Abstract: *Andrographis Paniculata* Gel and Periodontal Treatment

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บทคัดย่อ

โรคปริทันต์อักเสบ เป็นการติดเชื้อที่ปรากฏในเนื้อเยื่อรองรับฟัน การมีคราบแบคทีเรียใต้เหงือกเป็นสาเหตุหลักที่เริ่มต้นทำให้เกิดโรคปริทันต์อักเสบและการลุกลาม การขูดหินน้ำลาย และเกลารากฟันเป็นการรักษา เพื่อควบคุมการลุกลามของโรคปริทันต์อักเสบ อย่างไรก็ตามวิธีการนี้ต้องเข้าถึงเพื่อให้เห็นบริเวณที่จะรักษาได้ ในบางรายจึงยากที่จะกำจัดคราบแบคทีเรียและหินน้ำลายใต้เหงือกได้หมด จึงทำให้ไม่มีประสิทธิผล การมีร่องปริทันต์ที่ลึก ง่ามรากฟัน และแผ่นคราบแบคทีเรียในผิวรากฟัน เป็นปัจจัยจำกัดของการขูดหินน้ำลายและเกลารากฟัน นอกจากนี้การกำจัดเชื้อแบคทีเรียที่สามารถเข้าถึงเซลล์เนื้อเยื่อบุผิวและเนื้อเยื่อเกี่ยวพันใต้เนื้อเยื่อบุผิวของอวัยวะปริทันต์อาจเป็นไปไม่ได้ ยาต้านจุลชีพทางระบบและเฉพาะที่จะใช้ร่วมในการรักษาเพื่อที่จะใช้ฆ่าแบคทีเรียที่หลงเหลือเพื่อแก้ไขโรคปริทันต์อักเสบ จากการทบทวนวรรณกรรมนี้พบว่า ยาต้านจุลชีพที่ใช้เฉพาะที่ซึ่งประกอบไปด้วยสมุนไพรฟ้าทะลายโจรได้ถูกพัฒนาเพื่อใช้ร่วมกับการขูดหินน้ำลายและเกลารากฟัน เจลฟ้าทะลายโจรสามารถลดร่องลึกปริทันต์ และเกิดการสร้างกระดูกในส่วนบนที่ระยะเวลา 3 เดือน และ 6 เดือน ยิ่งกว่านั้นพบว่า อัตราส่วนของเชื้อแบคทีเรีย black-pigmented anaerobes ลดลงอย่างมีนัยสำคัญทางสถิติในตำแหน่งที่ใส่เจลฟ้าทะลายโจร การใส่เจลฟ้าทะลายโจรที่ใช้เสริมในการขูดหินน้ำลายและเกลารากฟันแสดงผลทางคลินิกที่ดีขึ้น เป็นการชี้ถึงประโยชน์ของเจลฟ้าทะลายโจรในการเสริมการรักษาโรคปริทันต์อักเสบแบบเรื้อรัง แต่เนื่องจากเจลฟ้าทะลายโจรไม่สามารถอยู่ในร่องลึกปริทันต์ได้เป็นเวลานาน ดังนั้น*เชื้อ P.gingivalis* จึงก่อตัวขึ้นมาใหม่ในตำแหน่งที่ใส่เจลฟ้าทะลายโจรภายหลังการรักษา 3 เดือน เนื่องจากเจลฟ้าทะลายโจร ยังรู้จักกันไม่กว้างขวางในขณะนี้ ดังนั้นทบทวนวรรณกรรมนี้จึงมีวัตถุประสงค์เพื่อให้ความรู้เกี่ยวกับเจลฟ้าทะลายโจรกับบุคลากรทางการแพทย์ ส่วนเรื่องจะนำไปใช้ในการรักษานั้นคงต้องไปศึกษากันต่อไป ดังนั้นในส่วนข้อจำกัดของการใช้ ก็ต้องติดตามในคู่มือวิธีการใช้ แต่จากผลการวิจัยในมนุษย์ ก็ยังไม่พบว่ามีผู้ใดเกิดอาการแพ้ขึ้น เนื่องจากเป็นยาที่ใช้ภายนอกร่างกายเท่านั้น ในอนาคตควรทำการศึกษาวิจัยเปรียบเทียบกับผลิตภัณฑ์ของต่างประเทศที่ใช้กันอยู่ในปัจจุบัน

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Abstract

Periodontitis is an infection occurring in the tooth-supporting tissues. The presence of subgingival plaque represents the principal etiologic factor which involves in the initiation and progression of periodontitis. The scaling and root planing were the treatment for controlling the progression of periodontal diseases. However, this technique needs accessibility to and visibility of the area. In some cases, complete subgingival plaque and calculus removal are hardly achieved and ineffective. The limited factors for scaling and root planing include deep pockets, furcation areas and bioflims in the cementum. In addition, it may not be possible to eradicate bacterial species that can reach epithelial cells and subepithelial connective tissues of the periodontium. In order to kill the remaining bacteria, systemically or locally administration of antimicrobial agent is used as an adjunctive treatment to improve the management of periodontitis. From this review article was found that the local drug delivery system containing an antimicrobial traditional herb, *Andrographis paniculata*, has been developed as an adjunct to scaling and root planing. The *Andrographis paniculata* gel (AP gel) has been shown to reduce probing depth and coronal bone fill in the AP gel-treated sites at 3 and 6 months. Moreover, the proportion of the black-pigmented anaerobes was significantly reduced in the AP gel-treated sites. The local application of AP gel as an adjunct to scaling and root planing showed better improvement of clinical parameters. It is indicated the benefit of AP gel as an adjunctive treatment in chronic periodontitis. But AP gel did not sustain in periodontal pocket for a long time. So *P. gingivalis* could be recolonized in the pocket treated with AP gel 3 months after treatment. Since the AP gel is not widely-known at this moment, therefore, this review article aimed to educate medical professionals about the AP gel. Regarding its therapeutic efficacy, further study of the AP gel required. The users' instruction provides more detailed information. Allergic reactions were not observed in these clinical trials. The AP gel is applied for external use only. There should be further study in order to compare with the recent foreign product.

Keywords: The *Andrographis paniculata* gel, Periodontitis

Introduction

Periodontitis is a chronic inflammatory disease characterized by connective tissue and alveolar bone destruction, eventually leading to tooth loss. It is commonly accepted that this disease occurs as a result of infection by a group of specific bacteria from the subgingival biofilms, particularly gram-negative anaerobes[1-4]. These bacteria specifically associated with destructive diseases, *Aggregatibacter actinomycetemcomitans* (previously *Actinobacillus actinomycetemcomitans*) and *Porphyromonas gingivalis*

have been considered as etiology agents. They are defined as the most relevant periodontal pathogens, together with *Tannerella forsythia* (previously *T. forsythensis*)[5]. There are many evidence supporting that scaling and root planing are effective therapy for periodontal diseases[6-7]. The therapeutic benefit results from the removal of microbial products and calcified deposits that contaminated the root surface, as well as the microorganisms colonizing both tissue and tooth sides of the periodontal pocket[8]. In addition, scaling and root planing are effective to reducing gingival inflammation, pocket depth and improving or maintaining attachment level[9].

Although, clinical trials have confirmed that plaque control combined with scaling and root planing are effective therapy for periodontitis, in particular cases there are limitation to the effectiveness of mechanical *debridment* due to depth of pocket[10-12], anatomy of root[13-15], operator skill, as well as the ability of some periodontal pathogens invading and residing in the periodontal tissue and on root surface[17-18].

The study of Waerhaug[12] demonstrated that the chances of removing all subgingival plaque and calculus from all surfaces of the pockets, less than 3 mm depth, were good. The chances of failure of the pocket depth ranges from 3 to 5 mm are greater than the chances of success and if the pocket depth greater than 5 mm, the chances of failure dominate. Some studies have shown the relationship of the effectiveness of scaling and root planing and the initial probing depths, the greater pocket depth, the more amount of residual calculus remaining on the root[16,19]. DeSanctis and Murphy[15] reported that furcations are freguently the cause of inaccessibility for adequate professional debridement, because their entrances were smaller than the size of periodontal instrument. In addition, they present with concavities and convexities. Brayer[16] found that more experienced operators had more calculus free on root surface in moderate (4-6 mm) and deep (> 6 mm) pockets. Fleischer[14] studied scaling and root planing efficacy in multirooted teeth, also demonstrated that the more experienced operators, the more proficient in removing calculus from furcations.

Mechanical therapy alone cannot completely eliminat microorganisms, such as *Aggregatibactor actinomycetemcomitans, Porphyromonas gingivalis*, due to theirs abilities to invading periodontal tissues or dentine tubules[17- 18, 20]. In addition, they may also reside in sites inaccessible to periodontal instruments, for example root concavities or furcations[17].

Therefore, the use of antimicrobial agents together with mechanical debridement may be advantageous to enhance the effectiveness of periodontal treatment by eliminating the bacteria inhabiting at the bottom of the deep periodontal pockets or in dentinal tubules. Theoretically, the two major approaches of drug administration for periodontal therapy are systemic and direct local placement. Each approach has advantages and disadvantages, as summarized in Table 1.

Table 1 Comparison of local and systemic antimicrobial therapy [21]

Issue	Systemic administration	Local administration
Drug distribution	Wide distribution	Narrow effective range
Drug concentration	Variable levels in different body compartments	High dose at low levels treatment site, elsewhere
Therapeutic potential biofilm	May reach widely distributed micro-organisms	May also act locally on associated
Problems	Systemic side effects	Re-infection from non-treated sites
Clinical limitations	Require good patient compliance	Infection limited to the treated site
Diagnostic problems Lesions identification	Identification of pathogens, choice of drug	Distribution pattern of lesions and pathogens, identification of sites to be treated

Systemic antimicrobials show efficacy in controlling subgingival microbiota since the administered drug can via serum, penetrate and affect all microbial eco-niches of the irrespective diseased or healthy sites. This may be a distinct advantage in situations where the periodontopathogens colonize non-dental sites, such as the dorsum of tongue or tonsillary crypts[21]. Moreover, the use of systemic antibiotic therapy cost less[22]. Disadvantages of systemic antibiotic therapy including inability to achieve high gingival crevicular fluid concentration, adverse effects, drug interactions, superinfection, bacterial resistance, hypersensitivity and gastrointestinal intolerance may occur[22-25].

Alternatively, local drug delivery system is the means of drug application to confined areas. Its benefits include the better patient compliance, enhanced or improved pharmacokinetic response, greater accessibility and ability to place the drug adjacent to the lesions. They consist of a local delivery devices and controlled-release local delivery devices. Local delivery devices are designed to deliver agents locally into the periodontal pocket but without any mechanism to retain therapeutic levels for a prolonged period of time. Controlled-release local delivery devices are designed to release a drug slowly for more prolonged drug availability and action[26].

Local drug delivery systems for the subgingival area have been developed in an effort to either prevent or treat periodontitis, particularly in non-responding sites or localized recurrent disease[21]. The drug concentration using local delivery systems in the periodontal pockets has been shown to be higher than systemic antimicrobial systems[21], thus drug dosage can be reduced. In addition, adverse effect and microbial resistance can be minimized. For these reasons, local drug delivery systems have been widely used as an adjunctive treatment in periodontal diseases. Several commercially available products of local drug delivery systems are introduced, such as tetracycline fibers, metronidazole gel, doxycycline polymer and

chlorhexidine chip[21,26]. However, they are very expensive since they have to be imported from foreign countries. Therefore, the attempt has been made to develop the controlled release local delivery devices using the active components from traditional herbs, *Andrographis paniculata*.

Pharmacological activities of *Andrographis paniculata*

Andrographis paniculata, a medicinal herb belonging to a subtribe in the the Acanthaceae family, is known in Thai as Fah Talai Joan or Nam Laai Phangphon. This herb consists of diterpenoid lactone compounds, flavonoid compounds, steroid, phenolic compounds and organic acids. The principal constituents are diterpenoid lactone compounds including andrographolide, dehydroandrographolide, neoandrographolide and deoxyandrographolide[27].

The pharmacological activities of *Andrographis paniculata*, studying in laboratory animals exhibit anti-inflammatory, antibacterial activity, antitumor activity, antipyretic, antivenom, antigastric ulcer, hypotensive effect, stimulation of smooth muscle, antifilarial activity[28], hepatoprotective effect[29] and immunostimulant effect[30]. Therefore they were introduced in the market for medical purposes in various forms.

The attractive pharmacological activities of *Andrographis paniculata* for periodontal treatment were antimicrobial, anti-inflammatory and immunostimulant activities. The antimicrobial activity of this herb against oral bacteria, *Streptococcus mutans* and *Porphyromonas gingivalis*, has been reported by using four sequential extraction fractions, i.e., hexane, methylene chloride, ethanol 95% and water, by agar diffusion method. The hexane and methylene chloride fraction showed inhibitory activity against *Streptococcus mutans*, while the ethanol fraction exhibited inhibitory activity against all tested bacteria. No inhibitory activity against all tested bacteria was observed from the water fraction[31].

The anti-inflammatory activity was tested in rats by intraperitoneal injection and oral administration. Intraperitoneal injection of the water extract (0.5-2.5 g/kg), the 50% ethanol extract (0.06-0.25 g/kg) and the 85% ethanol extract (1-2 g/kg) reduced inflammation. Oral administration of the 85% ethanol extract (2 g/kg) decreased carrageenin-induced pedal edema, while the water extract (0.05-2.5 g/kg) and the 50% ethanol extract (0.125-2 g/kg) had no effect[28].

Andrographis paniculata could also act as an immunostimulant agent. The immunostimulant activity was studied in mice using ethanol extract and purified diterpene andrographolide of *Andrographis paniculata*. These preparations induced significant stimulation of antibody and delayed type hypersensitivity response to sheep red blood cells in mice. It had also stimulated nonspecific immune response of the animals by increasing the proliferation of splenic lymphocytes[30].

Toxicity of *Andrographis paniculata*

The leaves extract of *Andrographis paniculata* at a dose of 10 ml/kg given subcutaneously in rabbit revealed no general toxic effect[32]. In mice, oral administration of a suspension of powdered leaves at dosees of 200 and 400 mg/kg on alternate days for 4 weeks demonstrated no effects on growth rate, major visceral organs, fertility or teratogenicity. However, oral administration of the leaves powder at 150 mg/kg on alternate days for 14 weeks in rats showed slightly slow growth rate, but no general toxic effects[33]. Acute toxicity test of the 50% alcoholic extract of *Andrographis paniculata* revealed no evidence of toxicity in mice when given 15 g/kg body weight. Lethal dose 50 of the extract administered via oral and subcutaneous were more than 15 g/kg body weight and that via intraperitoneal was 14.98 g/kg[34]. The toxicity effect of the plant powder was evaluated for 6 months in 96 Wister rats receiving 0.12, 1.2 and 2.4 g/kg/day which was equivalent to 1, 10 and 20 times the human therapeutic dose (6 g/day/50 kg). No abnormalities, such as growth rate, food consumption, clinical signs, hematological, serum biochemical values or histopathological changes were found[34].

Clinical trials of *Andrographis paniculata* gel

Komwatchara[35] formulated the *Andrographis paniculata* into controlled-release biodegradable gel for the periodontitis treatment. The extract of *Andrographis paniculata* was prepared using natural lipid and vegetable oil (soybean oil) as a delivery system. The natural oil mainly consisted of triglycerides of oleic and linoleic acids. When natural oil was added in the gel base and natural lipids, the crystal structure of the gel changed from cubic to reverse haxagonal form, which was found to have the most favorable sustained release properties. The physical characteristic of the gel base was good but incorporation of the *Andrographis paniculata* to crude extract had decreased its viscosity and stiffness when contacted with water. However, the resulting gel was still for subgingival application and was expected to retain in the gingival sulcus while slowly release into the pocket. The *Andrographis paniculata* gel (AP gel) showed better stability at 4°C and 30 °C than at 45 °C within 3 months storage, however, it was recommended to be stored at 4°C. The antimicrobial activity of the AP gel is not only from the constituents alone but also from the combination of substances in the crude extract. It could be degraded by hydrolysis, which is slow in an acidic condition, but the rate was increased in the alkaline condition.

Several investigation demonstrated that AP gel could be effectively used adjunct to mechanical debridement in the periodontal treatment.

Rassameemasmuang[36] studied clinical and microbiological effects of five treatment modalities in chronic periodontitis patient; scaling and root planing, subgingival administration of AP gel, scaling and root planing with subgingival application of AP gel, scaling and root planing with subgingival application of gel base and untreated sites as a control group. The study was evaluated for 49 days and the result showed that the used AP gel alone had not statistically significant changes in the treatment of chronic periodontitis similar to that responed when subgingival irrigations were utilized without mechanical root debridement. While the root planing with or without gel application provided the same clinical and microbiological results. The investigator commented that the result might be due to too few numbers of patients and characteristic of the AP gel which was not viscous enough to retain in the pocket and could freely diffuse out of the periodontal pockets. With this formulation, Atsawasuwan[37] compared the clinical and microbiological effects between subgingival application of the AP gel and metronidazole gel as adjunct to scaling and root planing. They found that both treatments improved clinical and microbiological parameters. Regarding microbiological findings, both treatments induce a significant shift in subgingival bacteria composition to be similar to the healthy patients. However, the AP gel tended to improve the disease condition faster than the metronidazole gel. Proportions of the black-pigmented anaerobes were also significantly reduced in the AP gel group, but not in the metronidazole gel group. The investigator suggested that AP gel could be used as an adjunctive treatment in chronic periodontitis, but its viscosity has to be improved. Later Narakorn38 improved the gel preparation by excluding the chlorophyll. The colorless AP gel was found to have the same antimicrobial activity against *P. gingivalis* as the former extract.

Boonchaipanichwatana[39] compared the clinical and microbiological effects of minocycline ointment and AP gel as an adjunct in the treatment of aggressive periodontitis. Both AP gel and minocycline ointment had similar effects in the reduction of probing pocket depth (PPD). In addition, significant improvement in PPD of the AP gel and minocycline ointment group was found when initial PPD were greater than 7 mm, when compared to scaling and root planing alone. Moreover, the AP gel group also demonstrated more consistent increased percentage of cocci and decreased in percentage of motile rods when compared to the 2% minocycline gel group throughout 4 months.

Chanarat[40] studied the effect of scaling and root planing with adjunctive administration of AP gel on bacterial lipids containing 3-hydroxy-15-methylhexadecanoic acid (3-OHiC17:0) on the root surface and in subgingival plaque in chronic periodontitis. It was found that bacterial lipid containing 3-OHiC17:0 from plaque and calculus-root surface penetrate the adjacent gingival tissue which could stimulated prostaglandin, leach to contribute to the periodontal destruction process. The AP gel used in combination with root planing and root planing alone were effective in decreasing bacterial lipid containing 3-OHiC17:0 on root surface and in subgingival plaque. But AP gel alone was only reduced bacterial lipid containing 3-OHiC17:0 on the root surface. Microbiological study revealed that no significant decrease in number of pigmented anaerobes in all groups. Two studies investigated the concentration of AP gel in periodontal pocket of periodontitis patients after applying the AP gel following root planing[41-42]. They determined the concentration of andrographolide which was a major constituent of the AP gel by using High Performance Liquid Chromatography. The results demonstrated that mean concentrations of AP gel in periodontal pocket after 3 hours and 6 hours loading were significantly less than that of 1 hour. AP gel concentrations were more than minimum inhibitory concentration (MIC) in all samples after 1 hour, 57.14% of samples at 3 hours and at 6 hours there was 52.38 % of teeth that retained the mean andrographolide concentration (537.708 µg/ml) more than MIC. After 24 hours, there was only one tooth from 15 teeth that could detect andrographolide from gingival crevicular fluid and its concentration was 201.964 µg/ml which was lower than MIC.

Sirirat[43] studied the effect of subgingival application of AP gel as an adjunct to scaling and root planing in the treatment of three periodontitis patients. The results revealed that all clinical parameters, i.e., probing depth, probing, clinical attachment level, bleeding on probing and gingival index, were improved. In addition, radiographic examination at 3 and 6 months following gel application revealed evidence of coronal radiopaque fill in the AP gel treated site.

Hamasakwattanakul[44] investigated the cytotoxicity of AP gel on human periodontal ligament fibroblast and its effect on the migration of these cell. It was found that AP gel at concentration of 5.625 mg/ml resulted in almost 100% cell death. At non-toxic concentration of AP gel, below 1.125 mg/ml, the attachment, chemotaxis and migration of fibroblast were observed. The number of attachment cell on dentin surface at the concentration of 1.125 mg/ml AP gel was more than control group but not statistically significant difference. The number of chemotaxis cells responded to the concentration of 0.5625 mg/ml AP gel was more than that of 0.75 mg/ml and 1.125 mg/ml AP gel, respectively. In dentin migration assay, the number of migrating cells at the concentration 0.5625 mg/ml and 0.75 mg/ml were more than control group. When comparing migrating distances, cell exposed to AP gel at the concentration of 0.5625 mg/ml was migrate more than the control group. The result from this study concluded that AP gel at the concentration 0.5625 mg/ml showed the most significantly enhanced effect on the number and distances of migration of human periodontal ligament fibroblast on dentin slab and strongly suggested that AP gel has beneficial effect on periodontal ligament cells growth and migration in vitro.

Taken together, the use of AP gel as an adjunct to scaling and root planing exhibited the improvement of periodontium condition by promoting wound healing and reducting bacterial virulence factors that involved in pathogenesis of periodontal disease.

Suwalee[45] studied the clinical and microbiological outcomes of locally delivered AP gel as an adjunct to scaling and root planing in the treatment of chronic periodontitis. Results showed the clinical outcomes of the scaling and root planing plus AP gel-treated sites showed a significant improvement ($p < 0.05$)

Discussion

Recently AP gel containing *Andrographis paniculata*, a medicinal plant with antimicrobial activity has been formulated[38] and used locally in periodontal pocket. Although several studies showed the benefit of AP gel[37,39,43], at least one clinical study had failed to show the significant benefit of AP gel[36]. This might be due to the rapid diffusion of the gel that had low viscosity resulting in low concentration of the active ingredient below the therapeutic levels. But Suwalee[45] studied the efficiency of new formula AP gel with increased viscosity was evaluated by assessing clinical and microbiological parameters at disease sites.

Clinical studies[41-42] investigating the concentration of AP gel in gingival crevicular fluid showed that at 24 hours after loading, andrographolide could be detected in the periodontal pocket of only one tooth from 15 teeth at the concentration of 201.964 µg/ml which was lower than MIC. Kuphasuk[46] examined the concentration of andrographolide in gingival crevicular fluid, saliva and blood plasma after application of AP gel into the periodontal pocket following treatment. They found that andrographolide could be detected in gingival crevicular fluid at 24 hours, only two cases from 12 cases still had andrographolide at the concentration of 0.969 ± 2.9638 µg/ml (< MIC). The andrographolide in saliva were found up to 1½ hours at the concentration of 0.274 ± 0.5354 µg/ml. It could not be detected in the blood plasma. These studies presented that AP gel did not sustain in periodontal pocket for a long time. It is not surprised that *P. gingivalis* could be recolonizd in the pocket treated with AP gel after treatment 1 or 3 months[45].

The clinical outcomes of AP gel showed the better improvement of periodontium. The beneficially clinical effects of the AP gel might be explained by the ability to induce the attachment, chemotaxis and migration of human periodontal ligament fibroblast[44], resulting in wound healing. In addition, the effect of AP gel on reparing periodontium was demonstrated by its ability to enhance alkaline phosphatase activity and induce mineralized nodule formation in gingival tissue, suggesting that AP gel can promote the differentiation of human PDL cells into bone-forming cells[47]. Furthermore, Sirirat[43] revealed that AP gel can improve the bone fill in the periodontal defects at 3 and 6 months after loading AP gel. Results of previous study clearly showed that AP gel as an adjunct to scaling and root planing improved the clinical parameters of the periodontitis when compared to the SRP only. These suggest that AP gel has benefit as an adjunct to scaling and root planing for treatment periodontal disease.

Since the AP gel is a Thai product which is not widely-known at this moment, therefore, this review article aimed to educate medical professionals about the AP gel. Regarding its therapeutic efficacy, further study of the AP gel is still in need. The users' instruction provides more detailed information. Allergic reactions were not observed in these clinical trials. The AP gel has to be applied for external use only.

Conclution

Recently the local drug delivery system containing an antimicrobial traditional herb, *Andrographis paniculata*, has been developed as an adjunct to scaling and root planning. The *Andrographis paniculata gel* (AP gel) has been shown to reduce probing depth and coronal radiopaque fill in the AP gel-treated sites at 3 and 6 months. The local application of AP gel as an adjunct to scaling and root planing showed better improvement of clinical parameters. Which indicated the benefit of AP gel as an adjunctive treatment in chronic periodontitis.

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