria.^[11] Lee *et al.*, demonstrated that children of caregivers that had certain pathogenic strains were 35 times more likely to have these strains when compared to children whose caregivers did not have the pathogenic strains.^[10] Alternatively, a horizontal transmission (through direct contact) model is prevalent in *P. gingivalis* cases.^[11]

During the course of infection, the number of commensal organisms substantially increases in biofilms and gingival regions.^[9, 11] Once the biofilm has established and colonization has transpired, a similar mechanism of invasion and recurrence is shared among these periopathogens. *P. gingivalis*, *A. actinomycetemcomitans*, *T. forsythensis*, and *F. nucleatum* are able to induce production of cytokines and other compounds responsible for inflammation and loss of the alveolar bone.^[12] Additionally, *P. gingivalis*, *A. actinomycetemcomitans*, and *F. nucleatum* also have similar mechanisms that induce their internalization into junctional and pocket epithelial cells.^[13] Internalization ensures protection from the external environment and any response by the host's immune system. This mechanism plays a major role in the development of chronic periodontitis, in which the pathogens are able to initiate subsequent attacks.

Of the four major periodontal pathogens listed above, *T. forsythensis* and *F. nucleatum* play a limited role in initiating colonization or attack at different stages of periodontitis. *T. forsythensis* is able to infect root canals, aid in the development of chronic apical periodontitis,^[14] and adhere to and invade oral epithelial cells with the help of *P. gingivalis*.^[4] *F. nucleatum* is important in the development of biofilms^[15] (along with *A. actinomycetemcomitans*),^[16] which harbor other pathogenic microorganisms and allow co-aggregation.^[17]

P. gingivalis, a major periopathogen, is involved in the development and recurrence of periodontitis. Although it is a natural component of the oral cavity's microflora, its numbers increase during adult (chronic) and juvenile (aggressive) periodontitis.^[2, 18] There are multiple strains with ranging virulence and pathogenicity, which ultimately determine the importance of this organism in periodontitis. *P. gingivalis* has specialized fimbriae that allow for greater adherence to cells,^[19] initiating internalization or production of cytokines. This periodontal pathogen also has a capsule that protects it from the host's immune system. *P. gingivalis*' lipopolysaccharide (LPS), enzymes, and antigens enable greater adherence to and activation of epithelial^[13] and immune cells (i.e. those involved in the release of cytokines that induce inflammation and degradation of

the alveolar bone).^[13, 20] Moreover, the most important virulence factor is *P. gingivalis*' ability to co-infect epithelial cells with *A. actinomycetemcomitans*.^[21]

The last putative pathogen, *A. actinomycetemcomitans*, is a non-motile, Gram-negative coccobacillus. It is a major etiological component in the pathogenesis of juvenile (aggressive) periodontitis,^[5] and it can be divided into five different serotypes (A through E). These serotypes determine *A. actinomycetemcomitans*' the varying degrees to which it can co-infect with *P. gingivalis*.^[16, 22] Like *P. gingivalis*, *A. Actinomycetemcomitans* has several virulence factors that enhance its adherence and attacks on oral epithelial cells, making it a major contributor in the development of periodontitis.^[23] *A. actinomycetemcomitans*' leukotoxins, peptidoglycans, proteins, and LPS induce the production and release of matrix metalloproteinases, cytokines, and prostaglandins, which are responsible for inflammation and loss of the alveolar bone.^[24] The leukotoxin produced by *A. actinomycetemcomitans* not only protects it from phagocytosis by neutrophils and various other immune cells (i.e. monocytes and macrophages), but it can even induce necrosis of these cells.^[25]

The mechanisms and etiology of periodontitis have been a focal point for researchers in recent years, due to the substantial data linking periodontal disease (periodontitis in particular) to several systemic diseases. These same organisms have been implicated in everything from cardiac problems to low birth weight. Treatment for periodontitis depends on the severity of the case. Patients might undergo tooth scaling and root planing in a mild case while full surgical treatments (pocket reduction surgery, soft tissue grafts, bone grafting and guided tissue regeneration) may be required for more severe cases. Non-surgical treatment of periodontitis (scaling and root planing) might also be accompanied with an antibiotic, be it in a mouth rinse or incorporated into threads and gels.^[26] Another popular treatment is the PerioChip, which comes into direct contact with the infected pocket and is impregnated with 2.5 mg of chlorhexidine.

Periodontal disease (including periodontitis) affects a significant portion of the population, and its implications far extend the reaches of the oral cavity. Four major periodontal pathogens have been continually isolated from patients, and these organisms are major players in this complex and multifaceted disease. Current treatment of severe periodontitis is surgery, and much milder (early stage) periodontitis is treated with antibiotics or chlorhexidine. The problems arise with these treatments due to an increased resistance to antibiotics^[27-29] and the cytotoxicity of chlorhexidine to the cells essential to the healing process.^[30, 31] More natural, effective and safer products^[32] should be introduced into the market that are able to stop the manifestations of periodontitis and return the gingival pockets to normal health.

To determine if SockIt! Oral Pain Gel had an effect on the growth of some of the most common periodontal pathogens, TK and MIC studies were conducted. SockIt! demonstrated natural antibacterial activity against these organisms. The results of these studies are presented in Tables 4 and 5.

Table 4: Time Kill (Log Reduction) with SockIt! (G0416A) Against Organisms Implicated in Periodontitis						
Microorganism	30 sec	5 min	1 hr	6 hrs	12 hrs	24 hrs
<i>A. actinomycetemcomitans</i> (ATCC 43718) (Inoculation level = 1.41 x 10⁵)						
Average (cfu/ml)	190	60	NG	NG	NG	NG
Log Reduction	2.42	4.37	6.15	6.15	6.15	6.15
<i>T. forsythensis</i> (ATCC 43037) (Inoculation level = 1.44 x 10⁵)						
Average (cfu/ml)	555	110	NG	NG	NG	NG
Log Reduction	2.31	4.12	6.16	6.16	6.16	6.16
<i>P. gingivalis</i> (ATCC 49417) (Inoculation level = 5.05 x 10⁵)						
Average (cfu/ml)	NG	NG	NG	NG	NG	NG
Log Reduction	5.75	5.75	5.75	5.75	5.75	5.75
<i>F. nucleatum</i> (ATCC 10953) (Inoculation level = 5.05 x 10⁵)						
Average (cfu/ml)	NG	NG	NG	NG	NG	NG
Log Reduction	5.75	5.75	5.75	5.75	5.75	5.75
*G = GROWTH, *NG = NO GROWTH						
<i>SockIt! is effective against all organisms tested within 30 seconds.</i>						

Table 5: MIC (Inhibition of Growth) with SockIt! (G0416A) Against Organisms Implicated in Periodontitis										
Microorganism	.02/9.8	.04/9.6	.06/9.4	.08/9.2	.1/9.0	.12/.88	.14/.86	.16/.84	.18/.82	.2/.8
<i>A. actinomycetemcomitans</i> ATCC# 43718	G	G	G	G	NG	NG	NG	NG	NG	NG
<i>P. gingivalis</i> ATCC# 49417	G	NG	NG	NG	NG	NG	NG	NG	NG	NG
<i>F. nucleatum</i> ATCC# 10953	G	G	G	G	G	NG	NG	NG	NG	NG
<i>T. forsythensis</i> * ATCC# 43037	1.0/9.0	1.5/8.5	2.0/8.0	2.5/7.5	3.0/7.0	3.5/6.5	4.0/6.0	4.5/5.5	5.0/5.0	5.5/4.5
	G	G	NG	NG	NG	NG	NG	NG	NG	NG
*G = GROWTH, *NG = NO GROWTH *(differing concentrations were applied to <i>Tannerella forsythensis</i>)										
<i>SockIt!</i> is effective against <i>A. actinomycetemcomitans</i> at a 10% concentration (1.0/9.0), <i>P. gingivalis</i> 4% (0.4/9.6).										

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