Review

Commercial Local Pharmacotherapeutics and Adjunctive Agents for Nonsurgical Treatment of Periodontitis: A Contemporary Review of Clinical Efficacies and Challenges

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Abstract: Periodontal infections tend to be site-specific, mostly confined to the periodontal pocket. With the surge of antibiotic-resistant bacteria, the trend is shifting towards other therapeutic modalities, especially locally delivered approaches that include other pharmacotherapeutic drugs and medical devices. This narrative review aimed to provide insights into the clinical efficacy of local drug delivery and adjunctive agents used in nonsurgical management of periodontitis. Electronic (PubMed/MEDLINE, CENTRAL, and EMBASE) and bibliographic searches of past systematic reviews were carried out to identify previous publications on the topic. Only relevant literature and randomized controlled trials published in English were selected. In addition, a literature review was developed based on the selected articles. Experimental drugs or agents were excluded. This review highlights the clinically proven and commercially available therapeutic agents related to the management of periodontal disease with comparisons of their clinical efficacies and challenges. A vast array of commercial local pharmacotherapeutic agents had been clinically tested, but the methodologies and clinical results varied within and between each agent used, causing difficulty in drawing conclusions and providing support to the superiority of one agent over another. Considering the benefit–cost ratio with the modest clinical results, the long-term usefulness of these agents remains debatable.

Keywords: periodontitis; anti-infective agents; local; anti-bacterial agents; periodontal debridement; periodontal pocket

1. Introduction

Periodontitis is defined as an inflammatory disease of the periodontium with progressive destruction of tooth-supporting tissues. Accumulation of dental biofilm on the tooth surface [1] will trigger the imbalance between oral commensal microorganisms and host defense [2] in a susceptible individual, leading to the development of periodontitis under suitable conditions of bacterial environment and specific periodontopathogens. Several risk factors, such as tobacco smoking [3,4], host genetic variations [5,6], and certain systemic conditions [7,8], can also influence the progression and severity of periodontitis [9]. If left untreated, periodontitis may lead to tooth loss, causing substantial functional and aesthetic and psychological impact to the affected individuals [10].

Over 90% of the general world population are estimated to be suffering from a certain form of periodontal disease [11]. The recent Global Burden of Disease Study [12] ranked severe periodontitis...
as the 11th most prevalent disease, affecting 10.5% or 750 million people worldwide. Given that periodontitis involves microbial etiology and pathogenesis related to inflammation, pharmacologic approaches based on antimicrobials [13], probiotics [14,15], natural products [16,17], and host modulation [18] have garnered considerable research interest in the past three decades. The Acute Market Reports [19] revealed that the global periodontal therapeutics market, which was valued at US$259.5 million in 2016, would expand at a compound annual growth rate of 9.2% and is expected to reach US$580.5 million by the year 2025. With 30.4% of the global population smoking daily [20], combined with the rising diabetes epidemic [21], these established risk factors are likely to increase the periodontitis incidence and further drive the global periodontal therapeutics market.

Reviews on local drug delivery (LDD) systems are abundant. However, they focus on antimicrobials. With the advent of the new periodontal classification that had merged both chronic and aggressive periodontal disease entities together [22], this contemporary literature review aimed to provide an overview of the local drug delivery and adjunctive agents (LDA) used in periodontal treatment and highlight the clinically proven and commercially available therapeutic agents related to the management of periodontal disease with comparisons of their clinical efficacies and the challenges of their application.

2. Classification of LDA for Nonsurgical Periodontal Therapy

LDD into periodontal pockets had been classically categorized as nonsustained-, sustained-, or controlled-release subgingival delivery [23,24]. With the introduction of adjunctive agents, including medical devices, we attempted to classify them, as illustrated in Figure 1.

![Figure 1. Classification of commercially available local drug delivery and adjunctive agents (LDA) for nonsurgical periodontal therapy.](image)

Nonsustained delivery commonly provides immediate release of the active agent by means of subgingival irrigation. Despite being categorized as LDD agents, mouthwash and supragingival irrigations cause no direct effect on subgingival microorganisms as they show no penetration of the gingival crevice or periodontal pockets [25]. Sustained-released devices are designed to carry high concentration of agents into periodontal pockets for a short duration (less than 24 h). By contrast, controlled delivery systems should be able to retain the active agent over an extended time period (more than 24 h) within the periodontal pockets [26].
A medical device is defined by the U.S. Food and Drug Administration (FDA) [27] as ‘an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related articles, including a component part or accessory’ used in the diagnosis, treatment, or prevention of disease or other conditions or intended to affect the body’s structure or function not by the primary metabolism and chemical action within the body. To date, the adjunctive agents registered as medical devices under FDA include hyaluronic acid and enamel matrix derivatives (EMDs). In addition, antimicrobial photodynamic therapy contains both drug and medical device components.

3. Indications for the Use of LDA in Periodontal Treatment

Enhanced patient compliance, improved efficacy, and few side effects have favored the use of local antimicrobials [28]. Evidently, LDD systems offer no advantages as a monotherapy [29]. Matesanz-Perez et al. [30] conducted a systematic review and meta-analyses on clinical studies evaluating the outcomes of locally delivered antimicrobials and found a statistically significant \( p = 0.000 \) overall probing pocket depth (PPD) reductions and clinical attachment level (CAL) gains of 0.407 and 0.310 mm, respectively, when used as adjuncts to scaling/root planning (SRP) compared with mechanical debridement alone.

Although one may find the resultant clinical parameters unremarkable, local antimicrobials have been advocated for local nonresponding or recurrent sites during supportive periodontal therapy [31], the presence of residual pockets in the aesthetic zone, in which surgery may compromise aesthetics or phonetics, and persistent bleeding pockets in the intrabony sites [32,33]. High-risk groups, such as smokers, diabetics, or those with erratic oral hygiene compliance and patients with relative or absolute contraindications to surgical intervention possibly benefit from the adjunctive effect of LDD [13,34,35].

4. Pharmacotherapeutic Agents Used as Local Adjuncts

A search was conducted using the PubMed/MEDLINE, CENTRAL, and EMBASE databases to identify any randomized controlled and professionally applied LDA used in healthy human intervention studies for treatment of periodontitis. The search considered works published from 1979 until November 2019 by using the keywords ‘periodont *’, ‘antimicrobial’, ‘photodynamic therapy’, ‘hyaluron *’, ‘enamel matrix derivative *’, ‘chlorhexidine’, ‘tetracycline’, ‘minocycline’, ‘metronidazole’, ‘doxycycline’, ‘non-surgical’, ‘scaling and root planing’, ‘adjunct’, ‘subgingival’, and ‘local delivery’. Bibliographies from previous systematic reviews on LDA were scrutinized [29,30,36–38]. Only relevant literature in English from electronic search were selected for the present review. The LDA had to be used as an adjunct and compared to a mechanical debridement control or placebo group. The use of systemic antimicrobials, banned, discontinued, and experimental drugs and agents were excluded. Search results were presented in accordance to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Figure 2).

Subsequent paragraphs include details on commercially available LDA reported in literature, with their clinical efficacies being based on the longest follow-up studies, as summarized in Table 1. Quantitative analysis was performed based on changes in PPD (Figure 3) and CAL (Figure 4) for the selected studies using RevMan 5.3 [39]. Risk of bias of included studies was presented as percentages in graph form (Figure 5). Six domains were assessed and judged as ‘low risk’, ‘unclear risk’, or ‘high risk’ of bias according to the Cochrane Handbook [40].
Figure 2. PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram.
Table 1. Summary of clinically tested commercial LDA for nonsurgical periodontal therapy based on longest follow-up period.

| Active Agent | Brand | Manufacturer | Dosage | Delivery Vehicle | Application and Duration (per Manufacturer/Study Design) | Longest Follow-Up Study | Authors | Study Design | Sample Size |
|--------------|-------|--------------|--------|------------------|--------------------------------------------------------|------------------------|---------|--------------|-------------|
| Chlorhexidine | Chlo-Site® | Ghimas Company, Italy | 1.5% CHX | Gel | 1 application 15 days treatment | 6 months | Paolantonio et al. 2009 [41] | Split-mouth | 98 |
| | Kranti et al. 2010 [42] | Split-mouth | 10 |
| | Jain et al. 2013 [43] | Split-mouth | 30 |
| | Matesanz et al. 2013 [44] | Parallel | 22 |
| | Jeffcoat et al. 1998 [45] | Parallel | 419 |
| | Grisi et al. 2002 [46] | Parallel | 20 |
| | Carvalho et al. 2007 [47] | Split-mouth | 28 |
| | Periochip® | Perio Products Ltd., Jerusalem, Israel | 2.5 mg CHX gluconate | Chip | 1 application 7 days treatment | 9 months | Jurco et al. 1998 [45] | Parallel | 419 |
| | Carvalho et al. 2007 [47] | Split-mouth | 28 |
| | PerioCol®-CG | Eucare Pharmaceuticals Ltd., Chennai, India | 2.5 mg CHX gluconate | Chip | 1 application 7 days treatment | 12 months | Reddy et al. 2016 [48] | Parallel | 48 |
| | EC40® | Biodent BV, Nijmegen, The Netherlands | 35% CHX diacetate | Varnish | 1 application 7 days treatment | 9 months | Cosyn et al. 2006 [49] | Parallel | 26 |
| Doxycycline | Atridox® | Atrix Laboratories, Fort Collins, CO, USA | 10% DOXY hyclate | Gel | 1 application 7 days treatment | 36 months | Bogren et al. 2008 [50] | Parallel | 132 |
| | Metronidazole | Elyzol® | Dumex, Copenhagen, Denmark | 25% MET benzolate | Gel | 2 applications 7 days treatment | 12 months | Buduneli et al. 2001 [51] | Split-mouth | 18 |
| | Arestin® | OraPharma, Inc., Warminster, PA, USA | 1 mg MINO hydrochloride | Micro-spheres | 1 application 14 days treatment | 24 months | Cortelli et al. 2008 [52] | Parallel | 30 |
| | Killeen et al. 2018 [53] | Parallel | 55 |
| | Minocycline | Dentomycin® | Lederle Dental Division, Gosport, Hampshire, UK | 2% MINO hydrochloride | Ointment | 3–4 applications 14 days treatment | 18 months | Timmerman et al. 1996 [54] | Parallel | 20 |
| | Periodontal Plus AB™ | Sunstar Corp., Tokyo, Japan | | | | | |
| | Tetracycline | Emdogain® | Institute Straumann AG, Basel, Switzerland | 30 mg/mL porcine enamel matrix derivative | Gel | 1 application 7 days treatment | 12 months | Mombelli et al. 2005 [55] | Split-mouth | 16 |
## Table 1. Cont.

| Active Agent   | Brand                 | Manufacturer                                      | Dosage                              | Delivery Vehicle | Application and Duration (per Manufacturer/Study Design) | Longest Follow-Up Study | Authors                          | Study Design | Sample Size |
|----------------|-----------------------|---------------------------------------------------|-------------------------------------|------------------|-----------------------------------------------------------|--------------------------|----------------------------------|--------------|--------------|
| **Hyaluronic acid** |                       |                                                   |                                     |                  |                                                           |                          |                                  |              |              |
| Hyaluronic acid| Aftamed®              | BioPlax Limited, London, UK                        | 240 mg/100 g sodium hyaluronate    | Gel              | 1 application                                             | 6 weeks                  | Omer at el. 2018 [56]            | Split-mouth | 33           |
|                | Aminogam®             | Errekappa Euroterapici, Spa, Italy                | Sodium hyaluronate, amino acids    |                  | 1 application                                             | 3 months                 | Bevilacqua et al. 2012 [57]      | Split-mouth * | 11           |
|                | Gengigel®             | Ricerfarma, Italy                                 | 0.2% and 0.8% sodium hyaluronate   |                  | 1 application                                             | 6 months                 | Eick et al. 2013 [58]            | Parallel *   | 42           |
|                | Healon GV®            | Pharmacia and Upjohn, Uppsala, Sweden.            | 14 mg/mL sodium hyaluronate        |                  | 3 applications                                           | 27 days treatment       | Engström et al. 2001 [59]        | Split-mouth * | 9            |
|                | EmunDo®               | A.R.C. laser GmbH, Germany                        | Indocyanine green (iodide-free)    |                  | 2–4 applications                                         | 3 months                 | Birang et al. 2015 [60]          | Split-mouth  | 20           |
|                |                       |                                                   |                                     |                  | 14–27 days treatment                                      |                          | Monzavi et al. 2016 [61]         | Split-mouth * | 25           |
| **Photosensitiser** |                       |                                                   |                                     |                  |                                                           |                          |                                  |              |              |
| Photosensitiser| HELBO®                | Bredent Medical, Germany                          | Phenothiazine chloride             | Dye Solution     | 1 application                                             | 12 months                | Lulic et al. 2009 [62]           | Parallel     | 10           |
|                | Periowave™            | Periowave Dental Technologies Inc, Canada         | Methylene blue                     |                  | 1–3 applications                                          | 6 months                 | Alwaeli et al. 2015 [63]         | Split-mouth * | 21           |
|                |                       |                                                   |                                     |                  |                                                           |                          | Petelin et al. 2015 [64]         | Parallel *   | 27           |
|                |                       |                                                   |                                     |                  |                                                           |                          | Tabernski et al. 2017 [65]       | Parallel     | 48           |
|                |                       |                                                   |                                     |                  |                                                           |                          | Berakdar et al. 2012 [66]        | Split-mouth  | 22           |
|                |                       |                                                   |                                     |                  |                                                           |                          | Muller Campanele et al. 2015 [67]| Split-mouth * | 28           |
| Photosensitiser| Fotosan®              | CMS Dental, Copenhagen, Denmark                   | Toluidine blue/tolonium chloride   |                  | 1–3 applications                                          | 6 months                 | Goh et al. 2017 [68]             | Split-mouth  | 27           |

CHX: Chlorhexidine; MINO: Minocycline; DOXY: Doxycycline; MET: Metronidazole; TET: Tetracycline. * Repeated application.
Figure 3. Meta-analysis of studies on changes in probing pocket depth (PPD) for control (mechanical debridement alone) versus use of adjuncts, sub-grouped by agent, based on random effects model; mean difference in units of millimeters.
Figure 4. Meta-analysis of studies on changes in clinical attachment level (CAL) for control (mechanical debridement alone) versus use of adjuncts, sub-grouped by agent, based on random effects model; mean difference in units of millimeters.
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4.1. Tetracycline

The first controlled-release LDD system to treat periodontitis, a device that included hollow fibers made of cellulose acetate containing tetracycline, was developed by Goodson and colleagues in 1979 [69]. With their bacteriostatic antimicrobial properties that inhibit bacterial protein synthesis, tetracyclines exhibit high substantivity to root surfaces [70] and periodontal pocket hard tissues [71,72]. However, a significantly long exposure time is required compared with other agents [73].

**Fibers:** Actisite® tetracycline fiber (ALZA Corporation, Palo Alto, CA, USA) was the first commercially available controlled-release LDD introduced in 1994. This substance is nonresorbable but biologically inert and packaged as a 0.5 mm diameter ethylene and vinyl acetate copolymer imbued with 25% w/w tetracycline which is equivalent to 12.7 mg tetracycline hydrochloride. The active drug can be maintained at a constant concentration in the gingival crevicular fluid (GCF) in excess of 1300 µg/mL over a period of 10 days [71] compared with 8 µg/mL in systemic administration [74].

Despite its clinical efficacy, fiber insertion was found to be complicated and time consuming, requiring 7–10 min for application [75] and with specific transient gingival redness observed upon removal [76]. In a five-year controlled clinical trial, Wilson and co-workers [77] reported no significant differences between treatments compared with their preliminary six-month data, demonstrating that adjunctive tetracycline fiber therapy featured better clinical parameters than SRP alone. This finding suggests that combination therapy may only provide temporal initial advantages. Following the development of other new biodegradable agents, the fibers were subsequently discontinued in 2003 [78,79].

Periodontal Plus AB™ (Advanced Biotech Products, Chennai, India) is a bioresorbable tetracycline fiber developed based on a collagen film system. The substance is available in vials containing 25 mg fibrillar collagen impregnated with 2 mg tetracycline hydrochloride. Application of this fiber removes the need of a second appointment for fiber removal because it biodegrades within the pocket [80]. However, a 12-month study conducted using the product reported insignificant clinical benefits [48].

4.2. Doxycycline

Doxycycline and minocycline are second-generation semisynthetic derivatives of tetracycline that exhibit superior antimicrobial activities compared with its predecessors, which include strains of tetracycline-resistant bacteria, owing to their improved binding properties and good absorption with prolonged duration of action [81].

**Gels:** Atridox® (Atrix Laboratories, Fort Collins, CO, USA) is the first FDA-approved resorbable doxycycline gel system; it is composed of two syringes of powder and liquid that are mixed together...
with 25 times of repetition. With its capability to down-regulate matrix metalloproteinase [18], the 10\% doxycycline hyclate thixotropic gel solidifies upon contact with the tissue fluid, and doxycycline levels can remain above 1000 µg/mL for 18 h in the GCF [82]. Studies have shown that doxycycline had persisted above the minimum inhibitory concentration (MIC) for periodontal pathogens (6.0 µg/mL) at local site for seven days, and 10–20 mg/mL of the detected drug was still observed at 3–5 days post-polymer removal [83]. A study conducted over a period of three years revealed improved clinical outcomes at three months; however, the findings failed to last until one year of follow-up examination, indicating that repeated annual application of doxycycline showed no long-term clinical and microbiological effect beyond mechanical debridement alone [50].

4.3. Minocycline

**Microsphere:** Minocycline in the form of microspheres, Arestin® (OraPharma, Inc., Warminster, PA, USA) was FDA-approved in 2001. Each syringe contains 4 mg of 20–60 µm diameter biodegradable microspheres, equivalent to 1 mg minocycline base in a poly (glycolide-lactide) carrier [84]. Initially in powder form, the polymer will hydrolyze immediately upon contact with GCF and adhere to the periodontal pocket. Administration will result in sustained release of minocycline concentration of 340 µg per mL through 14 days, exceeding the MICs for periodontopathogens [85]. Cortelli et al. [52] and Killeen et al. [53] failed to demonstrate that subgingival minocycline treatment enhances results of mechanical debridement in the long-term despite repeated application with three-month application in the former and six months in the latter over 24 months.

**Ointment:** Dentomycin® (Lederle Dental Division, Gosport, Hampshire, UK) and Periocline® (Sunstar, Osaka, Japan) are both biodegradable minocycline 0.5 mg ointments consisting of 2% minocycline hydrochloride (10 mg minocycline) in a matrix of hydroxyethyl cellulose, aminoalkyl methacrylate, triacetine, and glycerine. In a controlled 18-month clinical trial involving subjects with moderate to severe chronic periodontitis, repeated intermittent subgingival application of the gel provided no benefits to the subjects [54]. The authors suggested that the negative results were due to their optimal oral hygiene instruction and reinforcement, wherein other protocols were not emphasized.

4.4. Chlorhexidine

In addition to its immediate bactericidal action and prolonged bacteriostatic action on the tooth surface [86], chlorhexidine is a broad-spectrum antiseptic, which features a large dicaticionic molecule at physiological pH; this property enables chlorhexidine to bind to the bacterial cell wall and different surfaces within the mouth, with its substantivity maintaining antibacterial activity up to 12 h [87,88].

**Irrigation solution:** Various concentrations of chlorhexidine (0.02% to 0.2%) had been used in clinical studies. Two systematic reviews compared chlorhexidine subgingival irrigation as an adjunct to mechanical instrumentation, but both found no additional benefit to SRP alone [37,89]. The possible reasons for this finding could be the rapid clearance of the drug from the site due to constant GCF outflow [90] and/or the use of ineffective concentrations, which are further reduced in the pocket due to the high affinity of chlorhexidine for blood and salivary proteins [91–93].

**Chip:** A commercial FDA-approved biodegradable controlled-release chip containing 2.5 mg chlorhexidine gluconate in a gelatin matrix is sold under the trade name Periochip® (Perio Products Ltd., Jerusalem, Israel). The small chip measuring 4.0 mm × 5.0 mm × 0.35 µm releases chlorhexidine in a biphasic manner, with an initial peak of 2007 µg/mL within 2 h in the GCF post-insertion followed by maintenance of high concentrations (above 1000 µg/mL) for the following 96 h and complete biodegradation between 7 and 10 days after insertion [94]. An alternative form called Periocol®-CG (Eucare Pharmaceuticals Pvt. Ltd., Chennai, India) incorporates 2.5 mg chlorhexidine into a collagen membrane chip derived from fresh water fish [95]. Currently, no study compares the two chips within the same clinical trial. The use of chlorhexidine chips resulted in improved clinical parameters in a nine-month study by Jeffcoat et al. [45] and in a 12-month study by Reddy et al. [48]. However, Carvalho et al. [47] and Grisi et al. [46] observed no clinical nor microbiological effect beyond conventional SRP
over nine months. When grouped together, a weighted mean difference (WMD) of 0.24 mm in PPD reduction and 0.19 mm in CAL gain were observed.

**Gel:** Chlo-Site® (Ghimas s.p.a., Casalecchio di Reno, Italy) is a xanthan-based chlorhexidine gel containing a combination of 0.5% chlorhexidine digluconate and 1.0% chlorhexidine dihydrochloride. The carrier comprises of a saccharide polymer, which can increase liquid viscosity, providing it with mucoadhesive property to stick to the pocket [96]. Although Jain et al. [43] reported that xanthan gel treatment group promoted good improvement of bleeding score and pocket depth reduction until six months after treatment, Matesanz et al. [44] found limited improvement in clinical outcomes with no significant difference between groups in their six-month study. A WMD of 0.56 mm in PPD reduction and 0.53 mm in CAL gain were seen from our review.

**Varnish:** Although widely used in caries prevention, chlorhexidine varnish also shows value in treating periodontal disease. A nine-month study by Cosyn et al. [49] reported a 0.62–1.06 mm reduction in pocket depth with application of EC40® (Biodent BV, Nijmegen, The Netherlands), a highly concentrated solution of 35% chlorhexidine diacetate in 37% alcohol base stabilized by 27% sandarac, a naturally occurring resin. BioC® (Biodent BV, Nijmegen, The Netherlands) is another variant of the varnish in supersaturated concentration of 20% chlorhexidine diacetate [97]. Both drugs are packaged in a syringe containing 1.5 mL agent. A different varnish, Cervitec® Plus (Ivoclar/Vivadent AG, Schaan, Liechtenstein) comprising 1% chlorhexidine (equivalent to 10 mg/mL chlorhexidine) and 1% thymol in a viscous polyvinyl butyral base, was found to reduce anaerobic bacterial count within the periodontal pocket for up to three months with multiple applications [98,99].

### 4.5. Metronidazole

Whenever antibiotics are considered for use in periodontal therapy, metronidazole has often been the drug of choice owing to its bactericidal activity against obligate anaerobes by inhibiting DNA synthesis [100].

**Gel:** Elyzol® (Dumex, Copenhagen, Denmark) is a licensed drug that consists of 40% metronidazole benzoate in an oil-based (glyceryl mono-oleate and sesame oil) mixture which is slowly disintegrated by GCF enzymes into 25% metronidazole [101]. Upon subgingival application of the drug with a syringe applicator, it initially liquefies at body temperature and then changes to a highly viscous semisolid state upon contact with GCF [101]. According to Stoltze [102], metronidazole concentration above 1 µg/mL can be measured in the periodontal pocket up to 36 h, with concentrations above MIC₅₀ for susceptible periodontopathogens 24 h after administration without any systemic side effects [103]. Buduneli et al. [51] showed an average reduction of 3.2 mm in PPD and mean CAL gain of 2.1 mm for scaling plus adjunctive metronidazole gel, but was not superior to that of conventional periodontal therapy.

### 4.6. Povidone–Iodine

Iodine utilization is well known in the world of medicine for its broad-spectrum bactericidal efficacy including periodontopathogens [104].

**Irrigation solution:** Sahrmann et al. [105] observed that the adjunctive use of povidone–iodine to SRP resulted in a minimally statistical additional benefit of 0.28 mm reduction in PPD with no reported adverse side effects. No correlation was observed between the clinical results and antiseptic concentrations, which had ranged from 0.1% to 10%, possibly because the antibacterial action of the drug increases with the dilution degree [106]. Thus, maximum bactericidal effect could still be achieved despite dilution of highly concentrated preparations by GCF and blood in the pocket. However, certain studies have reported no evidence of effectiveness with adjunct use of povidone–iodine subgingival irrigation [107–109].
4.7. Sodium Hypochlorite

Sodium hypochlorite is the most prominent chlorine used in dentistry especially in endodontic therapy [110]. The antiseptic agent, which is easily accessible and inexpensive, exhibits broad-spectrum antimicrobial activity that inhibits bacterial enzymes [111].

**Irrigation solution:** A study by Bizzarro et al. [112] reported that a single episode of 0.5% sodium hypochlorite subgingival irrigation showed no significant clinical and microbiological improvement compared with mechanical therapy alone.

4.8. Natural Products

**Gel:** NBF Gingival Gel (NanoCureTech Co., Ltd., Seoul, South Korea) is a nanoemulsion gel with ingredients of vitamin C, vitamin E, propolis, aloe, and green tea extract, with claims of being an antibacterial, anti-inflammatory, and anti-oxidative. Debnath et al. [113] reported a statistically significant improvement in periodontal PPD and CAL at three months post-application compared with mechanical therapy alone with a difference of 0.74 and 0.71 mm, respectively, between both groups. However, it was the only study that utilized the gel as adjunct for periodontitis treatment with six participants therefore its efficacy is debatable.

4.9. EMD

Enamel matrix proteins were demonstrated in clinical studies as being secreted from Hertwig’s epithelial root sheath; therefore, they can promote new periodontal attachment formation [114–116]. Extracted from purified porcine embryonal enamel, the proteins were renamed as EMDs, and they have been broadly used in periodontal regenerative surgery to treat intrabony, furcation, and recession defects [117]. EMD is assumed to mimic the role of enamel matrix proteins in cementogenesis by inducing new cementum formation and stimulating matrix deposition on native cementum [118,119].

**Gel:** Emdogain® (Institute Straumann AG, Basel, Switzerland) is a gel containing 30 mg/mL EMD in a propylene glycol alginate carrier, which is available as 0.15, 0.3, and 0.7 mL syringes. The amelogenin content precipitates when in contact with physiological pH and body temperature, forming an insoluble protein layer on the root surface that remains for up to four weeks [120]. Three randomized controlled clinical studies compared the adjunctive use of EMD with the nonsurgical periodontal therapy [55,121,122]. Although the previous two studies reported no significant additional benefits with EMD, Graziani et al. [122] observed that application in deep pockets (≥6 mm) resulted in low D-dimer levels, indicating lower fibrinolysis and better periodontal healing of periodontal pockets compared with mechanical debridement alone. However, more studies would be needed to confirm its efficacy as an adjunct in the nonsurgical treatment of periodontitis for only one study had a long-term follow-up [55].

4.10. Hyaluronic Acid

Hyaluronan, a high-molecular-weight glycosaminoglycan, is an important constituent of the extracellular matrix of mineralized and nonmineralized tissues and particularly abundant in the nonmineralized component of periodontium [123,124]. In periodontal disease, the high-molecular-weight hyaluronan synthesized in the periodontal tissue undergoes massive degradation, transforming into its low molecular form as a result of bacterial enzyme action (hyaluronases) [125–127]. Thus, topical application of hyaluronan to inflamed periodontal sites was deemed to possess potential in inducing periodontal healing due to its role as a key element in wound repair [128,129].

**Gel:** Several commercial brands have been clinically tested for use in periodontal disease; these brands include Healon GV® (Pharmacia and Upjohn, Uppsala, Sweden), which is available in 0.85 mL syringes containing 14 mg/mL sodium hyaluronate derived from rooster’s comb [59]; Aminogam® (Errekappa Euroterapici, Spa, Italy) contains non-animal origin sodium hyaluronate combined with a pool of synthetic amino acids [57]; Aftamed® (BioPlax Limited, London, UK) includes 240 mg/100 g
synthetic sodium hyaluronate [56]; Gengigel® (Ricerfarma S.r.l., Milano, Italy), which contains sodium hyaluronate is derived from bacterial fermentation (Streptococcus equi) at concentrations of 0.2% [130] and 0.8% [58,131]. Their mucoadhesive properties are derived from polyacrylic acid crosslinked with a divinyl glycol (polycarbophil) carrier. WMD of 0.49 mm PPD reduction and 0.25 mm CAL gain were demonstrated based on four studies [56–59].

4.11. Antimicrobial Photodynamic Therapy (aPDT)

aPDT is an emerging trend in dentistry. This procedure utilizes a locally applied photosensitizer that is absorbed by bacteria, and upon irradiation with a specific wavelength light source, the photosensitizer would be activated and generate a cytotoxic singlet and triplet oxygen that disintegrates bacterial membranes [132,133]. aPDT applications have been shown to reduce microbial load [134,135], and studies have revealed that aPDT can be beneficial and relatively safe to adjunctively treat periodontitis [136,137]; however, whether aPDT could replace the use of antimicrobials remains inconclusive [138,139].

Dye solution: Several different types of photosensitizers, including methylene blue [66,67], toluidine blue [68], phenothiazine chloride [62–65], and indocyanine green [60,61], were studied for periodontal therapy use. All these dyes possess bactericidal properties and differ in their activation wavelength; therefore, the choice of photosensitizers is dependent on the light source used [140,141]. Commercial diode laser systems marketed for aPDT adjunctive use in periodontal therapy usually carry their own compatible photosensitizer dyes. Four commercially available aPDT systems demonstrated a WMD of 0.47 mm PPD reduction and 0.12 mm CAL gain in our review.

5. Occurrence of Adverse Effects with Use of LDA

While there are studies that observed no adverse events, safety and adverse effects with the use of LDA were often not reported in most of the studies. The few studies that described them included feeling of illumination of the eye with the use of laser [67], gingival tenderness after application of gel [54], experience of pain following therapy [49], dislodgment of chip after placement [47], gingival edema or abscesses [46], fever, headache, toothache, discomfort, and sensitivity [45].

6. Comparison of Clinical Efficacy between Different LDA

As documented, mechanical therapy alone is an effective treatment with long-term success in majority of affected individuals [142]. Although some individuals might respond inadequately to treatment, adjuncts may be pivotal in such cases, especially if surgical options are inapplicable. In general, all systematic reviews and meta-analyses that previously evaluated the efficacy of LDA systems had shown minimal but positive clinical results as adjuncts compared with mechanical therapy alone (summarized in Table 2).
### Table 2. Summary table of systematic reviews with meta-analyses comparing clinical efficacy of different LDA for nonsurgical periodontal therapy (scaling/root planning (SRP)).

| Author and Year (Ref.) | Study Period | Types of Studies | Treatment Arms | Weighted Mean Differences (WMD) (mm) [95% Confidence Interval (CI)] | Main Outcomes and Conclusion |
|------------------------|--------------|------------------|----------------|------------------------------------------------------------------|------------------------------|
|                        |              |                  |                | Probing Pocket Depth (PPD) | Clinical Attachment Level (CAL) * |
| Hanes and Purvis [37]  | ≥3 months    | 28 RCT, 2 CCT, 2 cohort | 1. CHX, 2.5 mg in gelatin matrix | 0.35 [n/a] | 0.16 [n/a] | 1. SRP alone showed sample-size adjusted mean reduction in PD of 1.45 mm (p = 0.002; CI = 0.56, 2.34), and adjusted mean gain in CAL was 0.89 mm (p = 0.001; CI = 0.55, 1.24). 2. Adjuncts WMD for PD reduction ranged from 0.06 mm to 0.51 mm. WMD for CAL ranged from −0.40 mm to 0.39 mm. 3. Significant PD reduction was reported for MINO gel and microencapsulated MINO. Significant CAL gain was observed in studies of CHX chip and DOXY gel. 4. All local CHX irrigation studies compared with SRP alone showed no additional benefits. 5. Adverse events were reported to be infrequent and minimal, with local effects of instrumentation and/or drug application contributing to majority of it. |
|                        |              |                  | 2. MINO, 2% gel or ointment; microencapsulated powder | 0.36; 0.26 (micro) [n/a] | 0.39; −0.40 (micro) [n/a] | |
|                        |              |                  | 3. DOXY, 8.5% in biodegradable matrix; 15% | 0.51 [n/a] | 0.34 [n/a] | |
|                        |              |                  | 4. MET, 5%; 25% gel | 0.06 [n/a] | 0.07 [n/a] | |
|                        |              |                  | 5. TET, 25% fiber | 0.21 [n/a] | −0.17 [n/a] | |
|                        |              |                  | 6. Sanguinarine, 5% gel | n/a | n/a | |
|                        |              |                  | 7. CHX, 2%, 12%, and 0.2% irrigation; ethyl cellulose | n/a | n/a | |
| Bonito et al. [38]     | No minimum duration | 50 RCT | 1. TET | 0.47 [0.22, 0.72] | 0.24 [0.07, 0.42] | 1. Adjunctive local antibiotics had PD reductions in the range of approximately 0.25 mm to 0.50 mm, and CAL gains in the range of approximately 0.10 mm to 0.50 mm. 2. The most promising adjunctive therapy by combining PD and CAL results were suggested to be local MINO, followed by local tetracycline. 3. Adverse events reported from these adjunctive therapies are relatively minor. 4. Whether the improvements are clinically meaningful is still doubtful. |
|                        |              |                  | 2. MINO | 0.49 [0.40, 0.58] | 0.46 [0.32, 0.60] | |
|                        |              |                  | 3. MET | 0.32 [0.20, 0.44] | 0.12 [0.01, 0.24] | |
|                        |              |                  | 4. CHX | 0.24 [0.13, 0.35] | 0.16 [0.04, 0.28] | |
|                        |              |                  | 5. Other antibiotics (DOXY; ofloxacin) | n/a | n/a | |
|                        |              |                  | 6. Other antimicrobials (amine fluoride; stannous fluoride; triclosan; hydrogen peroxide; povidone iodine; tetra-potassium perxy-diphosphate) | n/a | n/a | |
| Matesanz-Pérez et al. [30] | No minimum duration | 52 RCT | 1. CHX chip | 0.328 [0.447, 0.209] | 0.218 [0.329, 0.107] | 1. Statistically significant (p = 0.000) overall results was observed for both changes in PD (WMD 0.407 mm) and CAL (WMD 0.310 mm) 2. No significant differences were observed for bleeding on probing and plaque index. 3. Substantial benefit in PD reduction (WMD between 0.5 and 0.7 mm) demonstrated with subgingival application of tetracycline fibers, sustained released DOXY and MINO. 4. Minimal effect was observed with the local application of CHX and MET when compared with placebo (WMD between 0.1 and 0.4 mm). |
|                        |              |                  | 2. CHX varnish | 0.413 [0.655, 0.170] | 0.029 [0.550, −0.492] | |
|                        |              |                  | 3. CHX xanthan gel | n/a | 0.891 [0.914, 0.867] | |
|                        |              |                  | 4. DOXY | 0.573 [0.778, 0.367] | 0.218 [0.260, 0.176] | |
|                        |              |                  | 5. MET | 0.157 [0.303, 0.011] | −0.008 [0.091, −0.107] | |
|                        |              |                  | 6. MINO | 0.472 [0.520, 0.424] | 0.189 [0.251, 0.126] | |
|                        |              |                  | 7. TET fiber | 0.727 [0.759, 0.695] | 0.327 [0.552, 0.101] | |
|                        |              |                  | 8. TET strip | n/a | 0.463 [0.401, 0.163] | |
Table 2. Cont.

| Author and Year (Ref.) | Study Period | Types of Studies | Treatment Arms | Weighted Mean Differences (WMD) (mm) [95% Confidence Interval (CI)] | Main Outcomes and Conclusion |
|------------------------|--------------|------------------|----------------|---------------------------------------------------------------|-------------------------------|
|                        |              |                  |                | Probing Pocket Depth (PPD) | Clinical Attachment Level (CAL) * |
| Smiley et al. [29]     | ≥6 months    | 72 RCT           |                | 0.35 [0.15, 0.56] |                                                                 |
|                        |              |                  | 1. SDD         |                                                                     | 1. SRP alone had approximately 0.5 mm average improvement in CAL. |
|                        |              |                  | 2. Systemic antimicrobials | 0.35 [0.20, 0.51] | 2. A range of average CAL improvements between 0.2 and 0.6 mm was demonstrated in the combinations of assorted adjuncts compared with SRP alone. |
|                        |              |                  | 3. CHX chips    | 0.40 [0.24, 0.56] | 3. Moderate level of certainty for benefits in four adjunctive therapies compared with SRP alone: SDD, systemic antimicrobials, CHX chips and photodynamic therapy with a diode laser. |
|                        |              |                  | 4. DOXY hyclate gel | 0.64 [0.08, 1.28] |                                                                 |
|                        |              |                  | 5. MINO microspheres | 0.24 [−0.06, 0.55] | 4. Low level of certainty for benefits of the other included adjunctive therapies. |
|                        |              |                  | 6. PDT with diode laser | 0.53 [0.06, 1.00] |                                                                 |
|                        |              |                  | 7. Diode laser   | 0.21 [−0.23, 0.64] |                                                                 |
|                        |              |                  | 8. Nd:YAG lasers | 0.41 [−0.12, 0.94] |                                                                 |
|                        |              |                  | 9. Erbium lasers | 0.18 [−0.63, 0.98] |                                                                 |
| John et al. [36] *     |              | 61 RCT           | n/a            | n/a                | 1. Network meta-analysis identified DOXY hyclate and photodynamic therapy with diode laser as having the highest probabilities for ranking first and second SRP adjuncts in terms of CAL gain, respectively. |
|                        |              |                  |                |                    | 2. Adjuncts to SRP improved the response to SRP by 0.32 mm CAL over 6–12 months with no significant differences among the groups. |
|                        |              |                  |                |                    | 3. Evident publication bias was observed, and the lack of studies inflated the treatment effects by an estimated 20%. |

RCT: Randomized controlled trial; CCT: Case-controlled trial; n/a: not available; CHX: Chlorhexidine; MINO: Minocycline; DOXY: Doxycycline; MET: Metronidazole; TET: Tetracycline; SDD: sub-antimicrobial-dose doxycycline; Nd:YAG: Neodymium:yttrium-aluminum-garnet. * Negative (minus) sign indicates mean loss in CAL. * Network analysis of systematic review by Smiley et al. [29].
However, not all adjuncts showed additional benefits. Hanes and Purvis [37] reported no adjunctive advantage from the application of local subgingival antiseptic irrigants during or immediately after mechanical debridement, which is probably due to the rapid clearance by GCF flow [90]. Subsequent reviews excluded subgingival irrigation as a comparator; however, recent studies are still investigating their efficacy [112,143,144]. Thus, future meta-analyses should include these studies for clinicians to contemplate on their usage in their daily practice.

Most previous studies compared a single form of LDD against mechanical therapy rather than between other systems, and only a handful included more than one test group [145–148]. Many of these studies, including the recent ones, involved a short follow-up period of three months and less. Table 1 lists the longest duration of randomized clinical trials conducted for each LDA.

Smiley et al. [29] conducted the most comprehensive review to date on efficacy of adjuncts, with a recent supplement network analysis [36] determining that doxycycline hyclate gel and photodynamic therapy with diode laser featuring the greatest likelihood for CAL gain and with the results being retained until six months and beyond. With the aim of providing a companion evidence-based piece for the American Dental Association Clinical Practice Guidelines, the authors only included adjuncts available in the United States of America, therefore limiting the external validity of the review. Thus, the question of which LDA system is superior remains unanswered.

The authors had included both systemic and local adjuncts in their review. Comparing local and systemic antimicrobials might be inappropriate given that they feature their own indications and merits; however, the adjunctive benefits reported nearly similar clinical outcomes comparable with locally delivered antimicrobials, ranging from 0.2 mm to 0.8 mm PPD reduction and CAL gain when used to treat chronic periodontitis [29,149]. Several notable benefits of systemic antimicrobials use were observed in aggressive cases, with CAL gain of up to 1.0 mm after 12 months [149].

7. Use of LDA in Nonsurgical Treatment of Aggressive Periodontitis

The recent 2017 World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions had removed the term ‘aggressive periodontitis’ as previously defined by the 1999 Classification Workshop [150], citing insufficient evidence to distinguish both chronic and aggressive forms as separate diseases having distinct etiology and pathophysiological elements [22]. Literature on LDA that has been mentioned in this paper so far had focused on adjuncts used in the management of chronic periodontitis. Although there is no consensus on the use of antibiotics in managing periodontitis, adjunctive systemic antibiotics had been shown to have more pronounced clinical outcomes in aggressive forms of the disease [13,151]. Therefore, it would be expected that reviews on the adjunctive use of LDA in nonsurgical treatment of aggressive periodontitis would be lacking. Currently, there are three systematic reviews on the application of aPDT published in the same year, however with conflicting results on its beneficial use [152–154].

8. Challenges of LDA

Despite their indications for use, certain local delivery commercial devices had been discontinued due to the lack of profits, registration difficulties, and/or the costly requirements for continued approval [151]. The issue of substantivity [155] and rapid replacement of GCF within an inflamed periodontal pocket [90] posed a challenge for local mode of agent delivery. Substantivity by binding to soft or hard tissues surfaces is crucial to establish a reservoir for the drug to be slowly released within the pocket [156]. Goodson [90] estimated that GCF is replaced approximately 50 times per hour in a moderate periodontal pocket (4–5 mm).

An ecological concept describes periodontal disease as a mouth infection involving the tongue, saliva, and oral mucosa [157–159], limiting the use of localized agent therapy to residual deep periodontal pockets in the maintenance phase [160,161]. Clinicians should be aware that application of local adjuncts should not be used to overcome the shortcomings of adequate subgingival debridement. Bearing in mind the global rise of antimicrobial resistance, the usage of antibiotics should only be
limited for clear indications [162]. Concerns indicate that the high concentrations used in local delivery may suppress or eliminate normal microbiota and initiate the development of antibiotic-resistant species within the pocket itself [163]. However, studies have proven that such concerns were unfounded as no cases [164,165] or only a transient increase in resistance bacteria with no permanent change to the microbiota was observed [166].

9. Cost Effectiveness and Patient-Centered Outcomes

An optimum periodontal condition obtained through periodontal therapy is important to a clinician; in addition, decreasing the need for surgical interventions during the process is not only valuable economically, but also for patient-centered outcomes [167–169]. A systematic review by Niederman et al. [170] analyzed the cost effectiveness of local antimicrobial drugs that included the cost of agent, consumption, quantity of drug placements, mechanical therapy, and the working time of the clinician. The authors concluded that treating a single tooth at a dedicated visit would be the most expensive treatment (US$99 to US$126 per tooth in 2002) compared with treatment of a quadrant (US$28 to US$46 per tooth in 2002). Moreover, treating a quadrant as an added procedure would cost as low as US$20 (2002) per tooth as the setup cost is covered by the first procedure. Thus, using adjuncts for periodontal maintenance in an economic sense is favorable.

Considering treatment time, Wennström et al. [171] compared SRP with debridement (ultrasonic instrumentation) combined with LDD and observed that the latter procedure required less total treatment time (2 h against 3 h 11 min) in six months periodontal therapy. Adverse events were relatively minor with the use of LDD systems [37,38]. Meanwhile, Braegger [172] reported that local delivery devices feature potential cost savings and are less time consuming compared with conventional mechanical treatment given their similar six-month clinical outcomes. Heasman et al. [173] argued that cost effectiveness of systemic antimicrobials are pronounced through economic analysis. However, the analysis failed to consider that patient management could be influenced by the risk of increased bacterial resistance.

10. Limitations

There are plenty of studies published on LDA used in the nonsurgical treatment of periodontitis. However, the methodologies and clinical results varied within and between each agent used, causing difficulty in drawing conclusions and providing support to the superiority of one agent over another. Moreover, there is a lack of uniformity in the definition of periodontal disease severity. With the introduction of the new periodontal disease classification, we hope researchers would implement them in their future research. Our current review is limited by our selection of articles published only in the English language and use of commercial agents dictated by the length of their studies. This may lead to bias in the results and interpretations. Quantitative analysis was not performed for certain LDA as a minimum of two studies would be required [174].

11. Conclusions

LDA may still play a role in the management of periodontal disease, especially in combination with nonsurgical periodontal therapy, and could provide benefits in certain clinical situations as aforementioned. Overall, a vast array of commercially available local pharmacotherapeutic agents had been clinically tested. Based on our review of adjuncts with the longest follow-up studies, the mean differences of PPD reduction ranged from −0.21 to 1.91 mm and −0.56 to 1.35 mm of mean CAL gain. In general, most of these adjunctive agents had shown minimal but positive clinical results compared with mechanical debridement alone. However, considering the benefit–cost ratio with the modest clinical results, their long-term usefulness remains debatable. Additional carefully designed medium- to long-term randomized controlled studies preferably with a minimum six-month duration and stringent methodological criteria will be required for an accurate, universal assessment of the efficacy and sustainability of LDA before any ‘gold standard’ local adjunct could be recommended.
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References

1. Marsh, P.D.; Bradshaw, D.J. Dental plaque as a biofilm. J. Ind. Microbiol. 1995, 15, 169–175. [CrossRef]
2. Hajishengallis, G.; Lambris, J.D. Complement and dysbiosis in periodontal disease. Immunobiology 2012, 217, 1111–1116. [CrossRef]
3. Razali, M.; Palmer, R.M.; Coward, P.; Wilson, R.F. A retrospective study of periodontal disease severity in smokers and non-smokers. Br. Dent. J. 2005, 198, 495–498. [CrossRef]
4. Baharin, B.; Palmer, R.M.; Coward, P.; Wilson, R.F. Investigation of periodontal destruction patterns in smokers and non-smokers. J. Clin. Periodontal. 2006, 33, 485–490. [CrossRef]
5. Michalowicz, B.S.; Aeppli, D.; Virag, J.G.; Klump, D.G.; Hinrichs, E.; Segal, N.L.; Bouchard, T.J.; Pihlstrom, B.L. Periodontal Findings in Adult Twins. J. Periodontal. 1991, 62, 293–299. [CrossRef]
6. Hart, T.C.; Kornman, K.S. Genetic factors in the pathogenesis of periodontitis. Periodontology 2000 1997, 14, 202–215. [CrossRef]
7. Albandar, J.M.; Susin, C.; Hughes, F.J. Manifestations of systemic diseases and conditions that affect the periodontal attachment apparatus: Case definitions and diagnostic considerations. J. Clin. Periodontol. 2018, 45, S171–S189. [CrossRef]
8. Leong, X.; Ng, C.; Badiah, B.; Das, S. Association between hypertension and periodontitis: Possible mechanisms. Sci. World J. 2014. [CrossRef]
9. Kornman, K.S. Mapping the Pathogenesis of Periodontitis: A New Look. J. Periodontol. 2008, 79, 1560–1568. [CrossRef]
10. Durham, J.; Fraser, H.M.; McCracken, G.I.; Stone, K.M.; John, M.T.; Preshaw, P.M. Impact of periodontitis on oral health-related quality of life. J. Dent. 2013, 41, 370–376. [CrossRef]
11. Petersen, P.E.; Ogawa, H. The global burden of periodontal disease: Towards integration with chronic disease prevention and control. Periodontology 2000 2012, 60, 15–39. [CrossRef]
12. Collaborators, G. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017, 389, 1211–1259.
13. Jepsen, K.; Jepsen, S. Antibiotics/antimicrobials: Systemic and local administration in the therapy of mild to moderately advanced periodontitis. Periodontology 2000 2016, 71, 82–112. [CrossRef]
14. Gatej, S.; Gully, N.; Gibson, R.; Bartold, P.M. Probiotics and Periodontitis—A Literature Review. J. Int. Acad. Periodontal. 2017, 19, 42–50.
15. Fauzi, A.; Shafiei, Z.; Baharin, B.; Mohd, N. Isolation of lactobacillus from periodontally healthy subjects and its antimicrobial activity against periodontal pathogens. Sains Malays. 2013, 42, 19–24.
16. Moro, M.G.; Silveira Souto, M.L.; Franco, G.C.N.; Holzhausen, M.; Panunzi, C.M. Efficacy of local phytotherapy in the nonsurgical treatment of periodontal disease: A systematic review. J. Periodontal Res. 2018, 53, 288–297. [CrossRef]
17. Hamzah, N.; Aziz, S.; Fauzi, A.; Yusof, Y.; Razali, M.; Ibrahim, N.; Baharin, B. Effects of gelam honey (Melaleuca cajuputi) on alveolar bone loss in experimental periodontitis. J. Dent. Surg. 2014. [CrossRef]
18. Preshaw, P.M. Host modulation therapy with anti-inflammatory agents. Periodontology 2000 2018, 76, 131–149. [CrossRef]
19. Acute Market Reports Global Periodontal Therapeutics Market Size, Market Share, Application Analysis, Regional Outlook, Growth Trends, Key Players, Competitive Strategies and Forecasts, 2017 to 2025. Available online: https://www.researchandmarkets.com/reports/4431610/global-periodontal-therapeutics-market-size (accessed on 1 December 2018).
20. Collaborators, G. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015: A systematic analysis from the Global Burden of Disease Study 2015. Lancet 2017, 389, 1885–1906.
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21. Cho, N.H.; Shaw, J.E.; Karuranga, S.; Huang, Y.; da Rocha Fernandes, J.D.; Ohlrogge, A.W.; Malanda, B. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res. Clin. Pract. 2018, 138, 271–281. [CrossRef]

22. Papapanou, P.N.; Sanz, M.; Buduneli, N.; Dietrich, T.; Feres, M.; Fine, D.H.; Flemmig, T.F.; Garcia, R.; Giannobile, W.V.; Graziani, F.; et al. Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri—Implant Diseases and Conditions. J. Clin. Periodontol. 2018, 45, 162–170. [CrossRef]

23. Greenstein, G.; Tonetti, M. The role of controlled drug delivery for periodontitis. The Research, Science and Therapy Committee of the American Academy of Periodontology. J. Periodontol. 2000, 71, 125–140.

24. Rams, T.E.; Slots, J. Local delivery of antimicrobial agents in the periodontal pocket. Periodontology 2000 1996, 10, 139–159. [CrossRef]

25. Pitcher, G.R.; Newman, H.N.; Strahan, J.D. Access to subgingival plaque by disclosing agents using mouthrinsing and direct irrigation. J. Clin. Periodontol. 1980, 7, 300–308. [CrossRef]

26. Langer, R. New methods of drug delivery. Science 1990, 249, 1527–1533. [CrossRef]

27. Division of Industry and Consumer Education Medical Device Overview. Available online: https://www.fda.gov/ForIndustry/ImportProgram/ImportBasics/RegulatedProducts/ucm510630.htm (accessed on 25 March 2019).

28. Etienne, D. Locally delivered antimicrobials for the treatment of chronic periodontitis. Oral Dis. 2003, 9, 45–50. [CrossRef]

29. Smiley, C.J.; Tracy, S.L.; Abt, E.; Michalowicz, B.S.; John, M.T.; Gunsolley, J.; Cobb, C.M.; Rossmann, J.; Harrel, S.K.; Forrest, J.L.; et al. Evidence-based clinical practice guideline on the nonsurgical treatment of chronic periodontitis by means of scaling and root planing with or without adjuncts. J. Am. Dent. Assoc. 2015, 146, 525–535. [CrossRef]

30. Matesanz-Pérez, P.; García-Gargallo, M.; Figuero, E.; Bascones-Martínez, A.; Sanz, M.; Herrera, D. A systematic review on the effects of local antimicrobials as adjuncts to subgingival debridement, compared with subgingival debridement alone, in the treatment of chronic periodontitis. J. Clin. Periodontol. 2013, 40, 227–241. [CrossRef]

31. Etienne, D. Locally delivered antimicrobials for the treatment of chronic periodontitis. Oral Dis. 2003, 9, 45–50. [CrossRef]

32. Tonetti, M.S.; Cortellini, P.; Carnevale, G.; Cattabriga, M.; De Sanctis, M.; Pini Prato, G.P. A controlled multicenter study of adjunctive use of tetracycline periodontal fibers in mandibular class II furcations with persistent bleeding. J. Clin. Periodontol. 1998, 25, 728–736. [CrossRef]

33. Tonetti, M.S.; Lang, N.P.; Cortellini, P.; Suvan, J.; Eickholz, P.; Fourmousis, I.; Topoll, H.; Vangsted, T.; Wallkamm, B. Effects of a single topical doxycycline administration adjunctive to mechanical debridement in patients with persistent/recurrent periodontitis but acceptable oral hygiene during supportive periodontal therapy. J. Clin. Periodontol. 2012, 39, 475–482. [CrossRef]

34. Chambrone, L.; Vargas, M.; Arboleda, S.; Serna, M.; Guerrero, M.; de Sousa, J.; Lafaurie, G.I. Efficacy of Local and Systemic Antimicrobials in the Non-Surgical Treatment of Smokers with Chronic Periodontitis: A Systematic Review. J. Periodontol. 2016, 87, 1320–1332. [CrossRef]

35. Rovai, E.S.; Souto, M.L.S.; Ganhito, J.A.; Holzhausen, M.; Chambrone, L.; Pannuti, C.M. Efficacy of Local Antimicrobials in the Non-Surgical Treatment of Patients with Periodontitis and Diabetes: A Systematic Review. J. Periodontol. 2016, 87, 1406–1417. [CrossRef]

36. John, M.T.; Michalowicz, B.; Kotsakis, G.A.; Chu, H. Network meta-analysis of studies included in the Clinical Practice Guideline on the nonsurgical treatment of chronic periodontitis. J. Clin. Periodontol. 2017, 44, 603–611. [CrossRef]

37. Hanes, P.J.; Purvis, J.P. Local anti-infective therapy: Pharmacological agents. A systematic review. Ann. Periodontol. 2003, 8, 79–98. [CrossRef]

38. Bonito, A.; Lux, L.; Lohr, K. Impact of Local Adjuncts to Scaling and Root Planing in Periodontal Disease Therapy: A Systematic Review. J. Periodontol. 2005, 76, 1227–1236. [CrossRef]

39. The Cochrane Collaboration Review Manager (RevMan), version 5.3; The Nordic Cochrane Centre: Copenhagen, Denmark, 2014.

40. Higgins, J.; Green, S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. Available online: http://handbook-5-1.cochrane.org/ (accessed on 29 June 2018).
41. Paolantonio, M.; D’Ercole, S.; Pilloni, A.; D’Archivio, D.; Lisanti, L.; Graziani, F.; Femminella, B.; Sammartino, G.; Perillo, L.; Tetè, S.; et al. Clinical, Microbiologic, and Biochemical Effects of Subgingival Administration of a Xanthan-Based Chlorhexidine Gel in the Treatment of Periodontitis: A Randomized Multicenter Trial. *J. Periodontol.* 2009, 80, 1479–1492. [CrossRef]

42. Krammer, K.; Seshan, H.; Sameer, Z. Clinical evaluation of topical subgingival application of biodegradable xanthan based 1.5% Chlorhexidine gel for treatment of periodontal pockets. *J. Adv. Oral Res.* 2010, 1, 47–54.

43. Jain, M.; Dave, D.; Jain, P.; Manohar, B.; Yadav, B.; Shetty, N. Efficacy of xanthan based chlorhexidine gel as an adjunct to scaling and root planing in treatment of the chronic periodontitis. *J. Indian Soc. Periodontol.* 2013, 17, 439–443. [CrossRef]

44. Matesanz, P.; Herrera, D.; Echeverría, A.; O’Connor, A.; González, I.; Sanz, M. A randomized clinical trial on the clinical and microbiological efficacy of a xanthan gel with chlorhexidine for subgingival use. *Clin. Oral Investig.* 2013, 17, 55–66. [CrossRef]

45. Jeffcoat, M.K.; Bray, K.S.; Ciancio, S.G.; Dentino, A.R.; Fine, D.H.; Gordon, J.M.; Gonsolles, J.C.; Killoy, W.J.; Lowenguth, R.A.; Magnusson, N.I.; et al. Adjunctive Use of a Subgingival Controlled-Release Chlorhexidine Chip Reduces Probing Depth and Improves Attachment Level Compared with Scaling and Root Planing Alone. *J. Periodontol.* 1998, 69, 989–997. [CrossRef] [PubMed]

46. Grisi, D.C.; Salvador, S.L.; Figueiredo, L.C.; Souza, S.L.S.; Souza, A.B.J.; Grisi, M.F.M. Effect of a controlled-release chlorhexidine chip on clinical and microbiological parameters of periodontal syndrome. *J. Clin. Periodontol.* 2002, 29, 875–881. [CrossRef]

47. Carvalho, J.; Novak, M.J.; Mota, L.F. Evaluation of the Effect of Subgingival Placement of Chlorhexidine Chips as an Adjunct to Scaling and Root Planing. *J. Periodontol.* 2007, 78, 997–1001. [CrossRef]

48. Reddy, S.; Bhownick, N.; Singh, S.; Mgs, P.; Amir, A. A comparison of Chlorhexidine and Tetracycline local drug delivery systems in management of persistent periodontal pockets—A clinical study. *Int. J. Appl. Dent. Sci.* 2016, 2, 11–15.

49. Cosyn, J.; Wyn, I.; De Rouck, T.; Sabzevar, M.M. Long-Term Clinical Effects of a Chlorhexidine Varnish Implemented Treatment Strategy for Chronic Periodontitis. *J. Periodontol.* 2006, 77, 406–415. [CrossRef]

50. Bogren, A.; Teles, R.P.; Torresyap, G.; Haffajee, A.D.; Socransky, S.S.; Wennström, J.L. Locally Delivered Doxycycline During Supportive Periodontal Therapy: A 3-Year Study. *J. Periodontol.* 2008, 79, 827–835. [CrossRef]

51. Buduneli, E.; Tünger, A.; Evrenosoglu, E.; Bilgiç, A. Comparative clinical and microbiological effects of subgingival metronidazole application in adult periodontitis; 12-months results. *J. Int. Acad. Periodontol.* 2001, 3, 81–86.

52. Cortelli, J.R.; Aquino, D.R.; Cortelli, S.C.; Carvalho-Filho, J.; Roman-Torres, C.V.G.; Costa, F.O. A double-blind randomized clinical trial of subgingival minocycline for chronic periodontitis. *J. Oral Sci.* 2008, 50, 259–265. [CrossRef]

53. Killeen, A.C.; Harn, J.A.; Jensen, J.; Yu, F.; Custer, S.; Reinhardt, R.A. Two-Year Randomized Clinical Trial of Adjunctive Minocycline Microparticles in Periodontal Maintenance. *J. Dent. Hyg.* 2018, 92, 51–58.

54. Timmerman, M.F.; Van der Weijden, G.A.; Van Steenbergen, T.J.M.; Mantel, M.S.; de Graaf, J.; Van der Velden, U. Evaluation of the long-term efficacy and safety of locally-applied minocycline in adult periodontitis patients. *J. Clin. Periodontol.* 1996, 23, 707–716. [CrossRef]

55. Mombelli, A.; Brochut, P.; Plagnat, D.; Casagni, F.; Giannopoulou, C. Enamel matrix proteins and systemic antibiotics as adjuncts to non-surgical periodontal treatment: Clinical effects. *J. Clin. Periodontol.* 2005, 32, 225–230. [CrossRef]

56. Omer, B.; Satti, A.; Gismalla, B.; Hashim, N. The effect of local application of hyaluronan gel as an adjunctive to scaling and root planing in chronic periodontitis patients. *Afr. J. Dent.* 2018, 6, 163–170.

57. Bevilacqua, I.; Eriani, J.; Serroni, I.; Liani, G.; Borelli, V.; Castronovo, G.; Di Lenarda, R. Effectiveness of adjunctive subgingival administration of amino acids and sodium hyaluronate gel on clinical and immunological parameters in the treatment of chronic periodontitis. *Ann. Stomatol.* 2012, 3, 75–81.

58. Eick, S.; Renatus, A.; Heinicke, M.; Pfister, W.; Strautal, S.-I.; Jentsch, H. Hyaluronic acid as an adjunct after scaling and root planing: A prospective randomized clinical trial. *J. Periodontol.* 2013, 84, 941–949. [CrossRef]

59. Engström, P.-E.; Shi, X.-Q.; Tronje, G.; Larsson, A.; Welander, U.; Frithiof, L.; Engstrom, G.N. The Effect of Hyaluronan on Bone and Soft Tissue and Immune Response in Wound Healing. *J. Periodontol.* 2001, 72, 1192–1200. [CrossRef]
60. Birang, R.; Shahaboui, M.; Kiani, S.; Shadmehr, E.; Naghsh, N. Effect of nonsurgical periodontal treatment combined with diode laser or photodynamic therapy on chronic periodontitis: A randomized controlled split-mouth clinical trial. *J. Lasers Med. Sci.* 2015, 6, 112–119. [CrossRef]

61. Monzavi, A.; Chinipardaz, Z.; Mousavi, M.; Fekrazad, M.; Moslemi, A.; Azarpour, A.; Bagherpasand, O.; Chiniforush, N. Antimicrobial photodynamic therapy using diode laser activated indocyanine green as an adjunct in the treatment of chronic periodontitis: A randomized clinical trial. *Photodiagnosis Photodyn. Ther.* 2016, 14, 93–97. [CrossRef]

62. Lulic, M.; Leiggener Görög, I.; Salvi, G.E.; Ramseier, C.A.; Mattheos, N.; Lang, N.P. One-year outcomes of repeated adjunctive photodynamic therapy during periodontal maintenance: A proof-of-principle randomized-controlled clinical trial. *J. Clin. Periodontol.* 2009, 36, 661–666. [CrossRef]

63. Alwaeli, H.A.; Al-Khateeb, S.N.; Al-Sadi, A. Long-term clinical effect of adjunctive antimicrobial photodynamic therapy in periodontal treatment: A randomized clinical trial. *Lasers Med. Sci.* 2015, 30, 801–807. [CrossRef]

64. Müller Campanile, V.; Giannopoulou, C.; Campanile, G.; Cancela, J.A.; Mombelli, A. Single or repeated antimicrobial photodynamic therapy vs. local minocycline in addition to non-surgical therapy of deep periodontal pockets: A controlled randomized clinical trial. *Clin. Oral Investig.* 2017, 21, 2253–2264. [CrossRef] [PubMed]

65. Goh, E.X.; Tan, K.S.; Chan, Y.H.; Lim, L.P. Effects of repeated adjunctive antimicrobial photodynamic therapy on subgingival periodontal pathogens in the treatment of chronic periodontitis. *Lasers Med. Sci.* 2015, 30, 1647–1656. [CrossRef]

66. Tabenski, L.; Moder, D.; Cieplik, F.; Schenke, F.; Hiller, K.-A.; Buchalla, W.; Schmalz, G.; Christgau, M. Antimicrobial photodynamic therapy and effects of root debridement and adjunctive photodynamic therapy in residual pockets of patients on supportive periodontal therapy: A randomized split-mouth trial. *Photodiagnosis Photodyn. Ther.* 2017, 18, 342–348. [CrossRef]

67. Mueller Campanile, V.S.; Giannopoulou, C.; Campanile, G.; Cancela, J.A.; Mombelli, A. Single or repeated antimicrobial photodynamic therapy as adjunct to ultrasonic debridement in residual periodontal pockets: Clinical, microbiological, and local biological effects. *Lasers Med. Sci.* 2015, 30, 27–34. [CrossRef] [PubMed]

68. Goh, E.X.; Tan, K.S.; Chan, Y.H.; Lim, L.P. Effects of root debridement and adjunctive photodynamic therapy in residual pockets of patients on supportive periodontal therapy: A randomized split-mouth trial. *Photodiagnosis Photodyn. Ther.* 2017, 18, 342–348. [CrossRef]

69. Goodson, J.M.; Haffajee, A.; Socransky, S.S. Periodontal therapy by local delivery of tetracycline. *J. Clin. Periodontol.* 1979, 6, 83–92. [CrossRef]

70. Stabholz, A.; Kettering, J.; Aprecio, R.; Zimmerman, G.; Baker, P.J.; Wikesjö, U.M.E. Retention of Antimicrobial Activity by Human Root Surfaces after in Situ Subgingival Irrigation with Tetracycline HCl or Chlorhexidine. *J. Periodontol.* 1993, 64, 137–141. [CrossRef]

71. Tonetti, M.; Cugini, M.A.; Goodson, J.M. Zero-order delivery with periodontal placement of tetracycline-loaded ethylene vinyl acetate fibers. *J. Periodontal Res.* 1990, 25, 243–249. [CrossRef]

72. Christersson, L.A.; Norderyd, O.M.; Puchalsky, C.S. Topical application of tetracycline-HCl in human periodontitis. *J. Clin. Periodontol.* 1993, 20, 88–95. [CrossRef]

73. Tonetti, M.S. Local delivery of tetracycline: From concept to clinical application. *J. Clin. Periodontol.* 1998, 25, 969–977. [CrossRef]

74. Gordon, J.M.; Walker, C.B.; Murphy, J.C.; Goodson, J.M.; Socransky, S.S. Tetracycline: Levels Achievable in Gingival Crevice Fluid and in Vitro Effect on Subgingival Organisms: Part I. Concentrations in Crevicular Fluid After Repeated Doses. *J. Periodontol.* 1981, 52, 609–612. [CrossRef]

75. Norkiewicz, D.S.; Breault, L.G.; Wonderlich, S.T.; Malone, K.H. The Use of Chemotherapeutic Agents in Localized Periodontal Pockets. *Mil. Med.* 2001, 166, 940–946. [CrossRef] [PubMed]

76. Vandekerckhove, B.N.A.; Quirynen, M.; van Steenberghe, D. The Use of Tetracycline-Containing Controlled-Release Fibers in the Treatment of Refractory Periodontitis. *J. Periodontol.* 1997, 68, 353–361. [CrossRef] [PubMed]

77. Wilson, T.G.; McGuire, M.K.; Greenstein, G.; Nunn, M. Tetracycline Fibers Plus Scaling and Root Planing Versus Scaling and Root Planing Alone: Similar Results After 5 Years. *J. Periodontol.* 1997, 68, 1029–1032. [CrossRef] [PubMed]

78. U.S. Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. Available online: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=050653 (accessed on 2 August 2018).
79. Goodson, J.M.; Haffajee, A.D.; Socransky, S.S.; Kent, R.; Teles, R.; Hasturk, H.; Bogren, A.; Van Dyke, T.; Wennstrom, J.; Lindhe, J. Control of periodontal infections: A randomized controlled trial I. The primary outcome attachment gain and pocket depth reduction at treated sites. J. Clin. Periodontol. 2012, 39, 526–536. [CrossRef]

80. Sinha, S.; Kumar, S.; Dagli, N.; Dagli, R.J. Effect of tetracycline HCl in the treatment of chronic periodontitis—A clinical study. J. Int. Soc. Prev. Community Dent. 2014, 4, 149. [CrossRef]

81. Polson, A.M.; Garrett, S.; Stoller, N.H.; Bandt, C.L.; Hanes, P.J.; Killoy, W.J.; Southard, G.L.; Duke, S.P.; Stoller, N.H.; Johnson, L.R.; Trapnell, S.; Harrold, C.Q.; Garrett, S. The Pharmacokinetic Profile of a Biodegradable Controlled-Release Delivery System Containing Doxycycline Compared to Systemically Delivered Doxycycline in Gingival Crevicular Fluid, Saliva, and Serum. J. Periodontol. 1998, 69, 1085–1091. [CrossRef]

82. Vanderkerckhove, B.N.A.; Quirynen, M.; Van Steenberge, D. The use of locally-delivered minocycline in the treatment of chronic periodontitis. A review of the literature. J. Clin. Periodontol. 1998, 25, 964–968. [CrossRef]

83. Williams, R.C.; Paquette, D.W.; Offenbacher, S.; Adams, D.F.; Armitage, G.C.; Bray, K.; Caton, J.; Cochran, D.L.; Drisko, C.H.; Fiorellini, J.F.; et al. Treatment of Periodontitis by Local Administration of Minocycline Microspheres: A Controlled Trial. J. Periodontol. 2001, 72, 1535–1544. [CrossRef]

84. Hallmon, W.W.; Rees, T.D. Local Anti-Infective Therapy: Mechanical and Physical Approaches. A Systematic Review. Ann. Periodontol. 2003, 8, 99–114. [CrossRef] [PubMed]

85. Goodson, J.M. Gingival crevice fluid flow. Periodontology 2000 2003, 31, 43–54. [CrossRef] [PubMed]

86. Tomás, I.; García-Caballero, L.; López-Alvar, E.; Suárez, M.; Diz, P.; Seoane, J. In Situ Chlorhexidine Substantivity on Saliva and Plaque-Like Biofilm: Influence of Circadian Rhythm. J. Periodontol. 2013, 84, 1–15. [CrossRef]

87. Jenkins, S.; Addy, M.; Wade, W. The mechanism of action of chlorhexidine. A study of plaque growth on enamel inserts in vivo. J. Clin. Periodontol. 1988, 15, 415–424. [CrossRef] [PubMed]

88. Rindom Schiöstt, C. Effect of chlorhexidine on the microflora of the oral cavity. J. Periodontal Res. 1973, 8, 7–10. [CrossRef]

89. Hallmon, W.W.; Rees, T.D. Local Anti-Infective Therapy: Mechanical and Physical Approaches. A Systematic Review. Ann. Periodontol. 2003, 8, 99–114. [CrossRef] [PubMed]

90. Goodson, J.M. Gingival crevice fluid flow. Periodontology 2000 2003, 31, 43–54. [CrossRef] [PubMed]

91. Hjeljord, L.G.; Rolla, G.; Bonesvoll, P. Chlorhexidine-protein interactions. J. Periodontal Res. 1997, 32, 1–15. [CrossRef]

92. Polson, A.M.; Garrett, S.; Stoller, N.H.; Bandt, C.L.; Hanes, P.J.; Killoy, W.J.; Southard, G.L.; Duke, S.P.; Drisko, C.H.; Fiorellini, J.F.; et al. Treatment of Periodontitis by Local Administration of Minocycline Microspheres: A Controlled Trial. J. Periodontol. 2001, 72, 1535–1544. [CrossRef]

93. Jenkins, S.; Addy, M.; Wade, W. The mechanism of action of chlorhexidine. A study of plaque growth on enamel inserts in vivo. J. Clin. Periodontol. 1988, 15, 415–424. [CrossRef] [PubMed]

94. Rindom Schiöstt, C. Effect of chlorhexidine on the microflora of the oral cavity. J. Periodontal Res. 1973, 8, 7–10. [CrossRef]

95. Tomás, I.; García-Caballero, L.; López-Alvar, E.; Suárez, M.; Diz, P.; Seoane, J. In Situ Chlorhexidine Substantivity on Saliva and Plaque-Like Biofilm: Influence of Circadian Rhythm. J. Periodontol. 2013, 84, 1–15. [CrossRef]

96. Jenkins, S.; Addy, M.; Wade, W. The mechanism of action of chlorhexidine. A study of plaque growth on enamel inserts in vivo. J. Clin. Periodontol. 1988, 15, 415–424. [CrossRef] [PubMed]

97. Sinha, S.; Kumar, S.; Dagli, N.; Dagli, R.J. Effect of tetracycline HCl in the treatment of chronic periodontitis—A clinical study. J. Int. Soc. Prev. Community Dent. 2014, 4, 149. [CrossRef]

98. Rolla, G.; Loe, H.; Rindom Schiott, C. The affinity of chlorhexidine for hydroxyapatite and salivary mucins. J. Periodontal Res. 1970, 5, 90–95. [CrossRef]

99. Soskolne, W.A.; Chajek, T.; Flashner, M.; Landau, I.; Stabholtz, A.; Kolatch, B.; Lerner, E.I. An in vivo study of the chlorhexidine release profile of the PerioChip in the gingival crevicular fluid, plasma and urine. J. Clin. Periodontol. 1998, 25, 1017–1021. [CrossRef]

100. John, P.; Lazarus, F.; George, J.P.; Selvam, A.; Prabhuji, M.L.V. Adjunctive Effects of a Piscean Collagen-Based Controlled-Release Chlorhexidine Chip in the Treatment of Chronic Periodontitis: A Clinical and a Microbial Study. J. Clin. Diagn. Res. 2015, 9, ZC70–ZC74. [CrossRef]

101. Needleman, I.G.; Smales, F.C.; Martin, G.P. An investigation of bioadhesion for periodontal and oral mucosal drug delivery. J. Clin. Periodontol. 1997, 24, 394–400. [CrossRef] [PubMed]

102. Manthena, S.; Ramesh, A.; Srikanth, A.; Ramoji Rao, M.V.; Preethi, P.L.; Samatha, Y.P. Comparative evaluation of subgingivally delivered chlorhexidine varnish and chlorhexidine gel in reducing microbial count after mechanical periodontal therapy. J. Basic Clin. Pharm. 2015, 6, 24–28. [CrossRef] [PubMed]

103. Manikandan, D.; Balaji, V.R.; Niazi, T.M.; Rohini, G.; Karthikeyan, B.; Jesudoss, P. Chlorhexidine varnish implemented treatment strategy for chronic periodontitis: A clinical and microbial study. J. Pharm. Bioallied Sci. 2016, 8, S133–S137. [PubMed]
99. Sachdeva, S.; Grover, V.; Malhotra, R.; Kapoor, A.; Mohanty, K. Comparison of clinical effectiveness of single and multiple applications of 1% chlorhexidine varnish (Cervitec Plus) along with scaling and root planing in patients with chronic periodontitis. *J. Indian Soc. Periodontol.* 2018, 22, 523–528. [CrossRef]

100. Brogden, R.N.; Heel, R.C.; Speight, T.M.; Avery, G.S. Metronidazole in Anaerobic Infections. *Drugs* 1978, 16, 387–417. [CrossRef]

101. Norling, T.; Lading, P.; Engström, S.; Larsson, K.; Krog, N.; Nissen, S.S. Formulation of a drug delivery system based on a mixture of monoglycerides and triglycerides used in the treatment of periodontal disease. *J. Clin. Periodontol.* 1992, 19, 687–692. [CrossRef]

102. Stoltze, K.; Stellfeld, M. Systemic absorption of metronidazole after application of a metronidazole 25% dental gel. *J. Clin. Periodontol.* 1992, 19, 698–701. [CrossRef]

103. Norling, T.; Lading, P.; Engström, S.; Larsson, K.; Krog, N.; Nissen, S.S. Formulation of a drug delivery system based on a mixture of monoglycerides and triglycerides used in the treatment of periodontal disease. *J. Clin. Periodontol.* 1992, 19, 687–692. [CrossRef]

104. Greenstein, G. Povidone-Iodine’s Effects and Role in the Management of Periodontal Diseases: A Review. *J. Periodontal.* 1999, 70, 1397–1405. [CrossRef]

105. Sahrmann, P.; Puhan, M.A.; Attin, T.; Schmidlin, P.R. Systematic review on the effect of rinsing with povidone-iodine during nonsurgical periodontal therapy. *J. Periodontal Res.* 2010, 45, 153–164. [CrossRef]

106. Berkelman, R.L.; Holland, B.W.; Anderson, R.L. Increased bactericidal activity of dilute preparations of povidone-iodine solutions. *J. Clin. Microbiol.* 1982, 15, 635–639. [PubMed]

107. Ribeiro, É.D.P.; Bittencourt, S.; Ambrosano, G.M.B.; Nociti, F.H.; Sallum, E.A.; Sallum, A.W.; Casati, M.Z. Povidone-Iodine Used as an Adjunct to Non-Surgical Treatment of Furcation Involvements. *J. Periodontol.* 2006, 77, 211–217. [CrossRef] [PubMed]

108. Zanatta, G.M.; Bittencourt, S.; Nociti, F.H.; Sallum, E.A.; Sallum, A.W.; Casati, M.Z. Periodontal debridement with povidone-iodine in periodontal treatment: Short-term clinical and biochemical observations. *J. Periodontal.* 2006, 77, 498–505. [CrossRef]

109. Leonhardt, A.; Bergström, C.; Krok, L.; Cardaropoli, G. Healing following ultrasonic debridement and PVP-iodine in individuals with severe chronic periodontal disease: A randomized, controlled clinical study. *Acta Odontol. Scand.* 2006, 64, 262–266. [CrossRef]

110. Mohamed, D. P.; Bittencourt, S.; Ambrosano, G.M.B.; Nociti, F.H.; Sallum, E.A.; Sallum, A.W.; Casati, M.Z. Povidone-Iodine Used as an Adjunct to Non-Surgical Treatment of Furcation Involvements. *J. Periodontal.* 2006, 77, 211–217. [CrossRef] [PubMed]

111. Brosnahan, P.; Puhan, M.A.; Attin, T.; Schmidlin, P.R. Systematic review on the effect of rinsing with povidone-iodine during nonsurgical periodontal therapy. *J. Periodontal Res.* 2010, 45, 153–164. [CrossRef]

112. Bizzarro, S.; Van der Velden, U.; Loos, B.G. Local disinfection with sodium hypochlorite as adjunct to basic planing in chronic periodontitis: A clinico-microbiological study. *J. Indian Soc. Periodontol.* 2018, 22, 693–697. [CrossRef]

113. Slots, J.; Jorgensen, M.G.M. Effective, safe, practical and affordable periodontal antimicrobial therapy: Where are we going, and are we there yet? *Periodontology 2000* 2002, 28, 298–312. [CrossRef]

114. Zetterstrom, O.; Andersson, C.; Eriksson, L.; Fredriksson, A.; Friskopp, J.; Heden, G.; Jansson, B.; Lundgren, T.; Nilveus, R.; Olsson, A.; et al. Clinical safety of enamel matrix proteins on human teeth following periodontal surgery. *J. Clin. Periodontal.* 1997, 24, 697–704. [CrossRef]

115. Deschner, J.; Dard, M.; et al. Twenty years of enamel matrix derivative: The past, the present and the future. *Eur. J. Oral Sci.* 2002, 110, 693–697. [PubMed]

116. D.P.; Bittencourt, S.; Ambrosano, G.M.B.; Nociti, F.H.; Sallum, E.A.; Sallum, A.W.; Casati, M.Z. Povidone-Iodine Used as an Adjunct to Non-Surgical Treatment of Furcation Involvements. *J. Periodontal.* 2006, 77, 211–217. [CrossRef] [PubMed]

117. Leonhardt, A.; Bergström, C.; Krok, L.; Cardaropoli, G. Healing following ultrasonic debridement and PVP-iodine in individuals with severe chronic periodontal disease: A randomized, controlled clinical study. *Acta Odontol. Scand.* 2006, 64, 262–266. [CrossRef]

118. Mohammad, D. Sodium hypochlorite in endodontics: An update review. *Int. Dent. J.* 2008, 58, 329–341. [CrossRef]

119. Slots, J.; Jorgensen, M.G.M. Effective, safe, practical and affordable periodontal antimicrobial therapy: Where are we going, and are we there yet? *Periodontology 2000* 2002, 28, 298–312. [CrossRef]

120. Bizzarro, S.; Van der Velden, U.; Loos, B.G. Local disinfection with sodium hypochlorite as adjunct to basic planing in chronic periodontitis: A clinical study. *J. Clin. Periodontal.* 1997, 24, 697–697. [PubMed]
121. Gutierrez, M.A.; Mellonig, J.T.; Cochran, D.L. Evaluation of enamel matrix derivative as an adjunct to non-surgical periodontal therapy. J. Clin. Periodontol. 2003, 30, 739–745. [CrossRef]
122. Graziani, F.; Gennai, S.; Petrini, M.; Bettini, L.; Tonetti, M. Enamel Matrix Derivative Stabilizes Blood Clot and Improves Clinical Healing in Deep Pockets After Flapless Periodontal Therapy: A Randomized Clinical Trial. J. Clin. Periodontol. 2019, 46, 231–240. [CrossRef]
123. Rahemtulla, F. Proteoglycans of Oral Tissues. Crit. Rev. Oral Biol. Med. 1992, 3, 135–162. [CrossRef]
124. Bartold, P.M. Proteoglycans of the periodontium: Structure, role and function. J. Periodontal Res. 1987, 22, 431–444. [CrossRef]
125. Yamalik, N.; Kilinc, K.; Caglayan, F.; Eratalay, K.; Caglayan, G. Molecular size distribution analysis of human gingival proteoglycans and glycosaminoglycans in specific periodontal diseases. J. Clin. Periodontol. 1998, 25, 145–152. [CrossRef]
126. Bartold, P.M.; Page, R.C. The effect of chronic inflammation on gingival connective tissue proteoglycans and hyaluronic acid. J. Oral Pathol. Med. 1986, 15, 367–374. [CrossRef][PubMed]
127. Giannobile, W.V.; Al-Shammari, K.F.; Sarment, D.P. Matrix molecules and growth factors as indicators of periodontal disease activity. Periodontology 2000 2003, 31, 125–134. [CrossRef][PubMed]
128. Chen, W.Y.J. Functions of hyaluronan in wound repair. Hyaluronan 2002, 2, 147–156.
129. Koshal, A.; Patel, P.; Bolt, R.; Bhupinder, D.; Galgut, P. A comparison in postoperative healing of sites receiving non-surgical debridement augmented with and without a single application of hyaluronan 0.8% gel. Prev. Dent. 2007, 2, 34–38.
130. Soukos, N.S.; Goodson, J.M. Photodynamic therapy in the control of oral biofilms. Periodontology 2000 2011, 55, 143–166. [CrossRef]
131. Macdonald, I.J.; Dougherty, T.J. Basic principles of photodynamic therapy. J. Porphy. Phthalocyanines 2001, 5, 105–129. [CrossRef]
132. Sarkar, S.; Wilson, M. Lethal photosensitization of bacteria in subgingival plaque from patients with chronic periodontitis. J. Periodontal Res. 1993, 28, 204–210. [CrossRef]
133. Kömerik, N.; Wilson, M.; Poole, S. The Effect of Photodynamic Action on Two Virulence Factors of Gram-negative Bacteria. Photochem. Photobiol. 2007, 72, 676–680. [CrossRef]
134. Sculean, A.; Aoki, A.; Romanos, G.; Schwarz, F.; Miron, R.J.; Cosgarea, R. Is Photodynamic Therapy an Effective Treatment for Periodontal and Peri-Implant Infections? Dent. Clin. N. Am. 2015, 59, 831–858. [CrossRef][PubMed]
135. Azaripour, A.; Dittrich, S.; Van Noorden, C.J.F.; Willershausen, B. Efficacy of photodynamic therapy as adjunct treatment of chronic periodontitis: A systematic review and meta-analysis. Lasers Med. Sci. 2018, 33, 407–423. [CrossRef][PubMed]
136. Akram, Z.; Hyder, T.; Al-Hamoudi, N.; Binshabaib, M.S.; Alharthi, S.S.; Hanif, A. Efficacy of photodynamic therapy versus antibiotics as an adjunct to scaling and root planing in the treatment of periodontitis: A systematic review and meta-analysis. Photodiagnosis Photodyn. Ther. 2017, 19, 86–92. [CrossRef][PubMed]
137. Graziani, F.; Gennai, S.; Petrini, M.; Bettini, L.; Tonetti, M. Enamel Matrix Derivative Stabilizes Blood Clot and Improves Clinical Healing in Deep Pockets After Flapless Periodontal Therapy: A Randomized Clinical Trial. J. Clin. Periodontol. 2019, 46, 231–240. [CrossRef]
138. Azaripour, A.; Dittrich, S.; Van Noorden, C.J.F.; Willershausen, B. Efficacy of photodynamic therapy as adjunct treatment of chronic periodontitis: A systematic review and meta-analysis. Lasers Med. Sci. 2018, 33, 407–423. [CrossRef][PubMed]
139. Sculean, A.; Aoki, A.; Romanos, G.; Schwarz, F.; Miron, R.J.; Cosgarea, R. Is Photodynamic Therapy an Effective Treatment for Periodontal and Peri-Implant Infections? Dent. Clin. N. Am. 2015, 59, 831–858. [CrossRef][PubMed]
140. Wilson, B.C.; Patterson, M.S. The physics, biophysics and technology of photodynamic therapy. Phys. Med. Biol. 2008, 53, R61–R109. [CrossRef]
141. Hopp, M.; Biffar, R. Photodynamic therapies—blue versus green. Laser 2013, 1, 10–25.
142. Van der Weijden, G.A.; Timmerman, M.F. A systematic review on the clinical efficacy of subgingival debridement in the treatment of chronic periodontitis. J. Clin. Periodontol. 2002, 29, 55–71. [CrossRef]
143. Vitt, A.; Gustafsson, A.; Ramberg, P.; Slizen, V.; Kazeko, L.A.; Buhlin, K. Polyhexamethylene guanidine phosphate irrigation as an adjunctive to scaling and root planing in the treatment of chronic periodontitis. Acta Odontol. Scand. 2019, 77, 290–295. [CrossRef]
144. Denez, E.M.; Toma, S.; Lasserre, J.F.; Brex, M.C. Evaluation of a unique subgingival irrigation with 10% povidone-iodine after scaling and root planing: A randomized clinical trial. *Quintessence Int.* 2016, 47, 549–558.

145. Kinane, D.F.; Radvar, M. A Six-Month Comparison of Three Periodontal Local Antimicrobial Therapies in Persistent Periodontal Pockets. *J. Periodontol.* 2005, 76, 1–7. [CrossRef]

146. Gupta, R.; Pandit, N.; Aggarwal, S.; Verma, A. Comparative evaluation of subgingivally delivered 10% doxycycline hyclate and xanthan-based chlorhexidine gels in the treatment of chronic periodontitis. *J. Contemp. Dent. Pract.* 2008, 9, 25–32. [PubMed]

147. Radvar, M.; Pourtaghi, N.; Kinane, D.F. Comparison of 3 Periodontal Local Antibiotic Therapies in Persistent Periodontal Pockets. *J. Periodontol.* 1996, 67, 860–865. [CrossRef] [PubMed]

148. Lie, T.; Bruun, G.; Bøe, O.E. Effects of Topical Metronidazole and Tetracycline in Treatment of Adult Periodontitis. *J. Periodontol.* 1998, 69, 819–827. [CrossRef]

149. Keestra, J.A.J.; Grosjean, I.; Coucke, W.; Quirynen, M.; Teughels, W. Non-surgical periodontal therapy with systemic antibiotics in patients with untreated aggressive periodontitis: A systematic review and meta-analysis. *J. Periodontal Res.* 2015, 50, 689–706. [CrossRef]

150. Hussein, I.; Ranka, M.; Gilbert, A.; Davey, K. Does adjunctive antimicrobial therapy reduce the perceived need for periodontal surgery? *Periodontology 2000* 2011, 55, 205–216. [CrossRef]

151. Mombelli, A.; Cionca, N.; Almaghlouth, A. Does adjunctive antimicrobial therapy reduce the perceived need for periodontal surgery? *Periodontology 2000* 2013, 62, 218–231. [CrossRef]

152. Chatzopoulos, G.-S.; Doufexi, A.-E. Photodynamic therapy in the treatment of aggressive periodontitis: A systematic review. *Med. Oral Patol. Oral Cir. Bucal* 2016, 21, e192–e200. [CrossRef]

153. Vohra, F.; Akram, Z.; Safii, S.H.; Vaithilingam, R.D.; Ghanem, A.; Sergis, K.; Javed, F. Role of antimicrobial photodynamic therapy in the treatment of aggressive periodontitis: A systematic review. *Photodiagnosis Photodyn. Ther.* 2016, 13, 139–147. [CrossRef]

154. Souza, E.; Medeiros, A.C.; Gurgel, B.C.; Sarmento, C. Antimicrobial photodynamic therapy in the treatment of aggressive periodontitis: A systematic review and meta-analysis. *Lasers Med. Sci.* 2016, 31, 187–196. [CrossRef]

155. Heitz-Mayfield, L.J.A.; Lang, N.P. Surgical and nonsurgical periodontal therapy. Learned and unlearned concepts. *Periodontology 2000* 2013, 62, 1–6. [CrossRef]

156. Quirynen, M.; Teenbergh, W.; Soete, M.; Steenberghe, D. Topical antiseptics and antibiotics in the initial therapy of chronic adult periodontitis: Microbiological aspects. *Periodontology 2000* 2002, 28, 72–90. [CrossRef] [PubMed]

157. Mager, D.L.; Ximenezz-Fyvie, L.A.; Haffajee, A.D.; Scorzansky, S.S. Distribution of selected bacterial species on intraoral surfaces. *J. Clin. Periodontol.* 2003, 30, 644–654. [CrossRef] [PubMed]

158. Faveri, M.; Feres, M.; Shibli, J.A.; Hayacibara, R.F.; Hayacibara, M.M.; de Figueiredo, L.C. Microbiota of the Dorsum of the Tongue After Plaque Accumulation: An Experimental Study in Humans. *J. Periodontol.* 2006, 77, 1539–1546. [CrossRef] [PubMed]

159. Feres, M.; Figueiredo, L.C.; Soares, G.M.S.; Faveri, M. Systemic antibiotics in the treatment of periodontitis. *Periodontology 2000* 2015, 73, 167–172. [CrossRef] [PubMed]

160. Meinberg, T.A.; Barnes, C.M.; Dunning, D.G.; Reinhardt, R.A. Comparison of Conventional Periodontal Maintenance Versus Scaling and Root Planing with Subgingival Minocycline. *J. Periodontol.* 2002, 73, 167–172. [CrossRef]

161. Hussein, I.; Ranka, M.; Gilbert, A.; Davey, K. Locally Delivered Antimicrobials in the Management of Periodontitis: A Critical Review of the Evidence for their Use in Practice. *Dent. Update* 2007, 34, 494–506. [CrossRef]

162. Oral Health Division Ministry of Health Malaysia CPG. Management of Chronic Periodontitis, 2nd ed. 2012. Available online: http://www.moh.gov.my/moh/attachments/CPG%202014/Management_Orthodontic.pdf (accessed on 16 December 2019).

163. Slots, J.; Pallasch, T.J. Dentists’ Role in Halting Antimicrobial Resistance. *J. Dent. Res.* 1996, 75, 1338–1341. [CrossRef]

164. Walker, C.B.; Godowski, K.C.; Borden, L.; Lennon, J.; Nangó, S.; Stone, C.; Garrett, S. The Effects of Sustained Release Doxycycline on the Anaerobic Flora and Antibiotic-Resistant Patterns in Subgingival Plaque and Saliva. *J. Periodontol.* 2000, 71, 768–774. [CrossRef]
165. Goodson, J.M.; Tanner, A. Antibiotic resistance of the subgingival microbiota following local tetracycline therapy. *Oral Microbiol. Immunol.* **1992**, *7*, 113–117. [CrossRef]

166. Larsen, T. Occurrence of doxycycline resistant bacteria in the oral cavity after local administration of doxycycline in patients with periodontal disease. *Scand. J. Infect. Dis.* **1991**, *23*, 89–95. [CrossRef]

167. Killoy, W. The clinical significance of local chemotherapies. *J. Clin. Periodontol.* **2002**, *29*, 22–29. [CrossRef] [PubMed]

168. Loesche, W.J.; Giordano, J.; Soehren, S.; Hutchinson, R.; Rau, C.F.; Walsh, L.; Schork, M.A. Nonsurgical treatment of patients with periodontal disease. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endodontol.* **1996**, *81*, 533–543. [CrossRef]

169. Henke, C.J.; Genco, R.J.; Killoy, W.J.; Miller, D.P.; Evans, C.J.; Finkelmann, R.D. An economic evaluation of a chlorhexidine chip for treating chronic periodontitis: The CHIP (chlorhexidine in periodontitis) study. *J. Am. Dent. Assoc.* **2001**, *132*, 1557–1569. [CrossRef] [PubMed]

170. Niederman, R.; Abdelshehid, G.; Goodson, J.M. Periodontal therapy using local delivery of antimicrobial agents. *Dent. Clin. N. Am.* **2002**, *46*, 665–677. [CrossRef]

171. Wennstrom, J.L.; Newman, H.N.; MacNeill, S.R.; Killoy, W.J.; Griffiths, G.S.; Gillam, D.G.; Krok, L.; Needleman, I.G.; Weiss, G.; Garrett, S.; et al. Utilisation of locally delivered doxycycline in non-surgical treatment of chronic periodontitis. A comparative multi-centre trial of 2 treatment approaches. *J. Clin. Periodontol.* **2001**, *28*, 753–761. [CrossRef] [PubMed]

172. Braegger, U. Cost-benefit, cost-effectiveness and cost-utility analyses of periodontitis prevention. *J. Clin. Periodontol.* **2005**, *32*, 301–313. [CrossRef]

173. Heasman, P.A.; Vernazza, C.R.; Gaunt, F.L.; Pennington, M.W. Cost-effectiveness of adjunctive antimicrobials in the treatment of periodontitis. *Periodontology 2000* **2011**, *55*, 217–230. [CrossRef] [PubMed]

174. Valentine, J.C.; Pigott, T.D.; Rothstein, H.R. How many studies do you need? A primer on statistical power for meta-analysis. *J. Educ. Behav. Stat.* **2010**, *35*, 215–247. [CrossRef]