



Review article

The ever-changing landscape in modern dentistry therapeutics – Enhancing the emptying quiver of the periodontist

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ABSTRACT

Introduction/Objectives: Periodontitis comprises of a wide range of inflammatory conditions of the gums leading to soft tissue damage and attachment loss. The initiation of periodontitis constitutes a rather complex disease pathogenesis which is based on pathogenic shifts of the oral microbiota combined with the host-microbiome interactions. The severity of the periodontitis is multifactorial depending on genetic, environmental, as well as host immunity factors.

Data and sources: To make an inclusive analysis on the periodontitis therapeutics, reading of the recent relevant literature was carried out using the MEDLINE/PubMed database, Google Scholar and the NIH public online database for clinical trials (<http://www.clinicaltrials.gov>).

Conclusions: Tackling the inflammation associated periodontal defects can be succeeded with conventional therapy or resective and regenerative treatment. To date, the mechanical removal of the supragingival and subgingival biofilm is considered the “gold standard” of periodontal therapy in combination with the use of antibacterial compounds. The antimicrobial resistance phenomenon tends to turn all the currently applied antibacterials into “endangered species”. Ongoing efforts through the conduct of clinical trials should be focused on understanding the advantages of modern approaches in comparison to traditional therapies.

1. Introduction

Periodontitis is a term used to describe the various pathological conditions that affect periodontal tissues. In 1999, the International Workshop for Classification of Periodontal Diseases and Conditions set the basis for a widely accepted periodontal terminology with emphasis on the clinical evidence and the immunological causes [1, 2]. In 2017, the American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP) updated the 1999 classification of periodontitis and conditions [3]. Grade A periodontitis is the most common form of periodontitis occurring most commonly in adults and seniors, and is characterized by slow progression [4, 5]. The most severe forms of inflammatory periodontal pathology, called necrotizing periodontitis (NPD), include necrotizing gingivitis (NG), necrotizing periodontitis (NP) and necrotizing stomatitis (NS) which are characterized by three typical clinical features (papilla necrosis, bleeding, and pain) and are associated with host immune response impairments [6]. Significant

clinical findings for the diagnosis of NP are the presence of marginal necrosis, ulceration, severe pain and spontaneous bleeding, rapidly progressing to destruction of the underlying alveolar bone [7].

Periodontitis is considered among the major oral health problems worldwide following dental caries [8]. As a non-communicable disease it ranks sixth with a global prevalence of 45–50%, while stage IV periodontitis affects 5–20% of the adult population worldwide [8, 9, 10]. The pathogenesis of periodontitis includes (i) a pathological shift of the microbial oral ecology, (ii) the subsequent host immune response, and (iii) the involvement of environmental and genetic risk factors [11, 12, 13, 14]. The bacterial inhabitants of the oral cavity along with the putative presence of pathogenic yeasts and viruses and the host immune response play a pivotal role for the onset and the progression of the disease that eventually leads, if untreated, to tooth loss [14, 15, 16, 17, 18, 19]. Additionally, the genetic (single nucleotide polymorphisms), environmental and behavioral risk factors or modifiers (epigenetic alterations, non-communicable diseases, oral hygiene, obesity, smoking, alcohol

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abuse) exert strong impact on the clinical course of periodontitis [8, 14, 20, 21].

The bidirectional interaction between overall health and periodontitis has shown that not only specific systemic disorders can enhance predisposition to periodontitis, but also a diseased oral cavity can trigger the onset of several systemic disorders [22]. Latest news on Covid-19 global emergency, has brought at the spotlight intensive research of all inflammatory conditions as possible predisposing factors for the development of severe infection [23]. As such, periodontitis-related inflammatory pathways increasing immune response may play a critical role in the onset and the course of the Covid-19 infection. In terms of bidirectional connection, preserving a good oral health and low bacterial load in the oral cavity, also reduces Covid-19-related risk for complications [23].

This review emphasizes in the pathogenesis of periodontitis and brings on the spotlight the microbial ecology as well as the host–microbiome interplay to identify factors that govern the periodontal deterioration. The impact of novel systems-biology approaches towards tracing the pathways of periodontitis is being investigated. A special focus is also given on the limitations of conventional diagnostic tools and current molecular techniques in the research of periodontitis pathogenesis. Both conventional and modern aspects of therapeutic approaches are discussed.

2. Unveiling the microbial dysbiosis

Less than half of the microbial inhabitants of the oral cavity has been isolated by traditional cultivation methods. The results of 16S rRNA are publicly available at the expanded Human Oral Microbiome Database (eHOMD) which has validated approximately 772 prokaryotic species (70% cultivable, 30% uncultivable) [24]. The culture-independent profiling of the mouth has classified oral bacteria into six phyla including the Firmicutes, Actinobacteria, Proteobacteria, Fusobacteria, Bacteroidetes and Spirochaetes [24]. The 16S rRNA identification of the microbial populations has shown the predominance of more than 700 bacterial species of bacteria, fungi, viruses, archaea and protozoans [25]. The pyrosequencing method has though suggested that the human oral microbiome consists of a greater than 19,000 phylotypes if aligning unique tag sequences as Operational Taxonomic Units (OTUs) [28]. It has been discovered that the presence of periodontitis is associated with an imbalance of the microbial population [29]. Even today, pathogenic shifts in associated microbiota combined with the host-microbiome interactions have brought about a cloudy scenery in the comprehension of the periodontitis pathogenesis [30]. Thorough microbiological analyses pinpointed the association between the incidence of gingivitis with a proportional increase of particular bacterial species which are common in oral microbiota including gram-positive *Actinomyces viscosus*, and gram-negative *Campylobacter rectus* *Prevotella* spp. However, when gingivitis remains untreated a gradual shift to Gram-negative anaerobic communities also detected in periodontitis, is detected [31].

The first putative periodontal pathogens investigated by culture in 1950 included the “red complex” bacterial species, namely *Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola* [32]. The post-treatment incidence of the “red complex” microorganisms in periodontal pockets signalizes the recurrence of periodontitis [33]. Culture analysis and DNA-DNA hybridization disclosed another periodontitis-associated bacterial cluster named the “orange complex” containing *Fusobacterium* species, *Parvimonas micra*, *Prevotella* spp., *Streptococcus constellatus*, *Campylobacter* spp., and *Eubacterium nodatum* [34]. Integrated metagenomics and network analysis have been applied in the study of host microbial interactions in periodontitis and various extra-oral pathogenic conditions. In a study aiming to decipher the peri-implantitis and periodontitis key microbial players, the *Solobacterium moorei* and *Prevotella denticola* have been presented as an interesting network [35]. Metabarcoding studies have been only recently applied to find the association among periodontal disease and cystic fibrosis (CF) using matched control samples [36]. These matched control

networks including the oral microbiome as represented by *Streptococcus*, the *Fusobacterium* species, *Campylobacter* spp., *Treponema* and the *Prevotella* species to name a few, have exhibited meaningful connections with the pathogenesis of CF [36].

3. Subgingival biofilm communities in periodontitis

The concept of biofilm describes the natural environment of an organized aggregate of microorganisms of different species embedded in a self-produced matrix of extracellular polymeric substances (EPS), where cells stick to each other and often to a surface [29]. Bacterial clusters forming oral biofilms are distinguished in (i) cariogenic or periopathogenic, and (ii) supragingival or subgingival [37]. Supragingival biofilms are mainly related to caries and gingivitis, whereas subgingival biofilms are related to periodontitis and peri-implantitis resulting in the destruction of hard and soft supporting tissues [38]. Oral biofilm formation may precede upon auto-aggregation or co-aggregation [39]. Autoaggregation is generally mediated by self-recognition process, whereas coaggregation is a process by which genetically different species become attached to one another *via* specific molecules [40]. Biofilms achieve effective cell–cell intercommunication through the production of signaling molecules that accumulate in the local microenvironment or through direct cell–cell contact between genetically distinct cells and/or between individuals from the same population as well [41]. In addition, during oral biofilm development and maturation the surface of the dental plaque begins to change resulting in a change in its redox potential, pH and composition. In particular, granules and filamentous bacteria are reduced and Gram-negative anaerobic strains are developed, mainly spirochetes, forming the subgingival dental plaque [42].

After professional dental cleaning, the biofilm is formed primarily at supragingival sites and expands subgingivally. Furthermore, the microenvironment changes from aerobic to anaerobic [43, 44]. The subgingival biofilm structure is characterized by a Gram-negative and/or motile bacteria zone located adjacent to the epithelial lining of the periodontal pocket, while Gram-positive rods and cocci form a tightly adherent band on the enamel or root surface [42]. Below the gum line, the gingival crevicular fluid that bears compositional similarity to serum, seeps around the root surface to form a fluid phase [45, 46]. The subgingival anaerobic bacteria are continually exposed to gingival crevicular fluid, occupying a niche that is metabolically characterized by the catabolism of amino acids from proteases secreted proteins [47]. The abundance of these bacteria can activate a cascade of host defense mechanisms including the topical enhancement of cytokine expression [48]. Several studies have confirmed the presence of periodontitis-related microorganisms in the subgingival microenvironment and their implication in the increased levels of pro-inflammatory cytokines in the gingival fluid and gingival tissues [49, 50].

Poor oral hygiene has adverse effect in the microenvironment of the periodontal pockets by rapidly increasing the biomass of periodontal pathogens, leading to gingival detachment and finally bone loss [41]. Confocal laser scanning microscopy (CLSM) and scanning electron microscopy (SEM) exhibited that multispecies and single-species biofilms grow in a similar rate; hence the multispecies biofilms become thicker, and form bacterial networks showing a higher vitality than single-species biofilms [51].

4. Lessons learned in the study of periodontitis

Bacterial culture has long been regarded as the “gold standard” for periodontal sample analysis by detecting new bacterial species and identifying their susceptibility to antimicrobial agents [52]. However, culture-dependent techniques are time-consuming, require experienced technical personnel and strict quality assurance protocols. It has been univocally confirmed that culture-dependent methods for microbial community analysis do not reflect their true composition as only the cultivable species are detected [53]. Imaging techniques like

transmission- or scanning electron microscopy (TEM, SEM) as well as the high-resolution field emission scanning electron microscopy (FE-SEM) are used to visualize the microorganisms within subgingival biofilms [54, 55, 56].

More rapid unbiased techniques are required to examine large numbers of samples and reflect more reliably the real diversity of the microbial microbiota. These techniques embrace immunofluorescence using monoclonal or polyclonal antibodies, PCR amplification assays and hybridization using either whole-genomic DNA probes or oligonucleotide probes [57]. PCR-based techniques are applied as culture-independent methodologies for oral community-profiling [58]. 16S rRNA analysis, DNA microarray and next generation sequencing (NGS) allow the identification of the composition at mixed microbial communities (cultivable and uncultivable species) [59, 60, 61]. Even more complementary to NGS yet more costly, is the whole genome sequencing (WGS) analysis that provides information of genomic sequences of all microbial communities at strain-level, including prokaryotes, eukaryotes and viruses found in complex samples such as the oral microhabitats [62]. Fluorescence *in situ* hybridization (FISH) can be used to quantify and define the spatial configuration and display bacterial cell morphology, in microenvironments such as dental plaque [27]. However, one of the major drawbacks of FISH using oligonucleotide probes is the mutable and occasionally inadequate cell penetration of probes depending on the characteristics of each cell [63].

As mentioned above, *in vitro* systems also provide fundamental information on microbial species involved in periodontitis elucidating the host cellular response to periopathogens along with their byproducts and consequently defining the signaling pathways that are involved in periodontitis [64]. Animal models can mimic complex cellular processes that occur in humans. Mouse models are particularly used due to the genetically modified strains available for both gain and loss of function with regard to specific periodontitis-associated genes [65]. Small-animal models including for example rats, hamsters, rabbits, and ferrets, allow the researcher to generate substantial and relevant data on the interaction between soft and hard periodontal tissues, especially during inflammation, despite the limited dentition similarity with humans. The mechanism of systemic inflammation and the impact on periodontal healing processes can be studied *in vivo* using genetically produced transgenic and knockout animals [64].

5. Conventional periodontal therapies

The periodontal therapy initially intended to eliminate periodontal bacteria following resolution of inflammation. It involves either conventional therapy or resective and regenerative treatment to resolve the inflammation-associated periodontal defects [66]. Therapeutic approaches include cause-related (scaling, root planing, administration of antimicrobials) and surgical periodontal treatment. An increasing amount of information has emphasized the application of laser protocols in contemporary periodontal treatments (antimicrobial photodynamic therapy-aPDT or photothermal therapy-aPTT), yet there is no strong recommendation upon their application due to lack of evidence [67]. Although aPDT and aPTT have shown bacterial load reduction and clinical improvement when combined with conventional methods (surgical techniques or antimicrobials), laser therapies when applied alone require further studies to address light parameters (dosimetry, combinations) [68, 69, 70, 71].

Antimicrobial mouthwash solutions primarily aim at ensuring sufficient oral hygiene to limit the incidence of gingivitis and the progression of periodontitis [72, 73]. More specifically, the treatment of periodontitis frequently begins with a non-surgical phase that includes scaling and root planing (SRP) with hand and/or ultrasonic instruments as well as oral hygiene instructions and systemic antimicrobial prescription [75, 76, 77]. Non-surgical periodontal therapy by SRP is highly effective following adequate supragingival plaque control [78, 79, 80]. However, SRP does not always induce a shift of the subgingival microorganisms for

maintaining the long-term stability of the initially achieved clinical benefits [81]. Additionally, SRP has limited accessibility of deeper periodontal pockets, furcation areas, root concavities and periodontal pathogens residing in dentinal tubules [77].

Administration of antimicrobials additionally to SRP exhibits better results in the therapeutic process of patients with Grade C periodontitis considering age, comorbidities, pregnancy, pocket depth and attachment loss. To date, several studies have focused on the use of adjunctive systemic antibiotics alone or in combinations (amoxicillin with or without clavulanic acid, metronidazole, tetracycline, azithromycin, clindamycin, doxycycline) and have shown encouraging outcomes in cases of deep pockets (>6 mm) [82]. However, in the latest EFP workshop, Prof Chapple says about the use of antibiotics “the recommendation in the guideline is against to them not because of the evidence, but because of the high possibility of antimicrobial stewardship” [67]. In the case of localized periodontitis or in recurrent and nonresponding infection types, the administration of localized adjunctive and sustained-release agents such as Nonbiodegradable fibers, Biodegradable gels, Microspheres and Degradable films (example of commercial products: Actisite, Arestin, Atridox and PerioChip) is preferred [82, 83, 84]. Topically applied fibers, films, sponges, gels and formulations encapsulating micro- and nano-particles, possess the competitive advantage of enhanced bio-adhesion that subsequently increases retention time in the periodontal pocket and have been extensively studied for over three decades [85]. The development of the first localized systems of controlled drug release against periodontitis stems back in 1979, when cellulose acetate fibers containing tetracycline were introduced; though commercialization began in 1994 (Actisite®, P&G/Alza) [86]. The Food and Drug Administration (FDA)-approved formulations that exhibited improved clinical outcomes include the absorbable doxycycline gel (Atridox®, Atrix Laboratories) and the chlorhexidine gluconate biodegradable chip Periochip® (Perio Products Ltd.). Formulations with FDA or premarket (PMA) approval such as minocycline microspheres (Arestin®, Ora-Pharma, Inc.), and metronidazole gel (Elyzol®, Dumex) have shown no significant clinical benefit [87]. The main drawback of surgical procedures, such as gingivectomy, modified Widman flap and apically positioned flap with and without osseous recontouring is the loss of attachment and in gingival shrinkage to some degree [88, 89]. However, it should be mentioned that effective non-surgical treatment can also interfere with interdental tissue height and contour. Hence, independent of the treatment there is no guarantee of preservation of the pre-existing gingival aesthetics [89].

Regenerative techniques aim to restore the loss of supporting periodontal tissues involving bone grafting, guided-tissue regeneration, incorporation of biomaterials like derivatives and substitutes of bone or introduction of biological factors like enamel matrix derivatives (EMDs), leading to a cementum-like tissue formation [90, 91, 92, 93, 94, 95]. Tissue regeneration is the ultimate challenge in bone tissue engineering [96]. Hence, artificial bone grafts were fabricated, to mimic the extracellular matrix (ECM) allowing for effective bone mineralization, and regeneration of fractured or diseased bones [97]. Lately, the effectiveness of mesenchymal stem cells (MSCs) in the regeneration of periodontal tissues has been successfully studied [98, 99]. In particular, MSCs are isolated from the iliac crest marrow and then applied to the root surface and the periodontal defect. The use of MSCs in platelet-rich plasma (PRP) gel is quite helpful for periodontal tissue regeneration and treatment of esthetically sensitive periodontal sites [100].

6. Modern periodontal therapies

The emerging antimicrobial resistance has limited the unrestricted application of antimicrobials in controlling periodontitis [101, 102, 103]. Notably, pharmacokinetic and pharmacodynamics features of systemic antimicrobials (optimal concentration, treatment duration, patient collective, therapy onset during SRP, healing expectation time) have not been experimentally explored [104].

According to the FDA definition, several medical devices used in the treatment of periodontitis include the non-antibiotics sodium hyaluronate and the enamel matrix proteins (Emdogain®, Institute Straumann AG) embodied in glycol carriers [105, 106]. Recently, plant-derived polyphenols (Flavonoids, Phenolic acids, Lignans, Stilbenes) detected in fruits and legumes including grapes, black soybeans (*Glycine max*), blueberries (*Vaccinium angustifolium*) and *Aloe vera* have been screened due to their anti-inflammatory and anti-bacterial properties [107, 108, 109]. Surprisingly, over 300,000 herbs still need to be tested regarding their potential for antimicrobial function [110].

An example with great interest is curcumin, the biologically active compound extracted from the *Curcuma longa* rhizome, with pronounced antioxidant, anti-inflammatory, immunostimulant, antimicrobial, anti-neoplastic and wound healing properties among others [111, 112]. Researchers attempt to overcome the poor pharmacodynamic properties of curcumin through implementing synthetic analogues or strategies of enhanced delivery. Adjuvants, nanoparticles, micelles, liposomes and PEGylation are some techniques that have been proved to enhance curcumin bioavailability [113]. Searching for clinical trials on the NIH's public online database (<http://www.clinicaltrials.gov>) in October, 2020 using the keywords "periodontitis" and "curcumin" returned 5 registered trials (Numbers of Clinical Trials: NCT, numbers are mentioned below), three of which are completed (phase 4) and two still recruiting (early phase 1 and phase 3). According to the results, topical application of curcumin-based formulations (pastes, oral gels) as adjuncts to SRP have exhibited beneficial effects in periodontitis through alleviation of the inflammatory process (NCT02442453), reduction in probing depth (NCT04044417) and bone gain (NCT04032132).

PDT is a relatively non-invasive light based platform, established in the treatment of superficial tumors of the skin and the mucosa, oral diseases and age macular degeneration, whereas in dentistry PDT has been accessed for the photoinactivation of perio-pathogens [32]. The concept of photodynamic inactivation (PDI) requires microbial exposure to either exogenous or endogenous photosensitizer (PS) molecules, followed by visible light energy, at typical wavelengths in the red/near infrared region [114]. The most commonly applied biodegradable cationic PS include tricyclic dyes, chlorines, porphyrines, xanthenes, monoterpene, photofrin, hematoporphyrin derivatives, biologic conjugates and curcumin, selectively penetrate the bacterial or yeast cell membrane [115, 116, 117, 118, 119]. An ideal photosensitizer should be non-toxic and exhibit local toxicity only after activation by light [120].

Clinical application of aPDT is continuously growing because of the high availability in portable, amenable light sources [121]. However, the clinical benefits of aPDT over the classical SRP in the treatment of periodontitis remain vague and clinically unjustified [121, 122, 123]. This approach is an extension of PDT, which is minimally invasive by converting photon energy into intracellular heat, in order to eliminate targeted microbial cells [124]. In recent years a number of studies have focused on the use of PTT, with the use of indocyanine green (EmunDo) [125]. In aPDT this photosensitizer has experimentally achieved the greatest laser induced bactericidal effect, while the increase of the gingival temperature was only 5 °C, which is safe for periodontal tissues. Additionally, it has been suggested that *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* absorb a large amount of indocyanine green, which results in achieving microbial elimination up to 90%. It also does not cause discoloration to the surfaces of teeth [126]. Furthermore, it does not require oxygen to interact with cells or tissues as opposed to photodynamic therapy. PTT can be achieved only when a wavelength of 810 nm in combination with the use of indocyanine green is used. PTT and aPDT It can be a tool for biomedical applications in the future that will allow for any potential side effects to be discarded, as well as the development of drug resistance [127]. Additionally, it appears to be a promising treatment since intensive research over the last decade seems to have encouraging results, as it can eliminate the accumulation of periodontal bacteria by removing supra or subgingival biofilm but also endotoxins, such as lipopolysaccharides [126, 127].

However, there is controversy about the advantages of PDT and PTT in comparison to traditional therapies. A recent study showed that the use of photodynamic therapy using a 670 nm wavelength in combination with methylene blue as a photosensitizer does not offer more benefits in patients with Grade A periodontitis in comparison with conventional non-surgical mechanical treatment in a period of 6 months [128]. Another study concluded that the use of PDT with chloro-aluminum phthalocyanine did not provide more advantages than surgical scaling and root planing periodontal treatments of patients with Grade A periodontitis [129]. It seems reasonable to state that carefully designed studies are mandatory to clarify certain laser protocols and the exact laser settings that would be predictably beneficial.

7. Concluding remarks

An inclusive understanding of perio-pathogens, pathogenicity as well as host immunity factors are of essential importance for a better comprehension of the periodontal disease progress. In brief, the clinical signs of periodontitis are gums and clinical attachment loss, leading to tissue support loss. The mechanical removal of the supragingival and subgingival biofilm is considered the "gold standard" of periodontal therapy in combination with the use of antibacterial compounds. Nevertheless, the tough-to-reach periodontal sites challenges the mechanical debridement and thus, the reduction of the overall bacterial load. The probability of antimicrobial resistance for the target microorganism prompt the development of alternative antimicrobial concepts to overcome complications. However, mechanical protocols, mainly involving SRP are unable to completely eliminate subgingival bacteria especially in deep pockets. Furthermore, the repeated use of antimicrobials in residual periodontal pockets during maintenance care should be avoided. Notably, therapies involving herbs or light seem to be safe alternatives for periodontitis. Intensive research on current therapies could be a useful adjunct to SRP and antimicrobials to eliminate a variety of localized bacterial, fungal and viral infections. Yet, further clinical trials are needed to evaluate if modern therapeutic approaches can be clinically successful in comparison to conventional treatments in periodontal therapy.

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References

- [1] C. Wiebe, E. Putnins, The periodontal disease classification system of the American Academy of Periodontology- an update, J. Can. Dent. Assoc. 66 (11) (2000) 594–597.

- [2] P. Devi, A. Pradeep, Classification of periodontal diseases: the dilemma continues, *N. Y. State Dent. J.* 75 (4) (2009) 30–34.
- [3] J.G. Caton, G. Armitage, T. Berglundh, I.L.C. Chapple, S. Jepsen, K.S. Kornman, et al., A new classification scheme for periodontal and peri-implant diseases and conditions - introduction and key changes from the 1999 classification, *J. Clin. Periodontol.* 45 (Suppl 20) (2018) S1–S8.
- [4] B. Holtfreter, J. Albandar, T. Dietrich, B. Dye, K. Eaton, P. Eke, et al., Standards for reporting chronic periodontitis prevalence and severity in epidemiologic studies, *J. Clin. Periodontol.* 42 (5) (2015) 407–412.
- [5] L.M. Shaddox, C.B. Walker, Treating chronic periodontitis: current status, challenges, and future directions, *Clin. Cosmet. Invest. Dent.* 2 (2010) 79–91.
- [6] A. Magan-Fernandez, F. O'Valle, E. Pozo, J. Liebana, F. Mesa, Two cases of an atypical presentation of necrotizing stomatitis, *J. Periodontol. Implant Sci.* 45 (6) (2015) 252–256.
- [7] V. William, Stenberg Jr., Pediatric Dentistry, sixth ed., 2019.
- [8] P.E. Petersen, D. Bourgeois, H. Ogawa, S. Estupinan-Day, C. Ndiaye, The global burden of oral diseases and risks to oral health, *Bull. World Health Organ.* 83 (9) (2005) 661–669.
- [9] N.J. Kassebaum, E. Bernabe, M. Dahiya, B. Bhandari, C.J. Murray, W. Marcenes, Global burden of severe periodontitis in 1990–2010: a systematic review and meta-regression, *J. Dent. Res.* 93 (11) (2014) 1045–1053.
- [10] M. Sanz, A. Marco Del Castillo, S. Jepsen, J.R. Gonzalez-Juanatey, F. D'Aiuto, P. Bouchard, et al., Periodontitis and cardiovascular diseases: consensus report, *J. Clin. Periodontol.* 47 (3) (2020) 268–288.
- [11] T. Nishihara, T. Koseki, Microbial etiology of periodontitis, *Periodontol.* 2000 36 (2004) 14–26.
- [12] A. Cekici, A. Kantarci, H. Hasturk, T. Van Dyke, Inflammatory and immune pathways in the pathogenesis of periodontal disease, *Periodontol.* 2000 64 (1) (2014) 57–80.
- [13] S. Ji, Y.S. Choi, Y. Choi, Bacterial invasion and persistence: critical events in the pathogenesis of periodontitis? *J. Periodontol. Res.* 50 (5) (2015) 570–585.
- [14] J. Guthmiller, K. Novak, Periodontal Diseases, American Society for Microbiology, 2002.
- [15] R. Donlan, Biofilms: microbial life on surfaces, *Emerg. Infect. Dis.* 8 (9) (2002) 881–890.
- [16] S. Socransky, A. Haffajee, Evidence of bacterial etiology: a historical perspective, *Periodontol.* 2000 5 (1) (1994) 7–25.
- [17] D. Tatakis, P. Kumar, Etiology and pathogenesis of periodontal diseases, *Dent. Clin. North Am* 49 (3) (2005) 491–516.
- [18] R. Page, Milestones in periodontal research and the remaining critical issues, *J. Periodontol. Res.* 34 (7) (1999) 331–339.
- [19] P. Bartold, T. Van Dyke, Periodontitis: a host-mediated disruption of microbial homeostasis. Unlearning learned concepts, *Periodontol.* 2000 62 (1) (2013) 203–217.
- [20] E. Gaio, A. Haas, C. Rösing, R. Oppermann, J. Albandar, C. Susin, Effect of obesity on periodontal attachment loss progression: a 5-years population-based prospective study, *J. Clin. Periodontol.* 43 (7) (2016) 557–565.
- [21] M. Martins, Y. Jiao, L. Larsson, L. Almeida, C. Garaicoa-Pazmino, J. Le, et al., Epigenetic modifications of histones in periodontal disease, *J. Dent. Res.* 95 (2) (2016) 215–222.
- [22] F.Q. Bui, C.L.C. Almeida-da-Silva, B. Huynh, A. Trinh, J. Liu, J. Woodward, et al., Association between periodontal pathogens and systemic disease, *Biomed. J.* 42 (1) (2019) 27–35.
- [23] V. Sampson, N. Kamona, A. Sampson, Could there be a link between oral hygiene and the severity of SARS-CoV-2 infections? *Br. Dent. J.* 228 (12) (2020) 971–975.
- [24] D. Verma, P.K. Garg, A.K. Dubey, Insights into the human oral microbiome, *Arch. Microbiol.* 200 (4) (2018) 525–540.
- [25] L. Yeon-Hee, C. Sang Wan, A. Q-Schick, H. Seung-Jae, L. Yeon-Ah, et al., Progress in oral microbiome related to oral and systemic diseases: an update, *Diagnostics* 11 (7) (2021) 1283.
- [26] B.J. Paster, F.E. Dewhirst, Molecular microbial diagnosis, *Periodontol.* 2000 51 (2009) 38–44.
- [27] B.J. Keijser, E. Zaura, S.M. Huse, J.M. van der Vossen, F.H. Schuren, R.C. Montijn, et al., Pyrosequencing analysis of the oral microflora of healthy adults, *J. Dent. Res.* 87 (11) (2008) 1016–1020.
- [28] J.F. Lasserre, M.C. Brex, S. Toma, Oral microbes, biofilms and their role in periodontal and peri-implant diseases, *Materials* 11 (10) (2018).
- [29] M. Rylev, M. Kilian, Prevalence and distribution of principal periodontal pathogens worldwide, *J. Clin. Periodontol.* 35 (8 Suppl) (2008) 346–361.
- [30] S. Offenbacher, S. Barros, J. Beck, Rethinking periodontal inflammation, *J. Periodontol.* 79 (8) (2008) 1577–1584.
- [31] S. Socransky, A. Haffajee, M. Cugini, C. Smith, R. Kent, Microbial complexes in subgingival plaque, *J. Clin. Periodontol.* 25 (2) (1998) 134–144.
- [32] P. Kumar, A. Griffen, J. Barton, B. Paster, M. Moeschberger, E. Leys, New bacterial species associated with chronic periodontitis, *J. Dent. Res.* 82 (5) (2003) 338–344.
- [33] K. Divaris, K. Monda, K. North, A. Olshan, E. Lange, K. Moss, et al., Genome-wide association study of periodontal pathogen colonization, *J. Dent. Res.* 91 (7) (2012) 215–285.
- [34] K. Komatsu, T. Shiba, Y. Takeuchi, T. Watanabe, T. Koyanagi, T. Nemoto, et al., Discriminating microbial community structure between peri-implantitis and periodontitis with integrated metagenomic, metatranscriptomic, and network analysis, *Front Cell Infect. Microbiol.* 10 (2020) 596490.
- [35] J.R. Willis, E. Saus, S. Iraola-Guzman, E. Cabello-Yeves, E. Ksiezopolska, L. Cozzuto, et al., Citizen-science based study of the oral microbiome in Cystic fibrosis and matched controls reveals major differences in diversity and abundance of bacterial and fungal species, *J. Oral Microbiol.* 13 (1) (2021) 1897328.
- [36] R. Chandki, P. Banthia, R. Banthia, Biofilms: a microbial home, *J. Indian Soc. Periodontol.* 15 (2) (2011) 111–114.
- [37] A. Aruni, Y. Dou, A. Mishra, H. Fletcher, The biofilm community-rebels with a cause, *Curr. Oral Health Rep.* 2 (1) (2015) 48–56.
- [38] P. Kolenbrander, R. Andersen, D. Blehert, P. Eglund, J. Foster, R.J. Palmer, Communication among oral bacteria, *Microbiol. Mol. Biol. Rev.* 66 (3) (2002) 486–505, table of contents.
- [39] T. Trunk, H.S. Khalil, J.C. Leo, Bacterial autoaggregation, *AIMS Microbiol.* 4 (1) (2018) 140–164.
- [40] P. Kolenbrander, R. Palmer, S. Periasamy, N. Jakubovics, Oral multispecies biofilm development and the key role of cell–cell distance, *Nat. Rev. Microbiol.* 8 (7) (2010) 471–480.
- [41] A.W. Aruni, Y. Dou, A. Mishra, H.M. Fletcher, The biofilm community-rebels with a cause, *Curr. Oral Health Rep.* 2 (1) (2015) 48–56.
- [42] V. Zijngje, T. Ammann, T. Thurnheer, R. Gmür, Subgingival biofilm structure, *Front. Oral Biol.* 15 (2012) 1–16.
- [43] R. Teles, F. Teles, J. Frias-Lopez, B. Paster, A. Haffajee, Lessons learned and unlearned in periodontal microbiology, *Periodontol.* 2000 62 (1) (2013) 95–162.
- [44] R. Wassall, P. Preshaw, Clinical and technical considerations in the analysis of gingival crevicular fluid, *Periodontol.* 2000 70 (1) (2016) 65–79.
- [45] S. Barros, R. Williams, S. Offenbacher, T. Morelli, Gingival crevicular fluid as a source of biomarkers for periodontitis, *Periodontol.* 2000 70 (1) (2016) 53–64.
- [46] K. How, K. Song, K. Chan, Porphyromonas gingivalis: an overview of periodontopathic pathogen below the gum line, *Front. Microbiol.* 7 (2016) 53.
- [47] C. Sima, M. Glogauer, Macrophage subsets and osteoimmunology: tuning of the immunological recognition and effector systems that maintain alveolar bone, *Periodontol.* 2000 63 (1) (2013) 80–101.
- [48] V. Dosseva-Panova, C. Popova, V. Panov, Subgingival microbial profile and production of proinflammatory cytokines in chronic periodontitis, *Folia Med. (Plovdiv)* 56 (3) (2014) 152–160.
- [49] R. Peyyala, J. Ebersole, Multispecies biofilms and host responses: "discriminating the trees from the forest, *Cytokine* 61 (1) (2013) 15–25.
- [50] J. Park, J. Lee, H. Um, B. Chang, S. Lee, A periodontitis-associated multispecies model of an oral biofilm, *J. Periodontol. Implant Sci.* 44 (2014) 79–84.
- [51] P.M. Loomer, Microbiological diagnostic testing in the treatment of periodontal diseases, *Periodontol.* 2000 34 (2004) 49–56.
- [52] L.W. Hugerth, A.F. Andersson, Analysing microbial community composition through amplicon sequencing: from sampling to hypothesis testing, *Front. Microbiol.* 8 (2017) 1561.
- [53] R. Holliday, P.M. Preshaw, L. Bowen, N.S. Jakubovics, The ultrastructure of subgingival dental plaque, revealed by high-resolution field emission scanning electron microscopy, *BDJ Open* 1 (2015) 15003.
- [54] C. Gaertig, K. Niemann, J. Berthold, L. Giel, N. Leitschuh, C. Boehm, et al., Development of a point-of-care-device for fast detection of periodontal pathogens, *BMC Oral Health* 15 (2015) 165.
- [55] S. Ji, Y. Choi, Point-of-care diagnosis of periodontitis using saliva: technically feasible but still a challenge, *Front Cell Infect. Microbiol.* 5 (2015) 65.
- [56] J. Oliver, Antibody applications, *Mater. Methods* 3 (2013) 182.
- [57] W. Deng, D. Xi, H. Mao, M. Wanapat, The use of molecular techniques based on ribosomal RNA and DNA for rumen microbial ecosystem studies: a review, *Mol. Biol. Rep.* 35 (2) (2008) 265–274.
- [58] F.E. Dewhirst, T. Chen, J. Izard, B.J. Paster, A.C. Tanner, W.H. Yu, et al., The human oral microbiome, *J. Bacteriol.* 192 (19) (2010) 5002–5017.
- [59] M. Hamady, R. Knight, Microbial community profiling for human microbiome projects: tools, techniques, and challenges, *Genome Res.* 19 (7) (2009) 1141–1152.
- [60] K. Krishnan, T. Chen, B.J. Paster, A practical guide to the oral microbiome and its relation to health and disease, *Oral Dis.* 23 (3) (2017) 276–286.
- [61] E. Caselli, C. Fabbri, M. D'Accolti, I. Soffritti, C. Bassi, S. Mazzacane, et al., Defining the oral microbiome by whole-genome sequencing and resistome analysis: the complexity of the healthy picture, *BMC Microbiol.* 20 (1) (2020) 120.
- [62] K. Kubota, CARD-FISH for environmental microorganisms: technical advancement and future applications, *Microb. Environ.* 28 (1) (2013) 3–12.
- [63] A. Kantarci, H. Hasturk, T. Van Dyke, Animal models for periodontal regeneration and peri-implant responses, *Periodontol.* 2000 68 (1) (2015) 66–82.
- [64] T. Dana, J.K. Graves, Oelisoa Andriankajaja, Keisuke Wada, Carlos Rossa Jr., Animal models to study host-bacteria interactions involved in periodontitis, *Front. Oral Biol.* 15 (2012) 117–132.
- [65] A. Gupta, S. Kedige, K. Jain, Amnion and chorion membranes: potential stem cell reservoir with wide applications in periodontics, *Int. J. Biomater* 3 (2015) 1–9.
- [66] J. Kamma, Perio Insight puts spotlight on EFP guideline on periodontal treatment, *Perioinsight* (2020) 1–8.
- [67] S. Dalvi, S. Benedicenti, T. Salagean, I.R. Bordea, R. Hanna, Effectiveness of antimicrobial photodynamic therapy in the treatment of periodontitis: a systematic review and meta-analysis of in vivo human randomized controlled clinical trials, *Pharmaceutics* 13 (6) (2021).
- [68] R. Cosgarea, S. Eick, I. Batori-Andronescu, S. Jepsen, N.B. Arweiler, R. Rossler, et al., Clinical and microbiological evaluation of local doxycycline and antimicrobial photodynamic therapy during supportive periodontal therapy: a randomized clinical trial, *Antibiotics (Basel)* 10 (3) (2021).
- [69] C.P. Raut, K.S. Sethi, B.R. Kohale, A. Mamajiwala, A. Warang, Indocyanine green-mediated photothermal therapy in treatment of chronic periodontitis: a clinico-microbiological study, *J. Indian Soc. Periodontol.* 22 (3) (2018) 221–227.

- [71] J. Lin, Z. He, F. Liu, J. Feng, C. Huang, X. Sun, et al., Hybrid hydrogels for synergistic periodontal antibacterial treatment with sustained drug release and NIR-responsive photothermal effect, *Int. J. Nanomed.* 15 (2020) 5377–5387.
- [72] J. Krayner, R. Leite, K. Kirkwood, Non-surgical chemotherapeutic treatment strategies for the management of periodontal diseases, *Dent. Clin. North Am* 54 (1) (2010) 13–33.
- [73] C. Berchier, D. Slot, G. Van der Weijden, The efficacy of 0.12% chlorhexidine mouthrinse compared with 0.2% on plaque accumulation and periodontal parameters: a systematic review, *J. Clin. Periodontol.* 37 (9) (2010) 829–839.
- [75] C. Delatola, E. Adonogianaki, E. Ioannidou, Non-surgical and supportive periodontal therapy: predictors of compliance, *J. Clin. Periodontol.* 41 (8) (2014) 791–796.
- [76] J. Eberhard, S. Jepsen, P. Jervoe-Storm, I. Needleman, H. Worthington, Full-mouth treatment modalities (within 24 hours) for chronic periodontitis in adults, *Cochrane Database Syst. Rev.* 4 (2015), Cd004622.
- [77] P. Garcia Canas, I. Khoully, J. Sanz, P. Loomer, Effectiveness of systemic antimicrobial therapy in combination with scaling and root planing in the treatment of periodontitis: a systematic review, *J. Am. Dent. Assoc.* 146 (3) (2015) 150–163.
- [78] M. Feres, L. Gursky, M. Faveri, C. Tsuzuki, L. Figueiredo, Clinical and microbiological benefits of strict supragingival plaque control as part of the active phase of periodontal therapy, *J. Clin. Periodontol.* 36 (10) (2009) 857–867.
- [79] G. Petersilka, B. Ehmke, T. Flemmig, Antimicrobial effects of mechanical debridement, *Periodontol.* 2000 28 (2002) 56–71.
- [80] F. Teles, R. Teles, N. Uzel, X. Song, G. Torresyap, S. Socransky, et al., Early microbial succession in redeveloping dental biofilms in periodontal health and disease, *J. Periodontol. Res.* 47 (1) (2012) 95–104.
- [81] D. Zandbergen, D. Slot, R. Niederman, F. Van der Weijden, The concomitant administration of systemic amoxicillin and metronidazole compared to scaling and root planing alone in treating periodontitis: a systematic review, *BMC Oral Health* 16 (1) (2016) 27.
- [82] K. Jepsen, S. Jepsen, Antibiotics/antimicrobials: systemic and local administration in the therapy of mild to moderately advanced periodontitis, *Periodontol.* 2000 71 (1) (2016) 82–112.
- [83] P. Matesanz-Perez, M. Garcia-Gargallo, E. Figuero, A. Bascones-Martinez, M. Sanz, D. Herrera, 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.* 40 (3) (2013) 227–241.
- [84] D. Steinberg, M. Friedman, Sustained-release delivery of antimicrobial drugs for the treatment of periodontal diseases: fantasy or already reality? *Periodontol.* 2000 84 (1) (2020) 176–187.
- [85] O.L. Tan, S.H. Safi, M. Razali, Commercial local pharmacotherapeutics and adjunctive agents for nonsurgical treatment of periodontitis: a contemporary review of clinical efficacies and challenges, *Antibiotics (Basel)* 9 (1) (2019).
- [86] J.M. Goodson, A. Haffajee, S.S. Socransky, Periodontal therapy by local delivery of tetracycline, *J. Clin. Periodontol.* 6 (2) (1979) 83–92.
- [87] M.S. Tonetti, P. Cortellini, G. Carnevale, M. Cattabriga, M. de Sanctis, G.P. Pini Prato, A controlled multicenter study of adjunctive use of tetracycline periodontal fibers in mandibular class II furcations with persistent bleeding, *J. Clin. Periodontol.* 25 (9) (1998) 728–736.
- [88] G. Proestakis, G. Soderholm, G. Bratthall, B. Kullendorff, K. Grondahl, M. Rohlin, et al., Gingivectomy versus flap surgery: the effect of the treatment of infrabony defects. A clinical and radiographic study, *J. Clin. Periodontol.* 19 (7) (1992) 497–508.
- [89] R.M. Palmer, P.D. Floyd, *Periodontology: a clinical approach.* 4. Periodontal surgery, *Br. Dent. J.* 178 (8) (1995) 301–306.
- [90] M. Bottino, V. Thomas, Membranes for periodontal regeneration—A materials perspective, *Front. Oral Biol.* 17 (2015) 90–100.
- [91] S. Liu, B. Hu, Y. Zhang, W. Li, J. Song, Minimally invasive surgery combined with regenerative biomaterials in treating intra-bony defects: a meta-analysis, *PLoS One* (2016) e0147001.
- [92] L. Larsson, A. Decker, L. Nibali, S. Pilipchuk, T. Berglundh, W. Giannobile, Regenerative medicine for periodontal and peri-implant diseases, *J. Dent. Res.* 95 (3) (2016) 255–266.
- [93] D. Cochran, C. Cobb, J. Bashutski, Y. Chun, Z. Lin, G. Mandelaris, et al., Emerging regenerative approaches for periodontal reconstruction: a consensus report from the AAP Regeneration Workshop, *J. Periodontol.* 86 (2 Suppl) (2015) S153–S156.
- [94] M. Reynolds, R. Kao, P. Camargo, J. Caton, D. Clem, J. Fiorellini, et al., Periodontal regeneration - intrabony defects: a consensus report from the AAP Regeneration Workshop, *J. Periodontol.* 86 (2 Suppl) (2015) S105–S107.
- [95] J. Kim, C. Park, R. Perez, H. Lee, J. Jang, H. Lee, et al., Advanced biomatrix designs for regenerative therapy of periodontal tissues, *J. Dent. Res.* 93 (12) (2014) 1203–1211.
- [96] P. Bartold, S. Gronthos, S. Ivanovski, A. Fisher, D. Huttmacher, Tissue engineered periodontal products, *J. Periodontol. Res.* 51 (1) (2016) 1–15.
- [97] M. Prabhakaran, J. Venugopal, S. Ramakrishna, Electrospun nanostructured scaffolds for bone tissue engineering, *Acta Biomater.* 5 (8) (2009) 2884–2893.
- [98] J. Liu, F. Yu, Y. Sun, B. Jiang, W. Zhang, J. Yang, et al., Concise reviews: characteristics and potential applications of human dental tissue-derived mesenchymal stem cells, *Stem Cell.* 33 (3) (2015) 627–638.
- [99] M. Tobita, H. Mizuno, Adipose-derived stem cells and periodontal tissue engineering, *Int. J. Oral Maxillofac. Implants* (2013) e487–e493.
- [100] B. Sigusch, M. Engelbrecht, A. Völpel, A. Holletschke, W. Pfister, J. Schütze, Full-mouth antimicrobial photodynamic therapy in *Fusobacterium nucleatum*-infected periodontitis patients, *J. Periodontol.* 81 (7) (2010) 975–981.
- [101] R. Allaker, C. Douglas, Novel anti-microbial therapies for dental plaque-related diseases, *Int. J. Antimicrob. Agents* 33 (1) (2009) 8–13.
- [102] D. Herrera, B. Alonso, R. León, S. Roldán, M. Sanz, Antimicrobial therapy in periodontitis: the use of systemic antimicrobials against the subgingival biofilm, *J. Clin. Periodontol.* 35 (8) (2008) 45–66.
- [103] D. Sharma, L. Misba, A.U. Khan, Antibiotics versus biofilm: an emerging battleground in microbial communities, *Antimicrob. Resist. Infect. Control* 8 (2019) 76.
- [104] R. Buchmann, G. Conrads, A. Sulean, Short-term effects of systemic antibiotics during periodontal healing, *Quintessence Int.* 41 (4) (2010) 303–312.
- [105] S. Eick, A. Renatus, M. Heinicke, W. Pfister, S.I. Stratul, H. Jentsch, Hyaluronic Acid as an adjunct after scaling and root planing: a prospective randomized clinical trial, *J. Periodontol.* 84 (7) (2013) 941–949.
- [106] F. Graziani, S. Gennai, M. Petrini, L. Bettini, M. Tonetti, Enamel matrix derivative stabilizes blood clot and improves clinical healing in deep pockets after flapless periodontal therapy: a Randomized Clinical Trial, *J. Clin. Periodontol.* 46 (2) (2019) 231–240.
- [107] E. Millhouse, A. Jose, L. Sherry, D. Lappin, N. Patel, A. Middleton, et al., Development of an in vitro periodontal biofilm model for assessing antimicrobial and host modulatory effects of bioactive molecules, *BMC Oral Health* 14 (2014) 80.
- [108] K. Vellyyagounder, K. Ganeshnarayan, S. Velusamy, D. Fine, In vitro efficacy of diallyl sulfides against the periodontopathogen aggregatibacter actinomycetemcomitans, *Antimicrob. Agents Chemother.* 56 (5) (2012) 2397–2407.
- [109] K. Ganesan, B. Xu, A critical review on polyphenols and health benefits of black soybeans, *Nutrients* 9 (5) (2017).
- [110] L. Ngo, J. Okogun, W. Folk, 21st century natural product research and drug development and traditional medicines, *Nat. Prod. Rep.* 30 (4) (2013) 584–592.
- [111] C.D. Lao, Ruffin MTt, D. Normolle, D.D. Heath, S.I. Murray, J.M. Bailey, et al., Dose escalation of a curcuminoid formulation, *BMC Compl. Alternative Med.* 6 (2006) 10.
- [112] P. Anand, A.B. Kunnumakkara, R.A. Newman, B.B. Aggarwal, Bioavailability of curcumin: problems and promises, *Mol. Pharm.* 4 (6) (2007) 807–818.
- [113] P. Anand, S.G. Thomas, A.B. Kunnumakkara, C. Sundaram, K.B. Harikumar, B. Sung, et al., Biological activities of curcumin and its analogues (Congeners) made by man and Mother Nature, *Biochem. Pharmacol.* 76 (11) (2008) 1590–1611.
- [114] G. Tegos, M. Anbe, C. Yang, T. Demidova, M. Satti, P. Mroz, et al., Protease-stable polycationic photosensitizer conjugates between polyethyleneimine and chlorin(e6) for broad-spectrum antimicrobial photoinactivation, *Antimicrob. Agents Chemother.* 50 (4) (2006) 1402–1410.
- [115] Z. Mahdi, G. Habiboallh, N. Mahbobeh, Z. Mina, Z. Majid, A. Nooshin, Lethal effect of blue light-activated hydrogen peroxide, curcumin and erythrosine as potential oral photosensitizers on the viability of *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, *Laser Ther.* 24 (2) (2015) 103–111.
- [116] M. Pourhajbagher, N. Chiniforush, S. Parker, S. Shahabi, R. Ghorbanzadeh, M. Kharazifard, et al., Evaluation of antimicrobial photodynamic therapy with indocyanine green and curcumin on human gingival fibroblast cells: an in vitro photocytotoxicity investigation, *Photodiagnosis Photodyn. Ther.* 15 (2016) 13–18.
- [117] L. Karygianni, A. Al-Ahmad, A. Argyropoulou, E. Hellwig, A. Anderson, A. Skaltsounis, Natural antimicrobials and oral microorganisms: a systematic review on herbal interventions for the eradication of multispecies oral biofilms, *Front. Microbiol.* 6 (2015) 1529.
- [118] D. Khurana, B. Sharnamma, P. Rathore, P. Tyagi, Photodynamic therapy- A ray towards periodontics, *IOSR-JDMS* 13 (3) (2014) 64–71.
- [119] J.E. Gomes-Filho, G. Sivieri-Araujo, C.R. Sipert, L.M. da Silva Santos, I.O. de Azevedo Queiroz, C. Men Martins, et al., Evaluation of photodynamic therapy on fibroblast viability and cytokine production, *Photodiagnosis Photodyn. Ther.* 13 (2016) 97–100.
- [120] A.S.I. Sreedhar, P. Rajan, J. Pai, S. Malagi, V. Kamath, R. Barmappa, Comparative evaluation of the efficacy of curcumin gel with and without photo activation as an adjunct to scaling and root planing in the treatment of chronic periodontitis: a split mouth clinical and microbiological study, *J. Nat. Sci. Biol. Med.* (2015).
- [121] P. Haag, V. Steiger-Ronay, P. Schmidlin, The in vitro antimicrobial efficacy of PDT against periodontopathogenic bacteria, *Int. J. Mol. Sci.* 16 (11) (2015) 27327–27338.
- [122] T. Kikuchi, M. Mogi, I. Okabe, K. Okada, H. Goto, Y. Sasaki, et al., Adjunctive application of antimicrobial photodynamic therapy in nonsurgical periodontal treatment: a review of literature, *Int. J. Mol. Sci.* 16 (10) (2015) 24111–24126.
- [123] Z. Akram, S.A. Al-Shareef, U. Daood, F.Y. Asiri, A.H. Shah, M.A. AlQahtani, et al., Bactericidal efficacy of photodynamic therapy against periodontal pathogens in periodontal disease: a systematic review, *Photomed. Laser Surg.* 34 (4) (2016) 137–149.
- [124] X. Huang, M. El-Sayed, Plasmonic photo-thermal therapy (PPTT), *Alexandria J. Med.* 47 (1) (2011) 1–9.
- [125] I. Karoussis, S. Kotsovilis, A. Felutzis, J. Fourmousis, Diagnosis and treatment of peri-implantitis, *Hellenic Soc. Odontostomatol. Res.* 63 (1) (2009) 168–195.
- [126] R. Fekrazad, F. Khoei, A. Bahador, N. Hakimiha, Photo-activated elimination of Aggregatibacter actinomycetemcomitans in planktonic culture: comparison of photodynamic therapy versus photothermal therapy method, *Photodiagnosis Photodyn. Ther.* (2017).

- [127] A. Bucharskaya, G. Maslyakova, G. Terentyuk, A. Yakunin, Y. Avetisyan, O. Bibikova, et al., Towards effective photothermal/photodynamic treatment using plasmonic gold nanoparticles, *Int. J. Mol. Sci.* 17 (8) (2016).
- [128] F. Katsikanis, D. Strakas, I. Vouros, The application of antimicrobial photodynamic therapy (aPDT, 670 nm) and diode laser (940 nm) as adjunctive approach in the conventional cause-related treatment of chronic periodontal disease: a randomized controlled split-mouth clinical trial, *Clin. Oral Invest.* (2019).
- [129] I.A.A. Sena, D.N.A. Silva, M. Azevedo, N.T. da Silva, J.P.F. Longo, M. de Moraes, et al., Antimicrobial photodynamic therapy using a chloro-aluminum phthalocyanine adjuvant to nonsurgical periodontal treatment does not improve clinical parameters in patients with chronic periodontitis, *Photobiomodul Photomed. Laser Surg.* 37 (11) (2019) 729–735.